Exchange Transfusion in Severe Falciparum Malaria : A Simple Method Modified from Hemodialysis Circuit

BUNLUSAK ACHAVANUNTAKUL, M.D.*, SOMCHAI EIAM-ONG, M.D.**, TERAPONG TANTAWICHIEN, M.D.***, PENPAN NUALBOONMA, M.D.****, VIRA KASANTIKUL, M.D.****

Abstract

We set up a simple extracorporeal circuit, modified from the extracorporeal method generally used in conventional hemodialysis, for exchange transfusion. Temporary vascular access was used in exchange transfusion for both draining the infected blood and infusion of the freshly non-infected blood. This method of exchange transfusion was performed in 3 severe complicated falciparum malaria patients who had a percentage of parasitemia of 80, 40, and 35. The magnitude of parasitemia decreased immediately to less than one per cent and this value persisted twenty-four hours after the procedure. No complications of exchange transfusion were detected in all patients. Erythrocyte morphology determined by scanning electron microscopy was unaltered by exchange transfusion. Because of the simplicity, the effectiveness, and the safety of the procedure, this extracorporeal circuit modified from hemodialysis circuit would be a more beneficial exchange transfusion method in the treatment of severe complicated falciparum malaria than the manually-performed one.

Key word : Exchange Transfusion, Severe Falciparum Malaria, Hemodialysis, Erythrocyte Morphology

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Plasmodium falciparum is widely prevalent all over the world, particulary in tropical areas[1]. Malarial infection from this species is of greatest clinical importance because of the possibility of various life-threatening complications. This occurs because *P. falciparum* can

* Nephrology Unit, Medicine, Ubon Ratchathani Province Hospital, Ubon Ratchathani 34000,
** Division of Nephrology,
*** Division of Infectious Disease, Department of Medicine,
**** Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

invade erythrocytes of all ages, occasionally resulting in very high infection rates of 50 per cent or more(2). The currently essential treatment of falciparum malaria consists of two phases : first, a rapid reduction in parasite load and second, a complete elimination of all parasites including any resistance to the agents used in the first phase (3). Exchange transfusion has been shown to be a useful adjunct therapy in effective removal of asexual parasitemia in patients with severe falciparum malaria(4-20). In most previous reports, the exchange transfusion was performed by a manual procedure. Although the manually conducted exchange transfusion is simple, it is labor-intensive and time consuming, both of which could introduce undesired complications, particularly superimposed infections, to the transfused patients(18,21,22).

Indeed, the duration of exchange transfusion could be shortened by infusing the new blood with a conventionally peristaltic infusion pump, generally used for fluid infusion. With such a pump, the fluid is administered by occluding the fluid-administration tube until it becomes completely flat. This could traumatize red blood cells when the blood is infused especially when the infusion rate is high. Thus, the conventionally peristaltic infusion pump is not the appropriate instrument for exchange transfusion. On the other hand, the roller blood pump used in hemodialysis circuit does not significantly injure and change the erythrocyte morphology(23,24). Such a pump could be successfully used in exchange transfusion.

To circumvent all the problems that might occur in the conventionally manual exchange transfusion, we have set up a simple extracorporeal circuit for the procedure. The exchange transfusion circuit is modified from the extracorporeal one generally used in the conventional hemodialysis. The hemodialysis machine is not used in this new exchange transfusion procedure. Herein, the temporary vascular access is inserted in a major vein and is used in exchange transfusion for both draining the infected blood and infusion of the freshly non-infected blood. Temporary vascular access is superior to venesection, generally performed in the conventional procedure, since the former causes a very low incidence of venous obliteration(25,26). This vascular access could also be used for the hemodialysis procedure when dialysis is indicated. Our results have shown that this method of exchange transfusion is effective, simple, and safe, and, thus, would reduce all the mentioned disadvantages of the manual exchange transfusion.

PATIENTS AND METHOD

Patients

The study was approved by the Ethics Committee, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand. Since all the patients studied had impaired consciousness, the patients' closest relatives signed the consent form. Blood exchange transfusion was performed by the new method in three patients with severe complicated falciparum malaria. There were two male patients whose ages were 59 and 43 years old respectively. The age of the female patient was 28 years old. Clinical and laboratory features of severe complicated malarial cases were indicated by WHO criteria : CNS stuporous, restless = +, coma and convulsion = ++, impaired renal function test and oliguria = ++, pulmonary edema = +, pulmonary edema + hypoxia = ++, jaundice, bilirubin = 1-3 mg per cent = +, bilirubin > 3 mg per cent = ++, bleeding skin and mucosa = +, severe gastro-intestinal bleeding = ++(27). Severe hematologic manifestation was disseminated intravascular coagulation (DIC), the criteria for diagnosis of which included ischemia of end organs with concomitant findings of thrombocytopenia, increased fibrin degradation products (FDP) of more than 10 microgram/ml and one or more abnormalities of the following coagulation tests: prolongation of PTT, PT and TT, low fibrinogen, and/or positive fibrin monomer(27).

All three patients in the study had several mentioned features of severe complicated malaria. DIC was detected in all victims. The patients were given an initial loading dose of 20 mg of quinine dihydrochloride/kg body weight (Bw.), infused over four hours. This was followed by a maintenance dose of 10 mg/kg Bw every eight hours. Decision for exchange transfusion included one of the two major criteria : hyperparasitemia of more than 10 per cent accompanied by at least one severe systemic complication and/ or sustained symptoms of the severe systemic complication for more than 24 hours after receiving effective antimalarial drugs and full supportive therapy.

Exchange Transfusion Circuit

In most previous reports of exchange transfusion, irrespective of the methods performed, two major veins were used in the procedure. One was used for the infusion of new blood, whereas, the other was used for the exfusion of the infected blood. In general, venesection was conducted in at least one vein. This might cause permanent obliteration of the operated vein. In the present study, only one major vein was required for the procedure. Moreover, no venesection was needed. Thus, in the new method, a double lumen catheter was inserted into a major vein which may be the femoral or subclavian vein. This catheter was used for exchange transfusion as well as hemodialysis procedure. It is well established that the incidence of venous thrombosis from insertion of the double lumen catheter is very low(25,26).

The exchange transfusion was performed by a system modified from the extracorporeal circuit normally used in conventional hemodialysis. Fig. 1 illustrates the main components of the conventional hemodialysis circuit. Such a circuit resides in the hemodialysis machine. In the conventional hemodialysis procedure, the undialyzed blood from the arterial port of the double lumen catheter passed *via* a blood pump to the dialyzer. The dialyzed blood moved through the venous drip chamber, back to the venous port. It should be noted that the inside-catheter opening end of the arterial port of the double lumen catheter was more proximal to the canula of the catheter than that of the venous one. This means that the arterial opening was closer to the patient's cardiovascular system than the venous one (Fig. 1). Such a pathway of blood flow could ensure the effectiveness of dialysis procedure and would reduce the magnitude of access recirculation (AR) that might occur during the dialysis procedure.

Fig. 2 depicts the circuit modified for exchange transfusion. It should be re-emphasized that the hemodialysis machine was not used in the exchange transfusion procedure. In addition, the dialyzer and arterial pressure monitor in Fig. 1 were not involved in the exchange transfusion procedure and, thus, were discarded from the exchange circuit. Here, the roller pump was used as a blood pump for propelling the new non-infected blood into the patients. The new non-infected blood passed through the venous port of the double lumen catheter. The arterial port of the vascular access was used, in the exchange transfusion circuit, as the drainage pathway of the infected blood out of the patients. Another flow controlled pump was settled and used to regulate the flow rate of the drainage blood in order to match with that of the input blood. It should be noted that the blood pump in the exchange transfusion circuit was connected to the

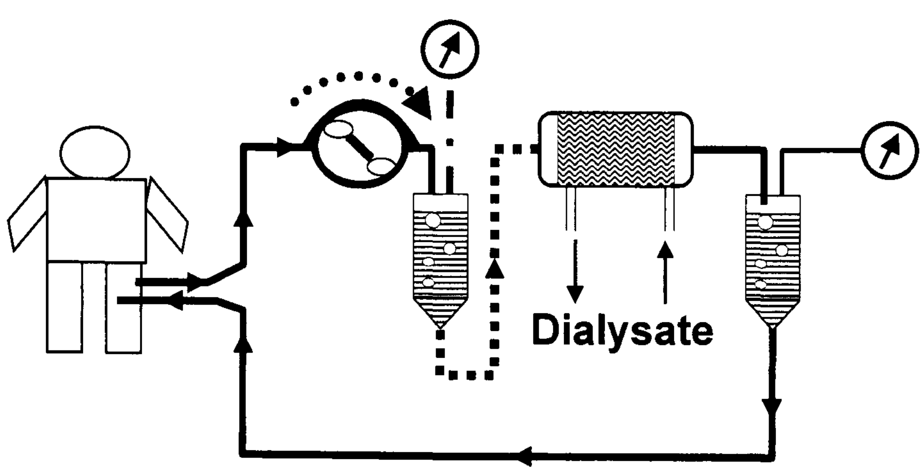

Fig. 1. Main components of extracorporeal circuit used in conventional hemodialysis.

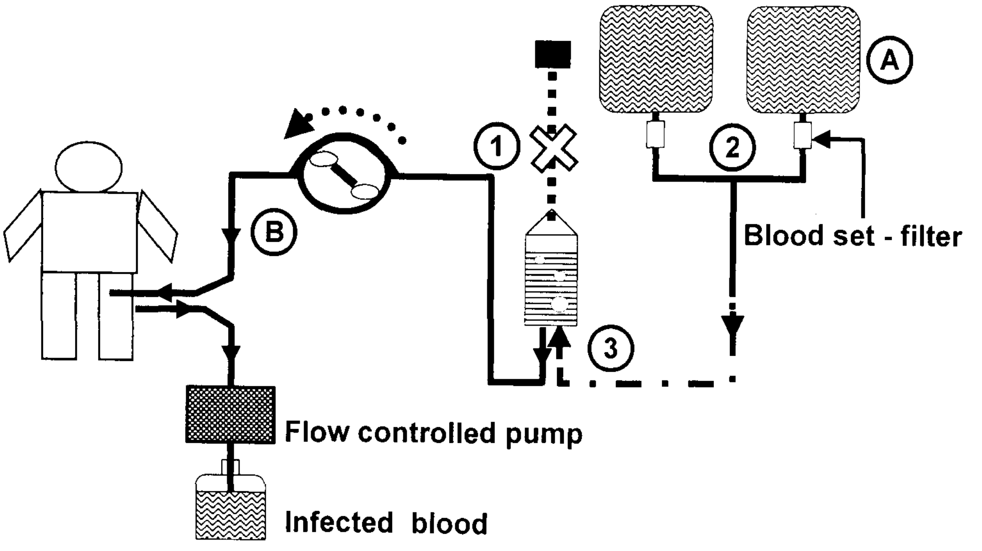

Fig. 2. Exchange transfusion circuit modified from extracorporeal circuit used in conventional hemodialysis.

venous port, whereas, the one in the hemodialysis circuit was linked to the arterial port of the double lumen catheter. Thus, the pathway of blood flow in the exchange transfusion circuit was in the opposite direction when compared with that in the hemodialysis circuit (clockwise *vs* counter-clockwise direction). Infusion of the new blood to the more distal site in the double lumen catheter and exfusion of the infected blood into the more proximal site would, in the same manner as observed in the hemodialysis procedure, guarantee the effectiveness of the exchange transfusion procedure. Thus, the new blood was infused into the more proximal site of the patients systemic circulation than that of the exfusion of the infected blood. (Fig. 2) Furthermore, the blood flow rate of only 50 ml/min used in exchange transfusion would create a very low percentage of AR.

For exchange transfusion purposes, the venous drip chamber in Fig. 1 has been changed in many aspects. First, the bloodline connected to the blood pump and the venous port was clamped (Site 1, Fig. 2). Second, the venous pressure monitor was substituted with the new blood bags used for exchange transfusion (Site 2, Fig. 2). Lastly, the direction of blood flow through the venous drip chamber in Fig. 2 was also placed opposite compared with that in Fig. 1 (Site 3, Fig. 2). As such, the venous drip chamber was eventually transformed into an air tapped chamber (Fig. 2).

The patients were treated with exchange transfusion in the intensive care unit. Indeed, fresh whole blood is the ideal blood component used in the exchange transfusion procedure. In real clinical practice, fresh whole blood, especially when a large amount is needed, is less available than the packed red blood cell. It is well established that infusion of packed red blood cell, which has a higher viscosity, would take a longer duration than fresh whole blood. This might further increase the incidence of superimposed infusion when the exchange transfusion is performed by a manual procedure. As such, it was our purpose to test the effectiveness of the modified circuit of exchange transfusion by using packed red blood cell. Packed red blood cell stored less than 5 days and fresh frozen plasma (FFP) were used in the procedure. The amount of blood for each exchange was about one blood volume which ranged from 10-12 units (each unit equals 1 unit packed red blood cell plus FFP 1 unit). The duration of each exchange transfusion was approximately 2 hours. During the exchange transfusion, blood pressure and heart rate were monitored and recorded at 10-minute intervals. Continuous monitoring of electrocardiography was performed on all transfused patients. The exchange transfusion was repeated if parasitemia was still over 10 per cent or the symptoms of severe systemic complications were sustained or became worse in the following 24 hours.

Studies of alterations in erythrocyte morphology induced by blood pumps

To examine whether the blood pump used for exchange transfusion in the present study could alter erythrocyte morphology or not, blood samples obtained from pre-pump and post-pump (Fig. 2 : site A and B respectively) were examined by a scanning electron microscopy[23,24]. The blood samples were smeared onto coverslips, washed and fixed in the buffer solution of 3 per cent glutaraldehyde for 30 minutes. It was washed in the buffer for another 10 minutes, followed by 2 per cent osmium tetroxide for 1 hour and dehydrated through an ascending ethanol series, then transferred to the critical point dryer. The specimen was stuck onto stubs using double sided adhesive tape and coated with gold to a thickness of 20 nm. Erythrocytes from contiguous fields were examined by a scanning electron microscope (SEM). (JEOL Model JSM 5300)

The SEM photographs were then studied with an image analyser (Global lab, SPO550). Normal and dysmorphic erythrocytes were differentiated on the basis of the circular shape factor (CIRF), defined by the following formula:

$$CIRF = 4\pi \times area / (perimeter)^2$$

This factor is equal to 1 for round shapes, while always less for other configurations[26]. As erythrocytes are not perfectly round, the CIRSF value for normal erythrocytes was established by measuring 100 obviously normal erythrocytes randomly chosen in all the photograhs. Only horizontal but not overlapping erythrocytes were considered.

RESULTS

Table 1 details the basic clinical data of the three patients at the time of admission. Fig. 3 depicts the percentage of parasitemia of the three victims at different time points. Exchange transfusion by this new method could effectively remove malarial parasites. In all three patients, the percentage of parasitemia decreased to less than one per cent immediately after transfusion and this value still persisted twenty-four hours after the procedure. We also determined the percentage of AR in all three patients. The magnitude of AR measured by stop-flow technique was less than 0.5 per cent in every patient.

Table 1. Clinical characteristics of the three patients with severe complicated malaria in the present studies.

Patient	Sex	Age (yr)	Percentage of parasitemia	Complications
1. B.P.	M	59	80	Cerebral, DIC
2. D.N.	F	28	40	Cerebral, DIC
3. S.J.	M	43	35	Cerebral, DIC

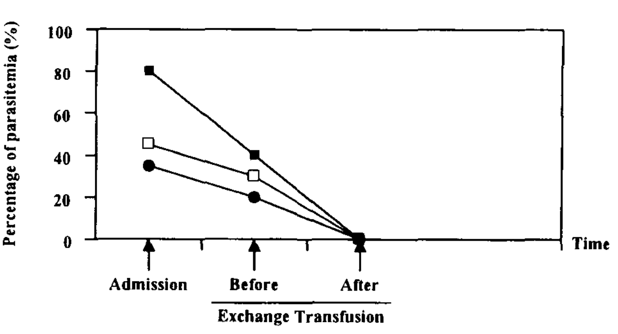

Fig. 3. Percentage of parasitemia at the time of admission, before, and after exchange transfusion.

The exchange transfusion was performed once in each patient. All the patients could tolerate the transfusion procedure very well. Their systemic hemodynamics and body temperature were stable during transfusion therapy. Acid-base status, determined by arterial blood gas and plasma bicarbonate levels, plasma potassium and calcium levels of all patients at the time after exchange transfusion were not significantly different from those before the treatment (Data not

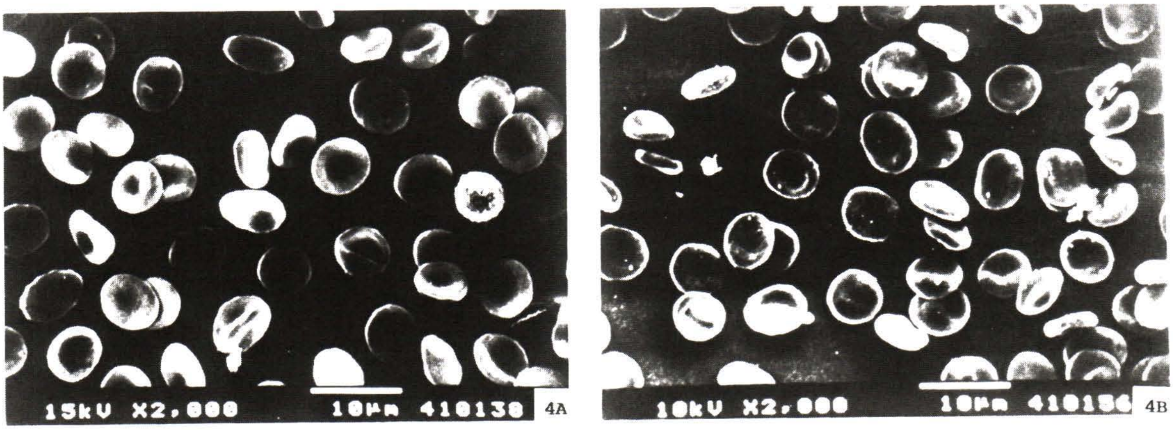

Fig. 4 **Scanning electron microscope photographs of erythrocytes at pre- (4A) and post- (4B) blood pump sites (Fig. 2, site A and B respectively).**

shown). No patients developed sepsis following the procedure. All patients completely recovered from the severe complicated falciparum malaria.

Fig. 4 illustrates erythrocyte morphology, determined by scanning electron microscopy, in the new non-infected blood bag and at the pre and post-blood pump sites (Fig. 2, site A and B respectively). By electron micrograph studies, The CIRF values (mean±SD) of sample A and B were 0.90±0.05 and 0.90±0.04, respectively. The results, therefore, showed no significant difference between the erythrocyte morphology of both sample groups.

DISCUSSION

Exchange transfusion has been successfully used in the treatment of various disorders including severe malaria, hepatic failure, hyperbilirubinemia, transfusion-transmitted babesiosis, pregnancy-related severe anemia, and a variety of diseases of infancy[1-22,28-32]. The treatment could be performed by one of the following methods : a manual procedure, and automated continuous-flow cell separator, and an exchange transfusion circuit equipped with special instruments including a three-way spring-loaded glass stopclock or a roller pump.

Regardless of the procedure performed, the benefit of exchange transfusion in removal of harmful blood components should be offset by the complexity of the process and various complications caused by massive blood transfusion[18,21]. The latter include bleeding due to dilution of clotting factors, hypothermia, citrate toxicity, electrolyte imbalance, particularly hypocalcemia and hyperkalemia, microemboli, 2,3 DPG deficiency, and various blood borne infectious agents. Infectious complications appear to correlate directly with the duration in performing exchange transfusion.

Manually performed exchange transfusion is the method most commonly used in the reported literature[3-22]. This method, however, has several disadvantages. In such procedure two separate venous sites, one for infusion of new blood and the other for exfusion of the patient's own blood, are used in the procedure. Venesection is performed in most reported patients and this could result in permanent obliteration of the operated vein after the exchange transfusion. Despite the simplicity of the method, exchange transfusion by manual procedure, is time-consuming and, thus, could cause an increase in superimposed infections to the patients. The risk of such infections could be further heightened by the type of blood component used in the procedure. As stated earlier, infusion of packed red blood cell, which is more available but has higher viscosity, would take a longer duration than fresh whole blood. Thus, manually performed exchange transfusion with packed red blood cell could further result in increased risk of the superimposed infections. As such, exchange transfusion by the conventional circuits is too complex and has too many disadvantages. Indeed, exchange transfusion with packed red blood cell could be performed in a short period of time, 1-2 hours, by an automated continuous flow cell separator used in blood bank. Such an instrument, however, is available only in a limited number of medical centers.

Regarding severe falciparum malaria, it appears that the mortality of the infection increases inexorably with the height of the percentage of parasitemia[1,2]. Despite appropriate chemotherapy, death often occurs within 24 hours after admission to the hospital and this is ussually accompanied by the persistence of parasites in the peripheral blood. Parasitized erythrocytes as well as plasma cytokines and mediators play the most important role in the pathogenesis of all severe complications including acute renal failure (ARF) [2]. Exchange transfusion has been reported to be an effective adjunct therapy in several patients with severe malaria. Besides the removal of parasitized erythrocytes and cytokine and mediator-rich plasma by the exchange transfusion procedure, the patients are simultaneously replaced with adequate plasma factors necessary for normal hemostasis status. Previous studies in severe falciparum malaria have shown that the duration and complexity of exchange transfusion would increase the risk of bacterial infection in a group of patients unusually susceptible to septicemia [18,32]. The manually conducted exchange transfusion might not be an appropriate procedure in patients with severe falciparum malaria. Thus, an exchange transfusion with a shorter duration and more simplicity is inevitably required in the management of such patients. Furthermore, in coping with hypercatabolic ARF occurring in falciparum malaria, hemodialysis is the preferable modality of dialysis treatment[1,2]. Thus, temporary vascular access is inserted and used for the hemodialysis procedure. As such, it would be more beneficial to the patients if the vascular access could be used for exchange transfusion as well as hemodialysis.

For a better outcome in performing exchange transfusion as the adjunct treatment of all the earlier mentioned disorders including severe complicated malaria, it is necessary to develop a new method of transfusion. The new method should be effective, simple and could solve all or most disadvantages incurred in the manual exchange transfusion procedures. The results in the present study have demonstrated that the exchange transfusion circuit modified from the extracorporeal one, generally used in conventional hemodialysis, could effectively remove parasitized erythrocytes as well as the cytokine-rich plasma in patients with severe malaria. (Fig. 3) Treated with the new exchange transfusion procedure, none of the patients in the present study suffered from any exchange transfusion-related complications stated above.

It is also obvious that this modified circuit of exchange transfusion is simple and easily set up. (Fig. 2) Moreover, when the patients recover from the underlying diseases and there is no need of continuing exchange transfusion treatment, the temporary vascular access could be removed without major deleterious consequences. The incidence of vein thrombosis attributable to the temporary vascular access is very low[25,26]. Regarding the traumatizing effect of the blood pump, our results have shown that no significant alterations in red blood cell morphology occurred during the procedure. This is in agreement with previous works[32,33].

As such, the method of exchange transfusion, modified from the extracorporeal circuit generally used in the conventional hemodialysis, is effective, simple, and safe in the treatment of severe complicated malaria.

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การแลกเปลี่ยนโลหิตทั้งร่างกาย ในผู้ป่วยฟาลซิปารัมมาเลเรียชนิดรุนแรง โดยวิธีการที่ดัดแปลงจากวงจรการฟอกเลือด

บรรลือศักดิ์ อาชวานันทกุล, พ.บ., สมชาย เอี่ยมอ่อง, พ.บ.**,*
*ธีระพงษ์ ตันติวิเชียร, พ.บ.***, เพ็ญพันธุ์ นวลบุญมา, พ.บ.****, วีระ กสานติกุล, พ.บ.*****

ได้รายงานวิธีการแลกเปลี่ยนโลหิตทั้งร่างกายในผู้ป่วยมาเลเรียที่มีความรุนแรงและมีภาวะแทรกซ้อน 3 ราย โดยการใช้วงจรซึ่งใช้ในเครื่องฟอกเลือด ผู้ป่วยมีปริมาณเชื้อมาเลเรีย 80, 40 และ 35 เปอร์เซ็นต์ พบว่าวิธีการแลกเปลี่ยนโลหิตทั้งร่างกายดังกล่าวมีประสิทธิภาพในการลดปริมาณเชื้อมาเลเรียลงเหลือต่ำกว่า 1 เปอร์เซ็นต์ทันทีภาย-หลังการรักษาและที่เวลา 24 ชั่วโมงภายหลังการรักษา ไม่พบภาวะแทรกซ้อนจากการรักษา การตรวจโดยกล้องจุลทรรศน์อิเลคตรอน ไม่พบการเปลี่ยนแปลงของรูปร่างของเม็ดเลือดแดง วิธีการแลกเปลี่ยนโลหิตทั้งร่างกายโดยวิธีดังกล่าวจึงมีประสิทธิภาพ มีความปลอดภัย และง่ายในการปฏิบัติ

คำสำคัญ : การแลกเปลี่ยนโลหิตทั้งร่างกาย, ฟาลซิปารัมมาเลเรียชนิดรุนแรง, การฟอกเลือด, รูปร่างของเม็ดเลือดแดง

บรรลือศักดิ์ อาชวานันทกุล, สมชาย เอี่ยมอ่อง,
ธีระพงษ์ ตันติวิเชียร, เพ็ญพันธุ์ นวลบุญมา, วีระ กสานติกุล
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 314–322

* หน่วยไต, อายุรกรรม, โรงพยาบาลสรรพสิทธิประสงค์, อุบลราชธานี 34000
** สาขาวิชาโรคไต,
*** สาขาวิชาโรคติดเชื้อ, ภาควิชาอายุรศาสตร์,
**** ภาควิชาพยาธิวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพฯ 10330