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Exchange Transfusion in Malaria with High Parasitaemia: A Case Series from a Pakistani Tertiary Care Centre

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Abstract

Introduction

High levels of parasitaemia are associated with a poor prognosis in severe malaria. Exchange blood transfusion (EBT) is an adjunct therapy used in these patients. The goal of this series was to review cases of malaria with high parasitaemia where patients received EBT.

Methods

We conducted a retrospective review of case-records from 2007-2015 at the Aga Khan University Hospital (AKUH), Karachi, Pakistan. Patients diagnosed with malaria via a positive peripheral blood smear who received EBT due to high levels of parasitaemia (>10%) were included. The changes in clinical haematology parameters after EBT were analyzed.

Results

30 patients were included. The mean age was 44.80 years (Standard deviation: 18.34). 16 patients had Plasmodium vivax infection, 10 had Plasmodium falciparum infection, and 4 had mixed infection. Mean length of stay was 7.87 days (standard deviation: 12.79). 27 patients survived through follow-up. Following EBT, haemoglobin and platelets were seen to improve by 7% and 90% respectively, although large patient to patient variation was observed.

Conclusion

EBT may benefit patients with haematological derangements such as anaemia and thrombocytopenia during severe malaria. Prospective studies should better evaluate EBT as it is an accessible intervention in low-resource areas of malarial endemicity.

Keywords: Parasitaemia, Exchange blood transfusion, Malaria, Anaemia, Thrombocytopenia

1. Background

Malaria is a highly prevalent infectious disease and is estimated to have caused around 250 million cases and over half a million deaths globally in 2020 [1]. It primarily affects low resource settings in tropical and subtropical regions that are more habitable for the mosquito vector [2]. Pakistan is a low-middle income country with endemic transmission of the vivax and falciparum species of malaria, resulting in an incidence of up to 3.5 million cases each year [3].
Malarial infection is characterized by symptoms such as fever, headaches, malaise, and myalgia [4]. Severe malaria with high levels of parasitaemia can manifest as a life-threating constellation of symptoms. Such patients may develop acute

dysregulation of haematological and circulatory parameters leading to life-threatening complications of shock and organ failure [5].

Exchange blood transfusion (EBT) is a therapeutic intervention where patients' blood is replaced with uninfected blood that is devoid of infected cells and toxic metabolites [6]. This technique has been used by clinicians as an adjunctive treatment to anti-malarial pharmacotherapy. EBT is thought to reduce parasite load, optimize blood rheology, and improve oxygen-carrying capacity and its efficacy is thus biologically plausible [7].

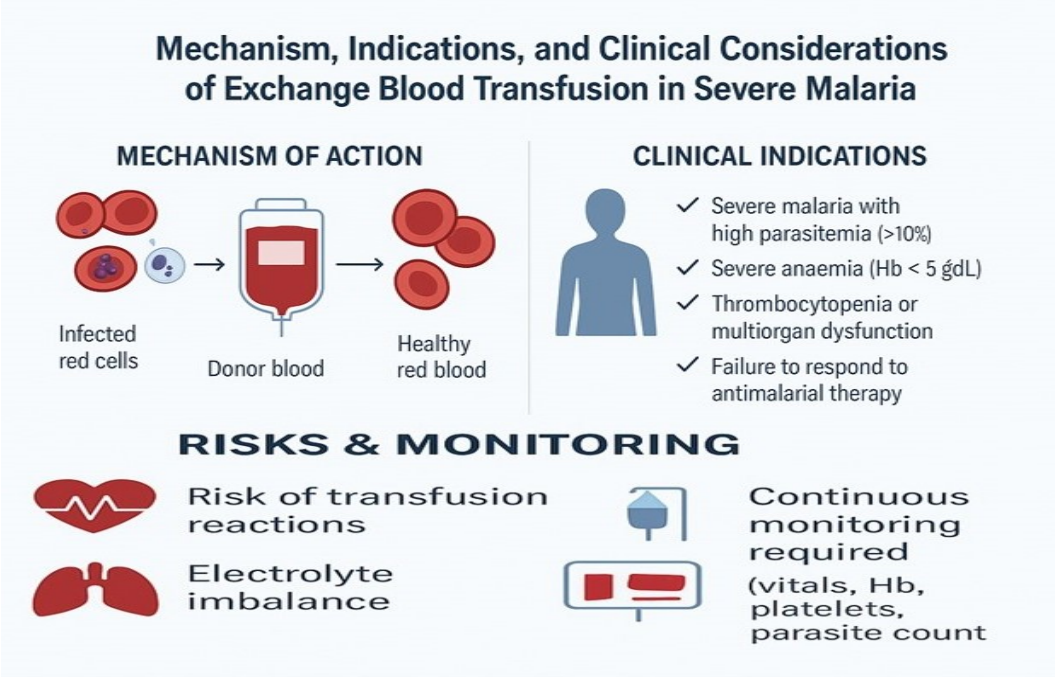

Figure 1: Exchange Transfusion in Malaria: Indications, Risks, and Mechanism of Action.

Although numerous case reports and series continue to report successful lowering of parasitemia after exchange transfusion, there is a dearth of published clinical evidence to support the use of EBT, including laboratory parameters, biomarkers, or clinical outcomes [8–10]. Given that EBT is reserved for use in severely ill patients, assessment of risk to benefit ratios must be individualized by clinicians looking at all dimensions of each case. The aim of this series was to demonstrate improvements in the hematological parameters of patients with severe malaria who received EBT at the Aga Khan University Hospital, a tertiary care center in Karachi, Pakistan. These data may provide useful information for clinicians making such judgements.

2. Methods

The AKUH institutional ethics review committee exempted this case series from the need to obtain participant consent due to the use of anonymized data extracted retrospectively. Records of all malaria parasite-positive cases admitted to AKUH between 2007 and 2015 were reviewed. Patients who had received EBT were identified for inclusion in the analysis.

For all included patients, diagnosis was confirmed via microscopic examination of peripheral blood smear obtained at the time of collection of blood for complete blood counts (CBCs). A peripheral blood smear was considered positive if any stage of the plasmodial life cycle was identified. EBT, specifically automated red cell exchange, was performed as an adjunctive therapy in patients with severe malaria and high parasitaemia (>10%; in line with WHO recommendations regarding severe malaria [10], based on multidisciplinary clinical decision-making involving the treating medical and transfusion services. Indications included a high parasite burden accompanied by clinical deterioration (e.g., hemodynamic instability, worsening organ function, or altered level of consciousness) and/or significant hematological derangements (e.g., severe anemia, hemolysis, or thrombocytopenia) despite appropriate antimalarial therapy. The procedure was conducted using automated apheresis devices, with packed red blood cells as the primary replacement component to remove parasitized erythrocytes, while fresh frozen plasma was administered as needed to maintain coagulation factor levels and plasma volume. The estimated exchange volume ranged from approximately one to two times the patient's calculated blood volume, performed in sequential cycles. The exact volume exchanged and number of cycles were individualized based on patient weight, clinical status, and response to therapy. Standard institutional transfusion protocols were followed throughout the procedure.

The data reviewed for each patient included the following parameters: demographic and clinical information, species of malaria causing infection, and both pre- and post-transfusion CBC reports. Categorical variables were reported as frequencies or percentages. For continuous data, normality was assessed using the Shapiro-Wilks test. Normally distributed data were

analyzed using the paired-sample t-test and non-normally distributed data using the wilcoxon signed-rank test.
All data were analysed using the Statistical Package for the Social Sciences (IBM SPSS) version 21. P-values less than 0.05 were considered statistically significant.

3. Results

The medical records of 95 patients diagnosed with malaria during the defined study period were retrieved from our institutional electronic health records. Of these, 30 patients (15 males and 15 females) had parasitaemia greater than 10% for which exchange blood transfusion was performed during management. These patients were subsequently included in the analysis.

Table 1: Patient Characteristics

Patient	Age	Sex	Species	Signs and Symptoms at Presentation	Duration	LOS	Outcome
1	21	Female	Mixed	Fever	10	2	Alive
2	53	Male	Vivax	NA	30	17	Alive
3	42	Male	Vivax	Fever, Hemoptysis	10	5	Alive
4	41	Male	Falciparum	Fever, Febrile Neutropenia, Pancytopenia	3	10	Alive
5	64	Female	Falciparum	Fever	NA	6	Alive
6	61	Male	Vivax	Fever, Vomiting	4	3	Alive
7	68	Female	Mixed	Fever, Chills, Rigours, Diarrhoea, Dry Cough	5	3	Alive
8	26	Female	Vivax	Fever, Chills	7	2	Alive
9	20	Female	Vivax	Fever, Vomiting	7	2	Alive
10	79	Male	Falciparum	Fever, Diarrhea	2	3	Alive
11	42	Female	Vivax	Fever	15	4	Alive
12	44	Male	Falciparum	Fever, Vomiting	21	3	Alive
13	77	Male	Falciparum	Fever, Chills, Generalized weakness	3	4	Alive
14	31	Female	Vivax	Fever, Diarrhea	5	5	Alive
15	50	Female	Vivax	Fever	3	8	Alive
16	60	Female	Vivax	NA	5	14	Alive
17	37	Female	Vivax	Fever, Chills, Vomiting	5	2	Alive
18	39	Male	Mixed	Fever	30	8	Alive
19	61	Male	Falciparum	Fever, Altered Mental Status	10	2	Expired
20	46	Male	Falciparum	Fever, Vomiting	NA	2	Expired
21	51	Male	Mixed	Fever, Nocturia, Dysuria	6	15	Alive
22	25	Female	Vivax	Fever, Headache, Abdominal symptoms	1	2	Alive
23	21	Female	Vivax	Fever, Headache	4	2	Alive
24	40	Female	Vivax	Fever, Vomiting	5	4	Alive
25	32	Male	Falciparum	Fever, Generalized weakness	4	12	Alive
26	29	Male	Vivax	Fever, Chills	6	2	Alive
27	70	Male	Vivax	NA	7	7	Alive
28	17	Female	Falciparum	Fever, Headache	NA	6	Alive
29	22	Male	Falciparum	Fever, Vomiting	5	8	Alive
30	75	Female	Vivax	Signs and Symptoms at Presentation	8	73	Expired

LOS: Length of Stay. Blank spaces marked with 'NA' indicates where data was missing from the retrieved record.

Patient characteristics are detailed in Table 1. Mean age was 44.80 years (SD: 18.34, range: 17-75). No patient had prior exposure to malarial infection. 16 patients had Plasmodium vivax infection, 10 had Plasmodium falciparum infection, and 4 had mixed (concomitant vivax and falciparum) infection. Mean length of stay was 7.87 days (SD: 12.79, range: 2-73) and 27 patients remained alive at the time of follow-up.

Table 2: Pre- and post-transfusion values of hematological parameters (All patients, n=30)

Hematological Parameter	Pre-Transfusion	Post-Transfusion	p-value
Hb	10.38 ± 1.91	11.11 ± 2.74	**0.003**
Hct	33.98 ± 6.76	29.68 ± 6.73	< **0.001**
RBC	4 ± 0.92	3.79 ± 0.67	**0.008**
MCV	83.79 ± 8.88	83.52 ± 7.44	0.491
MCH	27.47 ± 3.33	27.01 ± 4.13	0.21
MCHC	32.75 ± 1.34	32.86 ± 1.04	0.352
WBC	7.25 ± 4.57	10.01 ± 25.08	0.297
Neutrophils	69.93 ± 15.2	56.69 ± 15.16	< **0.001**
Lymphocytes	21.7 ± 13.07	30.36 ± 12.87	< **0.001**
Eosinophils	1.14 ± 1.31	1.63 ± 1.36	**0.038**
Monocytes	6.74 ± 4.64	11.18 ± 11.17	< **0.001**
Basophils	0.33 ± 0.29	0.45 ± 0.33	**0.008**
Platelets	63.36 ± 71.14	120.26 ± 109.24	< **0.001**

Hb: Haemoglobin, HCT: Haematocrit, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, WBC: white blood cells

Table 3: Pre- and post-transfusion values of hematological parameters (*P. vivax* infected patients, n=16)

Haematological Parameter	Pre-Transfusion	Post-Transfusion	p-value
Hb	10.2[11.8–8.9]	11.9[13.8–10]	**0.004**
Hct	33.3[39.35–30.6]	29.9[33.75–25.25]	<**0.001**
RBC	3.98[4.8–3.48]	3.72[4.16–3.4]	**0.011**
MCV	85[89.1–77.8]	84.6[87.9–79.3]	0.635
MCH	27.7[28.9–25.8]	27.95[28.8–25.8]	0.654
MCHC	32.5[33.2–32]	32.6[33.3–32]	0.23
WBC	5.7[7.9–4.3]	5.85[8.5–4.9]	0.287
Neutrophils	72[80.9–63.7]	59[67.8–44.8]	<**0.001**
Lymphocytes	21.3[27–13]	27.9[39.9–18.1]	<**0.001**
Eosinophils	0.95[1.8–0.35]	1.15[2.2–0.7]	0.82
Monocytes	5.8[9.6–3]	9.5[12.3–6.2]	**0.024**
Basophils	0.2[0.35–0.1]	0.3[0.6–0.2]	0.146
Platelets	40[81–25]	69[124–45]	**0.002**

Hb: Haemoglobin, Hct: Haematocrit, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, WBC: white blood cells

Table 4: Pre- and post-transfusion values of hematological parameters (*P. falciparum* infected patients, n=10)

Haematological Parameter	Pre-Transfusion	Post-Transfusion	p-value
Hb	9.9[10.9–9.3]	10.4[13.2–7.8]	0.692
Hct	31.75[38.9–25.5]	30.15[32.7–26.3]	**0.043**
RBC	4.14[4.64–2.76]	3.62[4.07–3.23]	0.676
MCV	86.35[90.2–81.3]	87.55[89.5–82.05]	0.222
MCH	29.05[29.8–26.4]	28.4[29.5–26.25]	0.187
MCHC	33.2[34.1–32.3]	33[33.3–32.6]	0.946
WBC	7.3[13.4–4.7]	6.35[10.45–5.2]	0.905

Haematological Parameter	Pre-Transfusion	Post-Transfusion	p-value
Neutrophils	74.05[86.1–66.2]	58.75[70.2–48.25]	**0.001**
Lymphocytes	17.5[24.3–8]	29.9[37.75–22.8]	**0.015**
Eosinophils	0.3[1.2–0.1]	1[1.9–0.6]	**0.023**
Monocytes	6.95[9.4–2.7]	9[12.9–7.2]	**0.002**
Basophils	0.2[0.6–0.1]	0.4[0.6–0.3]	0.248
Platelets	47[61–33]	72[167–44]	**0.006**

Hb: Haemoglobin, Hct: Haematocrit, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, WBC: white blood cells

Table 5: Pre- and post-transfusion values of hematological parameters (Mixed infection, n=4)

Haematological Parameter	Pre-Transfusion	Post-Transfusion	p-value
Hb	10.5[11.9–8.9]	11[12.1–10.8]	0.186
Hct	32.4[36.1–31.2]	29.4[35–25.8]	**0.019**
RBC	3.95[4.32–3.55]	3.65[4.23–3.33]	0.205
MCV	85.25[88.05–81.25]	84.5[89–77.6]	0.747
MCH	28.4[29.3–27.2]	28.3[29.4–26.6]	0.954
MCHC	33.2[33.9–32.45]	33.1[33.6–32.9]	0.766
WBC	6.8[9.4–5.7]	7.1[9–4.9]	0.956
Neutrophils	69.9[77.9–49]	55.4[62.9–48.3]	**0.001**
Lymphocytes	25[35.3–13.3]	29.9[42.3–24.6]	**0.01**
Eosinophils	1[1.6–0.4]	1.6[2.8–0.8]	**0.037**
Monocytes	6.4[9.9–2.3]	9.9[13.7–8.3]	**0.01**
Basophils	0.2[0.3–0.1]	0.5[0.6–0.4]	**0.026**
Platelets	54[115–35]	124[211–48]	**0.017**

Hb: Haemoglobin, Hct: Haematocrit, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, WBC: white blood cells

The analysis comparing pre- and post-transfusion values of haematological parameters are reported in Tables. 2-5 for the overall patient cohort and for patients subgrouped based on infective species. Across all patients, statistically significant increases were seen in haemoglobin, lymphocytes, eosinophils, monocytes, basophils, and platelets after exchange transfusion (all p-values <0.05). Statistically significant decreases were seen in haematocrit, red blood cells, and neutrophils (all p-values <0.05). Other changes in CBC parameters were not statistically significant. Similar results were seen in the subgroup of patients with Plasmodium vivax infection, with the exceptions that changes in eosinophil and basophil counts were not statistically significant in this group. In the 10 patients with falciparum malaria, statistically significant decreases in haematocrit and neutrophils were seen (all p-values <0.05). These changes were accompanied by statistically significant increases in lymphocytes, basophils, eosinophils, and platelets (all p-values <0.05). Across all results, the patient-to-patient variability in changes were large compared to the averages and the readers should note both the measures of central tendency as well as those of dispersion for each parameter as reported in the tables.

4. Discussion

This case-series summarizes the use of EBT in the management of malaria with high-parasitaemia at our institution from 2007-2015. Consistent with regional trends, vivax infections represented the majority of included cases. P. falciparum, which accounts for only 16% of malarial infections in Pakistan, was detected in one-third of the sample. This over-representation may have been due to the strain's greater proclivity for causing severe infection with high parasite load, which is the clinical population in which EBT may be considered [11].

We observed inconsistent changes across haematological parameters in patients who received EBT. There was an increase in haemoglobin concentration but decreases in haematocrit and RBC counts in the overall sample, with similar changes in the vivax group. In the falciparum subgroup, no changes in haemoglobin or RBC count were seen and decreases in haematocrit were seen after EBT. These results may indicate that the transfusions did not produce clear improvements in the malaria-induced anemia. A previous retrospective study also found no improvement in hemoglobin after transfusion in

falciparum patients [12]. However, this may not necessarily imply failure of EBT. It has been suggested that reductions in hematocrit might help reverse the pathologic rheology seen in malaria, as elevated hematocrit in malaria can contribute to increased systemic vascular resistance and subsequent peripheral hypoperfusion and end-organ damage [13]. Moreover, EBT enables the removal of circulating parasites, toxic metabolites, and inflammatory mediators. For example, hemozoin, which is produced by the germ's metabolism, is known to promote the development of a proinflammatory milieu through the activation of innate immunity and the release of interleukin 1-beta [14]. Thus, it is plausible that the effects of EBT on CBC parameters could help to reduce the complications of severe malaria by these mechanisms.

EBT was followed by a decrease in the neutrophil count across all subgroups. The role of neutrophils in malaria has been postulated to be a dual one; although they form one of the immune system's first responses to malarial infection, they also contribute to the pathogenesis of the disease [15, 16]. In the setting of malaria infection, neutrophils release neutrophil extracellular traps (NETs), produce reactive oxygen species, and release toxic granules. These processes can cause endothelial damage and lead to complications in states such as cerebral malaria [15, 16]. In fact, neutrophil activity is positively correlated with the severity of malaria infection [17]. However, it is not clear if the reduction in neutrophil count after EBT is associated with an improved prognosis and if this may reflect a causal relationship.

Thrombocytopenia is considered to be a diagnostic feature of malaria, with the degree of thrombocytopenia correlating with the degree of parasitemia [18–21]. Platelet count also serves as a predictor of the severity of infection as well as mortality [22–24]. Our case-series showed improved platelet counts across all groups, showing that EBT might have some utility in improving outcomes associated with thrombocytopenia. This contrasts with an older retrospective study which found no improvement in platelet counts [12].

In terms of survival, exchange transfusion showed some promise, with all but 3 of the included patients surviving. Of the 3 patients who did not survive, 2 were infected with the more malignant falciparum strain, with the remaining patient being one of the older patients in the sample at 75 years of age. Overall, the prognosis for most patients infected with the much more common vivax strain was good.

Currently, the CDC does not recommend the use of EBT for malaria [25]. Moreover, previous reviews have not found a found no survival difference advantage in patients who receive EBT [8, 26]. However, these recommendations and sources are over a decade old, and the authors of these reviews recognized that the meta-analysis performed was statistically underpowered. Clinicians have continued to publish case reports and series of EBT in extremely sick patients. One important fact to consider regarding the evidence on the efficacy of EBT is that it is typically reserved patients with a poor clinical course portending death or severe morbidity despite management. This may result in selection bias in the studies that have investigated the use of EBT in decreasing mortality in patients with malaria. These studies are mostly retrospective in nature, and no randomized trials have been attempted to assess the utility of EBT. Our study suffers from similar limitations, being a retrospective and uncontrolled case series.

In conclusion, our study provides descriptive data using pre- and post- analysis of haematological parameters in patients treated with EBT. EBT may be able to improve patients' anaemia and thrombocytopenia. Moreover, despite being a selected cohort of extremely sick patients with severe malaria, 90% of our patients were alive at last follow-up. Prospective studies are needed to synthesize additional evidence in this regard, and to determine whether these hematological changes translate to a reduction in morbidity and mortality.

5. Declarations

Ethics Approval and Consent to Participate

This study was approved and was granted waiver by Aga Khan University ethical review committee (AKU-ERC) due to retrospective nature of the study.

Consent for Publication

Not Applicable.

Data Availability Statement

The datasets used and analysed during the current study are available from the corresponding author on request.

Conflicts of Interest

The authors declare that they have no competing interests.

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Not Applicable.

Author Contributions

MSS and MAB designed and planned the study. QA, OM, and HJ contributed to data collection and writing of the initial draft of the manuscript. ARH and OM contributed in data analysis. AR provided critical input, editing and writing. All authors read and approved the final manuscript.

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