

Exchange blood transfusion in severe falciparum malaria: retrospective evaluation of 61 patients treated with, compared to 63 patients treated without, exchange transfusion

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Summary

The rationale for exchange blood transfusion (ET) in severe falciparum malaria is threefold: reduction of parasitaemia, reduction of presumptive 'toxic' factors, and improvement of the rheological quality of the blood. We evaluated the records of 61 patients treated with ET to describe the present status of malaria treatment in Germany, Austria and Switzerland and to assess the efficacy of ET. Clinical data of 61 patients treated with ET were compared to data of 63 patients treated in 2 hospitals where ETs were generally not performed. We found that exchange transfusion is applied according to the clinician's subjective impression rather than strict guidelines. Logistic regression analysis adjusting for the differences in clinical parameters between patients treated with or without ET did not identify treatment as a prognostic indicator (odds ratio for relative risk of death with ET: 1.3; 95% CI: 0.4-4.9). Exchange transfusion did not significantly improve the unfavourable prognosis in cases of severe falciparum malaria. However, failure to reach statistical significance may be due to the retrospective design of the study and therefore non-systematic approach.

keywords malaria, *Plasmodium falciparum*, treatment, exchange blood transfusion

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Footnote: Although the editors felt that there were real problems with the comparability of controls in this study, it was decided to publish it in view of the great difficulties in devising a satisfactory trial of this important intervention and in the hope of stimulating further work.

Introduction

Theoretically, exchange blood transfusion (ET) in patients with severe falciparum malaria offers advantages such as rapid reduction of parasitaemia, removal of infected erythrocytes responsible for sludging, reduction of presumptive toxic factors, e.g. cytokines (Salord *et al.* 1991b) or parasitic toxins, and improvement of the rheological qualities of the blood (Beards *et al.* 1994; Cook 1991). On the other hand, ET is associated with several dangers: non-cardiogenic pulmonary oedema by fluid overload, hypotension by rapid exfusion, and transmission of infectious diseases such as HIV infection or hepatitis. About 100 case studies have been published, the majority with successful or even spectacular outcomes (Gyr *et al.* 1974; Kurathong *et al.* 1979; Roncoroni & Martino 1979; Nielsen *et al.* 1979; Yarrish *et al.* 1982; Kramer *et al.* 1983; Files *et al.* 1984; Hall *et al.* 1985; Chiodini *et al.* 1985; Carpentier *et al.* 1986; Manquat *et al.* 1986; Schunkert & Gladziwa 1986; Lataste *et al.* 1987; Rouvier *et al.* 1988; Rudnitsky *et al.* 1987; Matsuura & Chou 1988; Heim *et al.* 1988; Pats *et al.* 1989; Miller *et al.* 1989; Le Camus *et al.* 1989; Lelarge *et al.* 1989; Bernardin *et al.* 1989; Bach *et al.* 1989; Elder *et al.* 1990; Saddler *et al.* 1990; Phillips *et al.* 1990; Smit *et al.* 1990; Malin *et al.* 1990; Looareesuwan *et al.* 1990; Salord *et al.* 1991a; Srichaikul *et al.* 1993; Shwe & Myint 1990; Wernli *et al.* 1991; Graber *et al.* 1991; Moorkens *et al.* 1991; Wong *et al.* 1992; Nehta *et al.* 1994; McCoslin *et al.* 1994; Green 1994; Van den Ende *et al.* 1994; Beards *et al.* 1994; Eisenman *et al.* 1995; Botella de Maglia *et al.* 1995). A randomized prospective controlled study in a sophisticated intensive care unit, however, is missing, and indications for use and the optimal method remain contentious.

Although its utility has not been proved, exchange transfusion is performed in several centres in Germany, Switzerland and Austria. We retrospectively analysed the records of these patients. The intent of the study was twofold: first, to describe the present status of malaria treatment in these countries and, secondly, to define subgroups that might benefit from exchange transfusion.

Patients and methods

Definitions

'Severe malaria' was defined according to the World Health Organization criteria (WHO 1990), including

>5% parasitaemia in non-immunes. In contrast to the WHO criteria, however, we used a practical definition of cerebral malaria: any impairment of consciousness or convulsions (Warrell 1993). Exchange of whole blood and exchange of red cells only were defined as exchange transfusion, irrespective of the volume. For calculating the transfused volume, the following unit volumes were assumed: packed red cells: 300 mL; whole blood: 500 mL.

Patient data

Short questionnaires asking whether ETs had been performed were sent to all infectious disease units and to all hospitals with more than 100 beds in Germany and Austria and with more than 80 beds in Switzerland ($n = 455$). When ETs were reported, standard forms asking for clinical data were mailed. Elicited data included: age, sex; parasitaemia; consciousness (unarousable coma, arousable somnolence or confusion); conventional chemotherapy; method of ET (packed cells, whole blood), volume of ET; creatinine, GOT, glucose, sodium, erythrocytes, leucocytes, platelets; pH, pO_2 , pCO_2 , ECG – all these data before therapy, after 24–48 hours and after 5–7 days. In addition we asked for complications of ET, infections after ET and complications at the time of leaving hospital. Clinical data were obtained of 61 patients with severe malaria treated by ET. For comparison the same clinical data were abstracted from the hospital records of 63 consecutive patients with 'severe malaria' treated in hospitals where ETs were not performed at all, even in the most severe cases (Tropenlinik Paul-Lechler-Krankenhaus, Tübingen, Germany, and Ospedale Generale, Bolzano, Italy).

Statistical analysis

Comparisons of variables of interest were based on the χ^2 -test or Fisher's exact test, where appropriate. For analysing the effects of major variables on death we used a stepwise logistic regression model (Kleinbaum 1994). Relative risks of dying were estimated as odds ratios with 95% confidence intervals.

Results

Present status of exchange blood transfusion

The short questionnaires asking whether ET had been

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performed were returned by 76% of the infectious disease units and hospitals (summer 1995). Nineteen centres (Germany 8, Austria 2, Switzerland 9) reported that ETs had been done in 56 patients (Germany 32, Austria 3, Switzerland 21).

Indications for ET

The most commonly reported indications for ET were hyperparasitaemia and multi-organ involvement (Table 1). The definition for hyperparasitaemia varied from >5% to 70% infected erythrocytes. In 9/61 patients high parasitaemia without any organ complication was considered as an indication for ET (parasitaemia in these patients: 6–70%). Organ complications were considered as an indication for ET only in combination with hyperparasitaemia. In all patients, ET was started directly after the diagnosis of malaria.

Data of patients treated by exchange transfusion

Clinical data were obtained from 49 of 56 patients treated with ET in Germany, Austria and Switzerland. The Prince Leopold Institute of Tropical Medicine, Antwerpen, Belgium, provided us with clinical data from another 12 patients that have been published elsewhere (Van den Ende *et al.* 1994). These data are included in our analysis. All patients were adult, non-immune Europeans. An overview of the clinical data and

laboratory findings is given in Tables 2 and 3. All ET patients were treated with quinine (loading dose in 82%), sometimes in combination with other drugs.

Data of patients treated without exchange transfusion

Clinical data and laboratory findings of 63 patients not treated by ET are given in Tables 2 and 3. Although only patients with severe malaria were included in this group, their morbidity markers were less severe and parasitaemia was lower than in the group treated by ET (Tables 2 and 3).

Method of exchange transfusion

Packed red cells were given to 46 patients, whole blood to 9 patients, packed red cells plus whole blood to 3 patients, and for 3 patients no information was available. Data on the volume of the exchange transfusion were available from 59 patients; the volume varied between 0.3 and 9.9 L (Figure 1; all patients were adults). According to logistic regression analysis, survival did not depend on the volume exchanged ($P = 0.97$).

Effect of major variables on death

Thirteen of 61 patients treated by ET died, as did 6/63 patients treated conventionally ($P = 0.084$). A logistic

Table 1 Indications for exchange transfusion in 61 patients

| Indication for exchange transfusion | Number of patients |
|---|--------------------|
| Hyperparasitaemia alone | 9 |
| Hyperparasitaemia + cerebral malaria | 14 |
| Hyperparasitaemia + renal failure | 3 |
| Hyperparasitaemia + respiratory insufficiency | 3 |
| Hyperparasitaemia + DIC | 1 |
| Hyperparasitaemia + cerebral malaria + renal failure | 9 |
| Hyperparasitaemia + cerebral malaria + respiratory insufficiency | 4 |
| Hyperparasitaemia + renal failure + respiratory insufficiency | 1 |
| Hyperparasitaemia + cerebral malaria + renal failure+ respiratory insufficiency | 11 |
| Hyperparasitaemia + cerebral malaria + respiratory insufficiency + DIC | 6 |

Indications as given by the different centres in the questionnaires; it has to be noted that hyperparasitaemia and organ manifestations were defined differently in the different centres; 46 patients had cerebral malaria (compare Table 2), but in 2 patients this was not considered as an indication for ET.

DIC, disseminated intravascular coagulopathy.

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| | With ET | Without ET | P value |
|-----------------------------|---------|------------|---------|
| Impairment of consciousness | 46/59 | 29/63 | 0.0004 |
| Unarousable coma | 5/47 | 3/63 | 0.28 |
| Acute renal failure | 16/51 | 7/63 | 0.01 |
| Artificial respiration | 17/49 | 4/63 | 0.0002 |
| ECG abnormalities | 5/37 | 7/54 | 1.0 |

Nominator: number of patients with complication; denominator: number of patients for whom data were available.

| | With ET | Without ET |
|-------------------------------------|---------------------------------|---------------------------------|
| Age (years) | 45.28 ± 11.64 (n = 60) | 43.41 ± 15.42 (n = 63) |
| Parasitaemia (% infected red cells) | 20.5 (13-35) (n = 60) | 9.5 (5.1-18.2) (n = 63) |
| Erythrocytes (10 ⁶ /ml) | 3.6 (3.2-4.5) (n = 37) | 4.3 (3.8-4.8) (n = 62) |
| Platelets (10 ⁶ /ml) | 27 000 (18 000-48 000) (n = 59) | 32 500 (21 000-79 000) (n = 62) |
| Creatinine (mg/dl) | 1.9 (1.3-3.5) (n = 58) | 1.3 (1.0-1.7) (n = 62) |
| Glucose (mg/dl) | 112 (89-141) (n = 58) | 106 (88-134) (n = 60) |
| GOT (U/l) | 52 (30-110) (n = 45) | 32 (23-79) (n = 55) |
| Sodium (mmol/l) | 130 (125-132) (n = 57) | 131 (128-135) (n = 50) |
| pH | 7.39 (7.34-7.45) (n = 33) | 7.42 (7.32-7.46) (n = 11) |
| RR, systolic (mmHg) | 106.8 ± 20.6 (n = 58) | 107.5 ± 21.6 (n = 61) |

For age and systolic RR, the arithmetic mean[pm]standard deviation are given; for the other data, the median (25th-75th percentile).

regression model was used to examine the effect of major variables with death as the outcome variable. Probability of survival was dependent on the level of parasitaemia (Figure 2). The most valuable prognostic indicator for death was respiratory failure with artificial respiration. The presence of cerebral

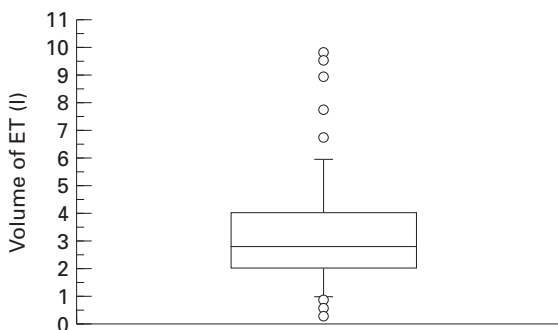


Figure 1 Box plot of exchanges volumes in patients treated with ET. The 10th, 25th, 50th, 75th and 90th percentiles of the exchanged blood volumes are displayed

Table 2 Clinical data of patients treated with and without ET

Table 3 Clinical data and laboratory findings in patients treated with ET and in patients treated without ET

symptoms and a high creatinine level indicating renal failure in this group of patients with severe malaria had

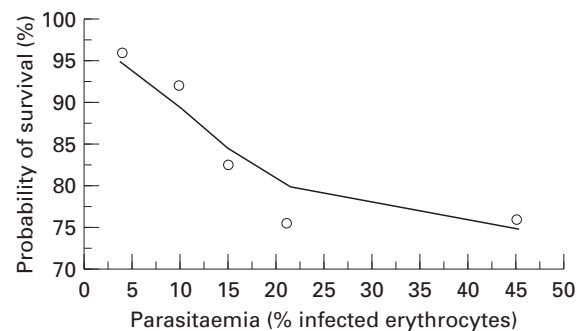


Figure 2 Observed and expected survival as a function of parasitaemia. ○ = Observations in different levels of parasitaemia. For the relationship between the probability of survival and the level of parasitaemia it was assumed that the following equation holds: $c + (1 - c)e^{-ap}$. p = % of parasitized erythrocytes. The parameters were estimated by maximum likelihood. The maximum likelihood estimates for c and a are 0.0072 and 0.056, respectively.

Table 4 Effect of major variables on death

| | Relative risk of death (odds ratio) | Confidence interval |
|---------------------------|-------------------------------------|---------------------|
| Organ complications | | |
| Cerebral malaria | 2.1 | 0.6-9.1 |
| Creatinine >1.5 mg/dl | 2.4 | 0.7-8.6 |
| Respiratory failure | 7.2 | 2.1-25.9 |
| Treatment | | |
| With exchange transfusion | 1.3 | 0.4-4.9 |

a lower prognostic value (Table 4). Using logistic regression concerning survival, no difference could be found between patients treated with ET or without ET (Table 4). Survival in subgroups of patients with or without ET was compared (Table 5). These subgroups included patients in whom >30% of red blood cells were parasitized, even in the absence of clinical complications; patients with >10% parasitaemia in the presence of cerebral malaria; patients over 60 years old with a parasitaemia >10%. No significant beneficial effect of exchange transfusion could be detected in these patients.

Other outcome variables

The mean parasitaemia of 25% declined to 5% within 24-48 hours after ET began. In those patients who were treated without ET, the parasitaemia reduced from 13 to 5% in 24-48 hours. Normalization of other laboratory parameters was similar in both groups (data not shown). Complications reported at the time of discharge from hospital in the group treated by ET were renal insufficiency (2 patients), hepatitis (1 patient), meningoencephalitis (1 patient), hearing loss (1 patient),

epileptic fits (1 patient) and mental disabilities (2 patients). Complications reported in the group without ET were hearing loss (5 patients), mental disabilities (1 patient) and a fracture of a vertebra, ascribed to an epileptic fit.

Discussion

Exchange blood transfusion as an adjunct to conventional drug therapy of severe falciparum malaria is applied frequently in some centres in Germany, Austria and Switzerland. Indications to perform an ET varied widely. 'Severe malaria' according to WHO criteria (WHO 1990) alone was not considered a sufficient indication; organ complications were considered an indication for ET only in combination with high parasitaemia. It is noteworthy that in 9 patients, hyperparasitaemia without organ complication was considered an indication for ET. In most cases this was cerebral malaria, reflecting the high frequency of this complication in falciparum malaria in general. In all centres, cerebral malaria was defined as any impairment of consciousness. In summary, we conclude that neither in Germany nor in Austria or in Switzerland is ET applied according to guidelines; obviously the subjective impression of the treating clinician is decisive.

We did a statistical evaluation of the data to look for major effects of ET that could be detected even in our rather limited number of patients. Because we included all consecutive patients with 'severe malaria' in the group of patients not treated by ET and because on the other hand 'severe malaria' alone was found not to be a sufficient indication for ET, a higher number of complications was found in the ET group. To account for these differences in the treatment groups, a logistic regression model was used to look for the effect of

Table 5 Effect of exchange transfusion in subgroups

| | Number of surviving patients Group with ET | Number of surviving patients Group without ET | Fisher's exact test |
|-----------------------------------|--|---|---------------------|
| Parasitaemia >30% | 13/15 (87) | 3/4 (75) | 0.5304 |
| Parasitaemia >10% | 30/38 (79) | 12/16 (75) | 0.7339 |
| Parasitaemia >10% + >60 years old | 4/5 (80) | 2/5 (40) | 0.5238 |

Volumes in parentheses are percentages.

major variables with death as the outcome variable. No significant difference between treatment with or without exchange transfusion could be found. The 95% confidence intervals, however, varied from 0.4–4.9, reflecting the uncertainty of this statement due to the small sample size (Table 5). The probabilities of survival were approximately the same with or without exchange transfusion for subgroups whom we tested according to recommendations by Wilkinson *et al.* (1994): parasitaemia >30%; parasitaemia >10% and cerebral malaria; parasitaemia >10% and age >60 years. The numbers of patients in these subgroups were small, but it is noteworthy that 3 of 4 patients with parasitaemias >30% did survive without exchange transfusion.

We also used logistic regression to look for the effect of other variables. Taking all patients together (with or without exchange transfusion), a clear correlation was found between the level of parasitaemia and probability of survival. Case fatality rapidly increases when more than 10% of erythrocytes are infected and approximates 30% when more than 20% of erythrocytes are infected. Although peripheral parasitaemia does not reflect the situation in the organs due to sequestration, it is thus a useful indicator of the severity of falciparum malaria (Field & Niven 1937). The most reliable prognostic indicator for death was respiratory failure with the necessity of artificial ventilation. Acute lung injury in patients with falciparum malaria appears to characterize a subgroup of patients whose illness is particularly severe (Gachot *et al.* 1995). The odds ratio of 7.2 indicates that the risk of death in these patients is increased by a factor of 7.2 compared to those without respiratory failure. The presence of cerebral symptoms and a high creatinine level had a lower prognostic value. Our data were not sufficient to calculate an APACHE score (Wilairatana & Looareesuwan 1995).

We could not find a benefit of exchange transfusion in our retrospective evaluation. The results' significance is limited by the small sample size, in addition to the lack of a standardized transfusion protocol, and observer bias contaminates the results. Unfortunately there are situations in clinical medicine when treatment decisions have to be made without sufficient data from prospective controlled clinical trials. In our opinion, the theoretical advantages of exchange transfusion justify its use in extremely ill patients with falciparum malaria. Such an ancillary treatment has also been

recommended in recent review articles (White 1996). We would suggest, however, that strict criteria are applied, e.g. on the basis of parasitaemia (Wilkinson *et al.* 1994). Data from these patients should be collected to enable a later evaluation, possibly with matched controls treated without exchange transfusion in other centres.

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Clinical data and laboratory findings of 12 patients treated in Munich will be evaluated separately in a doctoral thesis by W.J. Hartmann. The work presented in this publication is part of the doctoral thesis of J. Kröger. We thank Dr Hatz and Dr Gyr, Swiss Tropical Institute, Basel, as well as Dr Silvia Meier, Universitätsspital Zürich, Switzerland, for providing data from several patients treated with ET.

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