To artikler om post-injury malaria:

- *Postinjury malaria: a study of trauma victims in Cambodia*

- *Postinjury malaria: experiences from Cambodian doctors*

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En introduksjon til oppgaven

Vi har de siste 2-3 årene fått gjøre noen undersøkelser i samarbeid med Tromsø Mineskadesenter vedrørende et problem som rammer mange skadepasienter i en del områder i den tredje verden, det at de får malaria på sykehuset etter skaden.

Sommeren og høsten 2000 gjorde vi en retrospektiv epidemiologisk studie for å avdekke omfanget av problemet, samt identifisere risikofaktorer for denne komplikasjonen. Denne ble publisert i *Journal of Trauma* i februar 2002, og er en av de to artiklene i denne 5. årsoppgaven. Resultatene viste at problemet var stort, og vi skjønte at vi måtte arbeide videre med det for å finne en måte å forebygge komplikasjonen. Våren 2002 var vi derfor med på å sette i gang en behandlingsstudie i samarbeid med National Malaria Centre i Phnom Penh hvor alle skadepasienter blir rutinemessig screenet for malariaparasitter umiddelbart etter skade, og bærerne av falciparum-parasitter får startet opp antimalariabehandling umiddelbart.

Man vet lite om hvilken innvirkning og hva for komplikasjoner malaria gir i det postoperative forløpet for en semi-immun traumepasient. Da malaria er en forholdsvis ufarlig infeksjon for uskadde semi-immune, kunne en tenke seg at det å sette i gang med forebyggende virksomhet ville ha lite for seg. Det ble derfor viktig som en del av arbeidet å kartlegge effekten av malaria hos traumepasientene. Dette ble gjort som en kvalitativ studie, og er andre del av femteårsoppgaven. Vi trenger å innhente kommentarer fra noen samarbeidspartnere før artikkelen er helt ferdig og kan sendes inn til publisering.

Vi har dessverre ikke lenger tilgang på originaltabellene til den første artikkelen. Den første artikkelen er derfor vedlagt i formatet den ble publisert i. Tabellene er flettet inn i teksten, altså ikke i overenstemmelse med retningslinjene. Referansene i den andre artikkelen er angitt i Harvard-format etter retningslinjene til *Tropical Medicine and International Health* som vi har planlagt å sende den inn til.

Studiene er finansiert gjennom forskningsmidlene til Tromsø Mineskadesenter. Sommeren 2000 fikk vi også studentstipend fra Norges Forskningsråd.

Postinjury Malaria: A Study of Trauma Victims in Cambodia

Hans Husum, MD, Tove Heger, and Mads Sundet

Background: The pattern of host defense against plasmodium is comparable to the immune response to bacterial infection. Posttraumatic immunosuppression may therefore cause relapses of malaria secondary to trauma and trauma surgery in asymptomatic carriers of the parasites in endemic areas. To our knowledge this has not been validated in epidemiologic studies.

Methods: Postinjury malaria was registered retrospectively in 342 land mine and war victims from malaria-endemic areas in Cambodia. The incidence rate was analyzed in terms of age, gender, preinjury endemicity, evacuation times, anatomic injury severity, systolic blood pressure at admission, blood transfusion, and duration of the first surgical intervention as independent variables.

Results: The rate of postinjury malaria in the study patients was 33.3% (95% CI, 28.3–38.3%). Injury Severity Score (ISS) and surgical operation time were risk factors (area under the curve in receiver operating characteristic plots were 0.73 and 0.79, respectively). The impact of the other risk factors was nonsignificant.

Conclusion: Despite difficulties in diagnosing postoperative malaria in endemic areas, the study demonstrates that the rate of postinjury malaria is high. The results legitimate controlled trials of immediate postinjury chemoprophylaxis to severely injured in endemic areas. The authors recommend staged surgical operations with brief primary interventions in victims with severe injuries.

Key Words: Malaria, Postinjury malaria, Immunodepression, Damage control surgery, Land mine injury, Wartime injury, Cambodia.

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Epidemiologic studies from malaria-endemic areas indicate incidence rates of postoperative malaria from 6% to 50% secondary to elective surgery, most infections being caused by *Plasmodium falciparum*.[1–4] Severe *P. falciparum* infections are associated with substantial endothelial injury, sequestration of parasitized erythrocytes in the capillary beds of most organs, leukocyte infiltration into ischemic tissues, and activation of the coagulation cascade.[5–8] Some surgical centers in endemic areas recommend routine antimalarial chemoprophylaxis for surgical patients; other centers with low incidence rates do not.[9] However, antimalarials do not provide a simple solution to the problem: in most parts of the world, *P. falciparum* is now resistant to chloroquine, and in some areas also to mefloquine and most other antimalarials.[6]

Trauma surgeons in Congo and Cambodia claim that malaria is a common postoperative complication to primary surgery in wartime casualties (P. Bwale, personal communication, 1998; G. Strada, personal communication, 1998). In a study of postoperative malaria in war victims from World War II, Klark found a 10% incidence rate of postoperative malaria—the incidence being the same for minor and major surgery, and comparable to the in-hospital malaria incidence in nonsurgical patients.[10] To our knowledge, no recent reports have been published on studies of postinjury malaria in man except for a few case reports. In an experimental study, Aina found a significant postinjury elevation of *Plasmodium berghei* parasitemia in mice with severe injury compared with mice with less severe injury.[11]

In malaria-endemic areas where people are repeatedly infected all year round ("stable transmission"), asymptomatic malaria infections are common after childhood because of acquired low-grade immunity to the parasites.[12,13] It is well established that trauma, hemorrhage, and surgery affect inflammatory mediators and cause immunodepression with risk of bacterial infections.[14–16] Does the posttraumatic immunodepression also cause susceptibility to malaria infection secondary to injury?

It is well documented that $\gamma\delta$ T lymphocytes orchestrate the immune response to bacterial infections and other inflammatory stimuli by triggering production and secretion of cascade activating cytokines such as tumor necrosis factor, interleukins, and interferon-gamma. The cytokines activate neutrophils and macrophages to respond to bacterial and viral invasions.[17] Persisting pain and anxiety, reperfusion injury, and extensive and/or repeated surgery also trigger the inflammatory stress responses and may thus cause persistent cytokine production. Because some cytokines also exert a negative feedback on further production, this may be one reason for immunodepression secondary to major trauma.[18]

Also in malaria falciparum infection, $\gamma\delta$ T cells play a mandatory role by regulating the antimalarial activity of neutrophils and macrophages. When activated by a schizont-associated antigen and cytokines, the T cells stimulate macrophage-mediated killing of the intrahepatic stages of the parasite.[19,20] Neutrophils are primed by T-cell-induced cyto-

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kines and antimalarial antibody to kill intraerythrocytic parasites.[21–23] The immunologic response is differentiated: as in bacterial infections, also in malarial infections the levels of key cytokine mediators are higher in patients with severe infection. There are great individual differences in the patients' response. There are also certain differences between *P. falciparum* and *P. vivax* infections regarding white blood cell activation.[24–26]

The pattern of host defense against plasmodium is therefore comparable to the immune response to bacterial infection. Consequently, we may suspect that immunosuppression may cause relapses of malaria secondary to trauma and trauma surgery in asymptomatic carriers of the parasites in endemic areas. The aim of the present study was to examine the postoperative incidence of malaria infections in trauma victims from areas with different levels of malarial endemicity; and to find out if stress factors such as injury severity, evacuation times, and duration of surgery affected the incidence of postoperative relapses of malaria.

MATERIALS AND METHODS

The study was carried out in the Battambang province of Cambodia, an area with stable transmission of chloroquine-resistant falciparum malaria.[27] The province is infested by land mines, particularly so along the northwestern border with Thailand where falciparum malaria is high-endemic. Most mine accidents happen far from towns and cities, and prehospital evacuations are normally off-road, patients being transported in hammocks or on donkeys. There are few cars and no ambulance system. The data were gathered at the Emergency Surgical Center for War Victims in the city of Battambang. The hospital is run by the Italian nongovernmental medical relief organization "Emergency." It is the referral trauma center for the northwestern provinces of Cambodia. In general terms, the hospital follows the established procedures for advanced trauma life support and primary wartime trauma care.[28–30] However, damage control surgery (staged primary surgery with brief surgical interventions)—now a standard procedure in critically injured patients—is not done regularly at the "Emergency" hospital. The prevalence of malaria in Battambang City is low. For malaria prevention, all patients have mosquito bed nets. However, the bed nets are not sprayed with insecticide and the windows at the surgical departments are not screened. Blood for transfusions, both from the blood bank and from walking donors, is screened for parasites by microscopy. Donors are not given antimalaria treatment before blood is withdrawn, nor are recipients given antimalaria prophylaxis as recommended in previous studies of transfusion malaria.[4] Routine blood smears are not taken at admission. Other tests for parasitemia are not available.

The study patients were all land mine and war casualties consecutively admitted for in-hospital trauma care at the surgical center during a 24-month period from 1998 to 2000. The data were collected retrospectively in July 2000. Patients with incomplete data for the risk indicators (n = 3, see list of risk indicators below) and patients discharged from hospital within 24 hours after admission were excluded (n = 16). This left a study group of 342 patients, 277 mine victims and 65 suffering from bullet or fragment wounds. The criterion for postinjury malaria was positive malaria diagnosis within 10 days after the injury (malaria group). The conditions for positive diagnosis were either positive blood smear and clinical signs of malaria attack (criteria: fever, malaise, and chills) (n = 108); or negative smear, positive clinical diagnosis, and prompt response to antimalarial treatment (n = 6). The protocol for treatment was intramuscular artemisinin 4 mg/kg on day 1; intramuscular artemisinin 2 mg/kg on days 2 to 5; and peroral mefloquine 20 mg/kg on day 6. Data on postinjury morbidity other than malaria relapses was not collected.

The incidence of postinjury malaria (malaria group vs. nonmalaria group) was analyzed against several potential risk indicators: age, gender, residency in high-endemic versus low-endemic malaria areas, prehospital evacuation time, systolic blood pressure at admission, duration of the first surgical intervention, blood transfusion, and Injury Severity Score (ISS). Grouping of districts according to malaria prevalence was performed on the basis of public statistics: under the supervision of the World Health Organization, all provinces in Cambodia run continuous epidemiologic surveys of malaria. The statistics were validated by the authors during extensive interviews with the health workers who had gathered data for the public malarial program at the village and district levels. We used the noninjured population in the catchment area as the control group. The Abbreviated Injury Scale[31] was used for severity scoring, cases with unclear anatomic data being coded conservatively. Data for physiologic severity scoring other than systolic blood pressure was not available.

Epi Info[32] and CIA[33] were used for analysis of the data. The null hypothesis (no difference in outcome) was rejected if the 95% confidence interval for differences did not include zero. We used MedCalc[34] for analysis of receiver operating characteristics (ROC) curves. A test—in this case, a risk indicator—is said to have high accuracy if the area under the ROC curve (AUC) is 0.9 or larger and fair accuracy if AUC is 0.7 to 0.8.[35] AUC approaching 0.5 signifies a worthless test/indicator.

RESULTS

One hundred fourteen of the 342 study patients developed postinjury malaria (33.3%; 95% CI, 28.3–38.3%).

Of the 114 malaria-positive cases, 101 were caused by *Plasmodium falciparum*, 4 were caused by *Plasmodium vivax*, 3 were mixed, and 6 were unspecified. Most relapses of malaria occurred within 2 days after injury (54% of malaria-positive cases). Only 12% of postinjury malaria infections occurred more than 10 days after the injury (Fig. 1). The incidence of postinjury malaria in the study patients was as

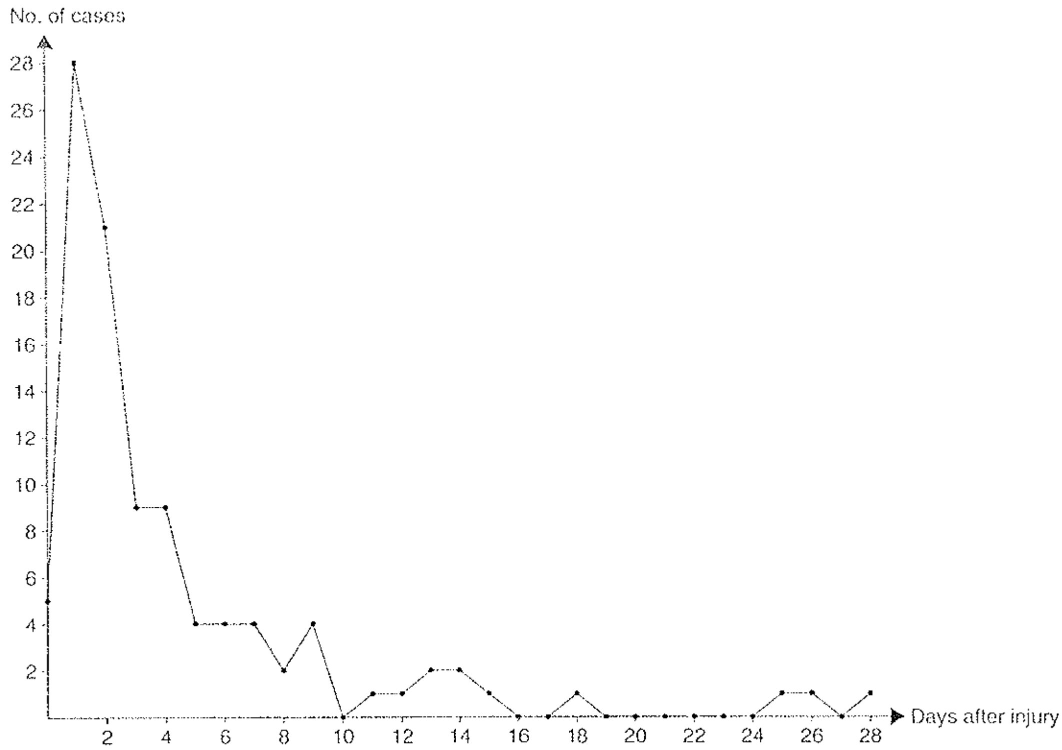

Fig. 1. *Malaria outbreaks by days after injury (n = 101).*

high during the dry season (January to May) as during the wet season (July to October, Fig. 2). For the entire population (n = 342) median ISS was 8 (range 1–38), mean prehospital evacuation time 11 hours (SD, 11.5 hours), and mean duration of the first surgical operation 2 hours (SD, 1.6 hours). Sixty-two patients had blood transfusion during the primary surgery with a mean of 2.8 units of blood per patient (SD, 1.7 units).

Of the eight potential risk factors examined, we identified four factors that predicted risk of postinjury malaria:

1. The patients' area of origin is a risk factor (Table 1): of the malaria-infected patients, 49 (45.8%) came from high-endemic areas and 65 (27.7%) came from low-endemic areas (95% CI for difference, 6.8–28.2%, Table 1). This corresponds to a 10-day incidence of postinjury malaria of 458 of 1000 for victims from high-endemic malaria areas, and 277 of 1000 for low-endemic areas. The corresponding baseline incidence for noninjured persons from the same areas is 11 of 1000 and 0.2 of 1000.
2. The risk increases with increasing injury severity: relapses occurred in 22% of patients with light injuries (ISS of 5 or less), whereas the incidence rate in patients with severe injuries (ISS of 15 or higher) was 40% (95% CI for difference, 0.6–35%). The overall accuracy of ISS as a risk predictor is fair (AUC < 0.8, Table 2).
3. The risk of postinjury malaria increases with increasing prehospital transit times. However, the effect of this risk factor is barely statistically significant (lower limit of confidence interval for the AUC is 0.53, Table 2 and Fig. 3).
4. The risk increases significantly with the duration of the primary surgical intervention. In patients with operation times less than 1 hour, the incidence rate was 20.4% as compared with 51.2% after surgery of more than 2.5 hours' duration (95% CI for difference, 20.0–41.7%). The overall accuracy for operation time as risk indicator is fair (AUC < 0.8, Table 2 and Fig. 3).

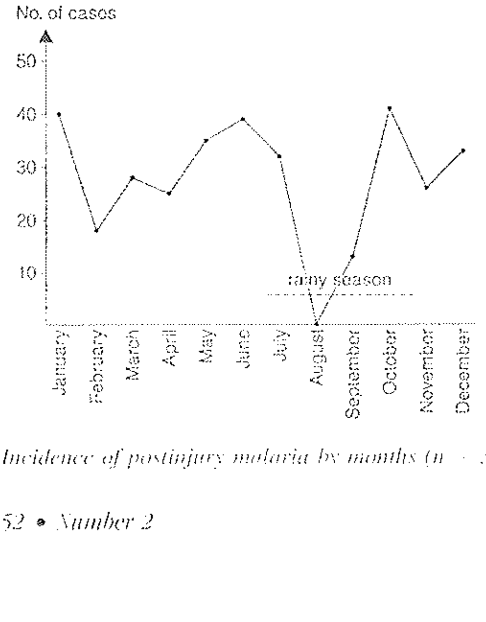

Fig. 2. *Incidence of postinjury malaria by months (n = 342).*

The four other variables (children vs. adults, gender, systolic blood pressure at admission, and blood transfusion) did not significantly affect the outcome (Tables 1 and 2).

Table 1 Postinjury Malaria, Risk Factors (n = 342)

	Malaria Group: Patients with Postinjury Malaria	Nonmalaria Group: Patients without Postinjury Malaria	Malaria Group versus Nonmalaria Group: 95% CI for Difference between Proportions	
No. of cases (%)	114 (33.3)	228 (66.7)		
Mean age (yr)	25.2 (95% CI, 23.0–27.4)	29.5 (95% CI, 27.6–34.1)		
Children (%)	27 (23.7)	36 (15.8)	–1.2%	–17%
Adults (%)	87 (76.3)	192 (84.2)		
Female (%)	12 (10.5)	31 (13.6)	–10.2%	–4.1%
Male (%)	102 (89.5)	197 (86.4)		
From high-endemic area (%)	49 (43.0)	58 (25.4)	–6.8%	–28.2%
From low-endemic area (%)	65 (57.0)	170 (74.6)		
Blood transfusion (%)	20 (17.5)	42 (18.4)	–9.5%	–7.7%
No blood transfusion (%)	94 (82.5)	186 (81.6)		

95% CI, 95% confidence interval.

The subpopulations from high- and low-endemic areas are not comparable: compared with the patients from areas with low endemicity, the patients from high-endemic malaria areas had more severe injuries ($p < 0.01$). This is demonstrated by a plot of ISS for the two subpopulations showing overlapping confidence intervals for all levels of injury severity (Fig. 4). Also, patients from high-endemic areas had higher evacuation times ($p < 0.001$). For the other variables the two subpopulations are comparable. The intercorrelation between the five other variables was low ($\chi^2 < 1$, Pearson's r −0.12 to 0.3, Table 3).

The overall hospital mortality rate was low, 2.6% (n = 9). Six patients died within 24 hours after injury from hemorrhagic shock, and three died after several reoperations because of bacterial infectious complications. Of the nine nonsurvivors, one was malaria-positive and eight were malaria-negative. The duration of the hospital stay was significantly longer ($p < 0.001$) in the malaria group (median, 23 days; range, 3–38 days) compared with the nonmalaria group (median, 11 days; range, 1–115 days).

DISCUSSION

We report the incidence rate of postinjury malaria for the first time since Klark studied war victims from the World War II.[10] Contrary to Klark's findings, our study demonstrates that injury increases the risk of postoperative malaria attacks in trauma victims from areas where falciparum malaria is endemic. The study was carried out in an area where multiresistant malaria falciparum is endemic. One out of three patients in the study population had postoperative malaria relapses, which represents a more than 40 times increased incidence rate compared with the noninjured population in the catchment area. Injury severity and surgery are risk factors: we registered a significantly higher rate of postoperative malaria in victims with severe as compared with light injuries, 22% versus 40%. Extensive primary surgical interventions further increase the risk, regardless of injury severity: 20% of patients had relapses after operations of less than 1 hour's duration, and the risk is doubled if the operation time is extended to more than 2.5 hours.

Several variables in our study are not well controlled and need to be discussed:

1. How accurate was the diagnosis of malaria in the study patients? We did not control the quality of the microscopy ourselves. However, the laboratory technicians were experienced. In several cases, more than five negative smears were reported before the positive slide turned up and treatment was started. A quality control study of 10 clinics at the Thai-Burma border reports sensitivity at 92% to 96% and specificity at

Table 2 Postinjury Malaria, ROC Analysis of Risk Factors

	Malaria Group: Patients with Postinjury Malaria	Nonmalaria Group: Patients without Postinjury Malaria	Malaria Group versus Nonmalaria Group
Evacuation time, hr[I]	8 (2.5–48)	6.8 (0.2–72)	AUC[II] 0.59 [0.53–0.64] $p < 0.01$
Injury Severity Score[I]	9 (1–38)	5 (1–38)	AUC 0.73 [0.68–0.77] $p < 0.001$
Systolic BP on admission[I]	120 (60–160)	120 (70–170)	AUC 0.51 [0.45–0.56] $p < 0.6$
Duration of first surgical[I] intervention (min)	75 (0–330)	30 (0–360)	AUC 0.79 [0.74–0.83] $p < 0.001$

[I] Median values (range).
[II] AUC, area under receiver operating characteristics curve (95% confidence intervals for AUC in brackets).

93% to 98% in malaria diagnosis by simple light microscopy by experienced technicians.[26] In our study, an old light microscope was used for the diagnosis of the patients hospitalized during the first 12

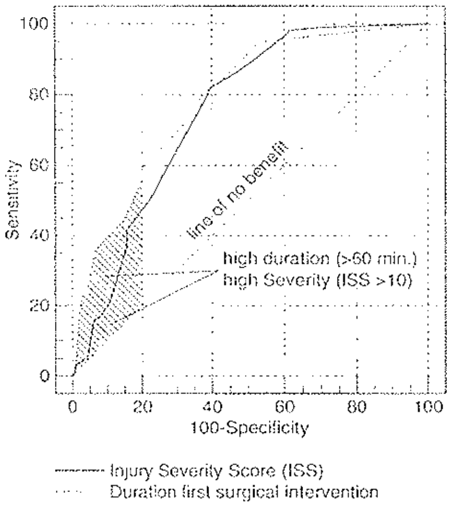

Fig. 3. *Comparison of ROC curves for the main risk factors.*

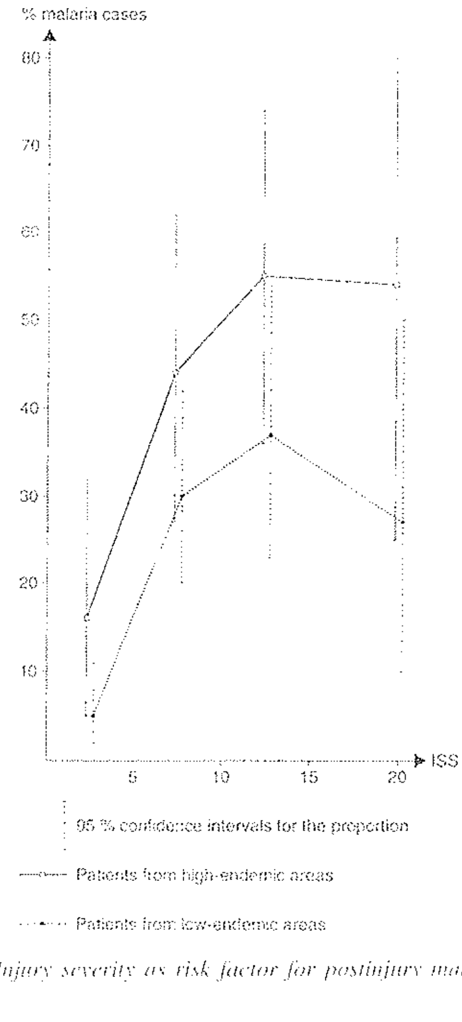

Fig. 4. *Injury severity as risk factor for postinjury malaria (n = 342).*

months of the study period. In this period, we found several patients registered with typical clinical symptoms of malaria attack, and up to 10 negative slides. Therefore, there may be some underreporting of postinjury malaria in the study patients. On the other hand, we may have false-positive diagnoses in the study group. Positive blood smear and clinical signs observed by experienced clinicians are probably not enough to establish a correct diagnosis in all cases. In high-endemic areas, positive smears can be found also in asymptomatic and semi-immune carriers of the parasite. Also, effect of antimalarials is not a solid diagnostic criterion: in postoperative patients we can see transient fever of noninfectious origin that settles spontaneously.[9] Measuring levels of parasitemia would definitely have given more exact diagnosis. However, in the minimum resource setting where the present study was done, we had not the necessary means for that.

2. The baseline prevalence of malaria may be incorrect. After validating the public statistics, we cannot rule out significant underreporting of malaria in rural areas where the villagers buy drugs themselves or are not treated at all, and are therefore not registered at clinics. However, even if the incidence of malaria relapses in the noninjured population is doubled, trauma and trauma surgery still lead to a 20-fold risk increase.
3. Missed malaria-positive cases: malaria outbreaks in study patients discharged from hospital before 10 days after injury were not registered. These are mainly victims with light injuries and possibly less risk of contracting postinjury malaria. Thus, the true rate of postinjury malaria in our study population may be somewhat higher than 33.3%.
4. Postinjury malaria transmission may cause false-positive counts. The risk of in-hospital transmission is probably small. The city of Battambang is a low-endemic area and bed nets were used for protection. Patients may also have been infected during the transport. The incubation time for falciparum malaria is 6 to 12 days for adults, and somewhat longer for children. The bulk of relapses occurred during the first 4 postoperative days and there were no peaks on the incidence plot later on (Fig. 1). By setting cut-off at 10 days after injury, the risk of false-positive counts because of postinjury transmission in our study population is therefore small.
5. We observed higher rates of postoperative malaria in patients inhabiting areas with high malaria endemicity (Table 1). However, local differences in preinjury endemicity are a confounding variable in this study. The epidemiology of land mines differs. In the districts where malaria prevalence is highest—in the remote forested areas along the Thai border—there are also more bounding fragmentation mines. Consequently,

Table 3 Postinjury Malaria, Correlation of Risk Factors (Pearson's *r*)

	Age	Evacuation Time	Systolic Blood Pressure	Injury Severity Score	Duration of Surgery	Units of Blood Transfusion
Age		0.10	−0.07	0.40	0.25	−0.13
Evacuation Time	0.15		−0.12	−0.01	−0.02	0.03
Systolic blood pressure	−0.07	−0.12		−0.08	−0.06	−0.20
Injury Severity Score	0.40	−0.01	−0.08		0.20	0.27
Duration of surgery	0.25	−0.02	−0.06	0.20		0.35
Units of blood transfusion	−0.13	0.03	−0.20	0.27	0.35	

many mine victims from these areas suffer from multiple fragmentation injuries. There is therefore a tendency that patients with severe injuries and long prehospital transit times are from areas with high endemicity. When we correct for differences in severity, we find that the preinjury endemicity is not a significant risk factor (overlapping confidence intervals, Fig. 4). The impact of evacuation times was statistically significant, but very small and hardly of medical significance.

Gender and age did not affect the rate of postinjury malaria in this study. Persons living continuously in areas with stable transmission of malaria acquire a low-grade immunity, partly because of humoral factors, and partly because of continuous presence of activated $\gamma\delta$ T cells after the infection has been cleared.[37] The immunity in infants is inherited from the mother by transplacental transfer of protective antibodies. In childhood, when the host's defenses are being built in the course of repeated attacks of malaria, the immunity is still fragile and easily upset by nutritional deficiencies and intercurrent diseases.[13] We found an overrepresentation of children with postoperative malaria, but the difference between children and adults was not significant (Table 1). Studies on postinjury immunodepression indicate that male patients are more commonly affected than female patients.[38,39] The overrepresentation of malaria-positive female patients in our study material was slight and nonsignificant (Table 1). However, the number of child and female victims was small (n = 63 and n = 43, respectively); studies of far larger cohorts are necessary to validate the clinical effect of age and gender in this regard.

Malaria parasites may be transmitted by blood transfusion. In a review article, Gibney claims that detection and exclusion of parasitized blood donors in endemic areas is often impossible. He therefore recommends chemoprophylaxis for donors and recipients.[9] Despite lack of chemoprophylaxis, the rate of postoperative malaria was not increased in the 62 patients who had transfusions in our study (Table 1). Because the cohort is small, our result does not necessarily indicate that routine microscopic screening of blood before transfusion is a sufficient precaution in malaria-endemic areas.

Anatomic and surgical risk factors only partially explain the high rate of malaria complications (low accuracy in risk prediction, Table 2 and Fig. 3). There are probably physiologic risk factors as well, which we did not identify. Experimental studies have demonstrated that physiologic impairment—in particular, the severity and duration of hemorrhagic shock—aggravates postinjury immunodepression.[40] We studied a selected population in the sense that severely injured victims probably had died during long and rough prehospital evacuations. In wartime injuries, one expects prehospital mortality rates of 30% to 40% in scenarios with protracted evacuations.[41–43] The mean time of evacuation for our patients was 11 hours, and most prehospital survivors were admitted in a fairly stable circulatory state (median systolic blood pressure at 120 mm Hg, Table 1). Also, catabolism secondary to malnutrition may cause immunodepression. In the catchment area of our study, malnutrition is not uncommon, since land mines occupy agricultural land. We did not collect data on nutritional parameters in the study.

What is the effect of postinjury malaria? For several reasons, our study does not answer this question:

1. We did not collect data on outcome indicators other than mortality.
2. Malaria as complication to injury did not affect the mortality rate in our study patients. Of the nine patients who died (2.6%), only one had postinjury malaria. The low hospital mortality rate is probably attributable to high prehospital transit times and skewed severity among the study patients. The trivial impact of postinjury malaria on mortality in the study is probably not representative for cohorts of higher severity.
3. Malaria relapses are seldom severe in noninjured patients with acquired immunity. Most outbreaks of malaria in the study patients were quickly resolved when they received antimalarials in the early phases of the infection. The medical treatment would not necessarily have been that efficient in a population with high-severity injuries.

What can be done to reduce the risk of postinjury malaria? Some authors recommend routine antimalarial prophylaxis after surgery in endemic areas,[44,45] and others recommend a selective strategy with chemical prophylaxis only to patients with suspected impaired immunity to the parasite.[9] None of these recommendations are made on the basis of controlled trials. Taking into consideration the high rate of postinjury malaria in our study, controlled double-blind trials of chemoprophylaxis to patients with severe injuries are indicated. If possible, the prophylactic treatment should start at the time of injury because most trauma victims in malaria-endemic areas have long prehospital evacuation times, and antimalarial treatment takes time to become effective. However, the problem remains that "history has demonstrated only too clearly the ease with which *P. falciparum* can become resistant to any antimalarial to which it is exposed."[46]

Another strategy is to reduce the impact of risk factors. We found that the risk of postoperative relapses increased with the duration of the surgical operation. In persons with injury severity higher than ISS of 10, operation times of more than 1 hour were, in fact, a heavier risk factor than the injury severity (shaded area in the ROC plot, Fig. 3). This is in accordance with the "two-hit" hypothesis. Postinjury surgery and other stress factors acts as additional trauma on an immunosystem already primed by the injury, disturb the mediator cascade, and lead to an uncontrolled inflammatory response. "Our increased understanding of cellular effects of inflammatory mediators released with injury, as well as the complex physiologic and metabolic changes, has led to new approaches to management based primarily on preventing further injury."[47] The effect of surgery as a trauma is also demonstrated in experimental studies. Xu and others report that laparotomy or other major surgery combined with hemorrhage produces a more protracted impairment in immunity than surgery or hemorrhage alone.[14,15] Staged surgical operations with brief primary interventions ("damage control") and delayed surgical repair reduce the rate of postoperative infections and organ failure after severe injury.[48] In view of these findings, it would be wise to restrict the duration of the primary surgical intervention in severely injured patients in areas with high malarial endemicity.

CONCLUSION

It is difficult to diagnose postoperative malaria in semi-immune patients living in endemic areas. Still, the study indicates that at least one of three trauma victims in these areas develops postinjury malaria. The risk increases with the severity of the anatomic injury. Extensive primary surgery further adds to the risk. The study was done on a population with very long evacuation times and low injury severity among the prehospital survivors. The rate of postoperative malaria is likely to be higher after high-severity injuries. As the study did not include morbidity parameters, the impact of malaria relapses on postoperative morbidity remains unclear. The high rate of postinjury malaria legitimates controlled trials of immediate postinjury chemoprophylaxis to severely injured in endemic areas. Also, staged surgical operations with brief primary interventions should be considered in victims with severe injuries.

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Postinjury malaria: experiences from Cambodian doctors

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Summary

Objective: According to one epidemiological study, one third of trauma victims in malaria endemic areas of Cambodia develop postinjury malaria. The aim of this actual study was to assess the impact of the complication on postinjury morbidity and mortality.

Methods: All local doctors with trauma care surgical experience in the Battambang province of Cambodia were interviewed regarding their experiences with postinjury malaria (n = 18). The data were processed according to the Editing Analysis Style method (Malterud 1996)

Results: In the study area, postinjury malaria has been a well-known complication to trauma for years. The complication is reported to adversely affect the general condition of the trauma patients, increase the risk of wound infections, and delay postoperative recovery. The knowledge of this problem did not come from the medical schools or textbooks, but exclusively from personal clinical experience.

Introduction

Where malaria is endemic, the populations are also hit by "the epidemic of trauma" (Krug 1999). In a recent retrospective study the authors reported that one third of trauma victims in Cambodia develop postinjury symptomatic malaria, mainly of the Falciparum type (Husum et al 2001). Rates of postoperative symptomatic malaria from 6% to 50% are also reported from Kenya (Gakuu 1997), Burkina Faso (Diako et al 1994), Cameroon (Takongmo et al 1993) and Sudan (Alla et al 1996). One may speculate that postinjury immunodepression initiated by tissue injury, haemorrhage, and surgery cause susceptibility to symptomatic malaria in carriers of the parasite, and that the problem therefore is most pronounced where the physiological capacity of the trauma victims is poor. However, the problem of postinjury malaria is not discussed in textbooks, and there are no available reports on the impact of symptomatic postoperative malaria in trauma victims.

This qualitative study was conducted in districts in Cambodia where Falciparum malaria is endemic, where the majority of the population suffers from poverty and malnutrition, and where land mine injuries are common and evacuation of trauma victims protracted. The aims of the study were to evaluate the impact of postinjury malaria in trauma victims based on assessments done by experienced local doctors.

We find it important to assess this impact because it may be possible to prevent the complication pharmacologically. To determine how big resources one should spend on this prevention, one has to have a clear idea of how big the problem is.

We were also interested in where their knowledge about this complication came from. Was it a recognized problem that they learned about in university, or did they just find out about it from experience?

Materials and methods

We interviewed all the surgeons that were working on the four surgical hospitals in the Battambang province at the time of our visit. Some surgeons might have been temporarily absent and therefore not included, but these are few. These were local doctors having provided trauma surgery for more than ten years in this province, situated along the Thai-border in north-western Cambodia. The group of informants thus comprised of 18 doctors, all of them having extensive experience with trauma victims from various parts of the province. In this area, the endemicity of kloroquine-resistant falciparum malaria has remained high for years (personal information from the National Malaria Centre, Phnom Penh). The majority of the informants (n=11) had been trained by Khmer Rouge surgeons. The other informants had been trained at Phnom Penh University, in the French medical tradition.

The data gathering was done at the informants' workplaces using a semi-structured interview where some questions were illustrated with cartoons. The translators were medically trained, but not certified translators. Information was also gathered from one focus group with all doctors and medics at on district hospital in the catchment area, where a discussion on post-injury malaria was conducted in Khmer language and later translated to English. Each interview lasted for 1-1.5 hours and were taped before being transcribed by the authors. The transcripts were continuously discussed and roughly coded during the in-field study period. Based on new information, additional elements were included in the questionnaire. The translators took active part in the data gathering and formulation of new questions. We used the computer program *Open Code* to process the data (Umeaa University 2001). The transcripts were read through, and we constructed 6 different "codes" (called "epidemiology", "etiologi", "general condition", "severity", "treatment" and "compliations") that the information could be sorted into. After this sorting, we could read through what the different informers said about the same subjects, and from this we could start drawing the conclusions stated in this paper. This is called the "Editing Analysis Style" of qualitative analysis (Malterud 1996)

Results

The informants' estimates of the actual prevalence of postinjury malaria in the study hospitals ranged from 10% to 80%. All informants agreed that the risk of developing postinjury malaria depended on the pre-injury location of the patient – poor patients from high endemic areas was uniformly said to carry higher risk for postinjury symptomatic malaria compared to "city people". Informants from one district hospital close to the Thai border claimed that almost all of the trauma patients from " the forests" – that means patients living in makeshift villages inside the jungle – develop postinjury malaria, whereas the risk was less for people living in the local town. "It's the poor people who get malaria. The rich people don't go to the Thai-border".

The informers agreed that postinjury malaria of the severe type was rare in semi-immune patients (severe malaria is defined as symptomatic malaria plus one of following signs: disturbed consciousness, convulsions, fever higher than 39°C, severe anaemia, icterus, vomiting/dehydration, or haemoglobinuria (National Malaria Centre Phnom Penh 1999)). Some pointed out that severe anemia is common in these patients, and if a malaria patient has severe anemia, the malaria is by definition severe. Delayed diagnosis and treatment of symptomatic postoperative malaria could provoke severe complications such as cerebral malaria, icterus, or black-water fever – especially if the patient is "weak". All informants agreed that the overall prevalence of postinjury malaria was higher some years ago. One reason for the decreasing prevalence was said to be the recent national campaigns including distribution of repellent-impregnated mosquito nets for the population in high-risk areas. Several informants claimed that poor people working and sleeping "in the forests" do not use mosquito nets. Most patients with postinjury malaria develop symptoms within one to five days after the injury. As the incubation time of the Falciparum parasite is 15 days, all informants held that the probable reason for the complication was post-traumatic immuno-depression in semi-immune parasite carriers. "The more severe injury, the higher is the risk". Reasons for the immunodepression was said to be the injury itself, and also blood loss.

All informants said that postinjury malaria had adverse effect on the patients' general condition. Even if the malaria is of the non-severe type, the patients with the complication would suffer more from pain – general muscle pain, spasms, and headache – compared to patients without the complication. Several informants said that the pain problem caused sleeplessness and depression. "They are more depressed because they can't move and eat because of fever and pain. With only one trauma – and no malaria – they can walk and eat". It was generally agreed that postinjury malaria caused anorexia, also in non-severe cases. This was held to be a serious problem delaying recovery since many trauma victims also suffered from pre-injury malnutrition.

The main adverse effect of postinjury malaria was said to be a considerably increased susceptibility to wound infections and delayed wound healing. This was particularly emphasised by informants from the former Khmer Rouge areas close to the border. Several informants thought that anaemia was the main reason for infectious problems, the malaria relapse causing haemolysis that aggravated an already existing anaemia from traumatic blood loss and pre-injury malnutrition. All of the informers pointed out that anemia was a very common complication. Other infectious complications, like pneumonia, was also said to be more common in the trauma patients with malaria.

Some informants said that it could be difficult to differentiate between postoperative fever from bacterial infection and malaria fever. One informant said: "Before, we assumed that the postoperative fever came from the wound infection, so we treated them with antibiotics. But despite this treatment, the patients had still fever, and the wound did not heal. It took a long time to treat these patients because we didn't know this problem with malaria at that time." Almost all informants agreed that the trauma patients with malaria had to stay for a longer time in the hospital than patients without the complication. Since most trauma victims were young and middle-aged males from poor families, protracted recovery was said to have severe impact on the incomes of the patients' families.

All the informants underlined that it was important to start the treatment with antimalarials early. If the diagnosis and treatment were delayed, simple symptomatic malaria could develop into severe and complicated malaria within hours. One of the doctors said that a delay of even five hours could be crucial. All informants agreed that when malaria was diagnosed and treated early, the patient would probably not develop severe postinjury malaria. However, during the wartime, when they didn't have microscopes and there was shortage of antimalarial drugs, the informants from Khmer Rouge districts claimed that 20-30% of the trauma patients would die from severe postinjury malaria. Some informants recommended blood screening and start of antimalaria treatment in all parasite carriers immediately after the injury, in that way preventing the development of the hemolysis before it starts, and thereby preventing anemia and wound infections.

All informants said that their knowledge of postinjury malaria was based exclusively on personal clinical experience. "This knowledge don't come from the books, but from experience. In the university they teach about trauma and malaria separately." Also the doctors having been trained "in the jungle" by Khmer Rouge surgeons during the war confirmed that the knowledge had been acquired through clinical experience. "In the past, patients with malaria and wounds were very difficult to treat and we used to fail. We didn't think about the postinjury malaria then. We had no microscopes, and had to look for the signs and symptoms after the operation. We could not know if complications were due to malaria. Now we take a blood smear immediately when the trauma victims arrive in the clinic."

Discussion

The study confirms that postinjury malaria in semi-immune parasite carriers is a well-known medical problem in the study area. However, the assessments of the impact of postinjury malaria differ somewhat among the informants. All doctors agreed that the complication affects the general condition of trauma patients and delays recovery. More than the university-trained doctors, the Khmer Rouge-trained informants (KR group) emphasised the correlation between postinjury malaria, anaemia, and wound infections. This difference in opinions may be due to differences of medical background. The KR doctors had been trained by teachers belonging to the "barefoot doctor" tradition; during the wartime they had been working in makeshift clinics in the rural area, and now they ran district hospitals located inside the areas with highest malaria endemicity. Unlike the KR doctors, the university trained informants were working in hospitals in Battambang City where malaria is not endemic.

Some methodological problems in the study need to be addressed:

1. The qualitative interview method is not optimal for obtaining the answers we wanted, but for practical and economical reasons we still chose to use it. The results are based on the personal experience and memories of the informers, which in this case is not the same as the "truth" of the matter. They might actually have some beliefs that are simply wrong, like all other medical communities also has. A retrospective, quantitative approach would be better, but it is difficult because of a lack of documentation in the hospitals, and a prospective study is difficult for financial and logistical reasons. One hospital actually had good enough documentation for some statistical conclusions that will be published later.
2. Both interpreters were medical teachers and supervisors in a local trauma system (Trauma Care Foundation Cambodia, TCF). Most informants were actually their staff members and had a close personal relation to the interpreters. This relation made it possible to conduct the data gathering in an atmosphere of mutual trust and understanding where the informants openly shared their ideas and told about faults from their own medical practice. On the other hand, the informants knew that TCF and The National Malaria Centre in Phnom Penh planned a post-injury malaria program including upgrading of diagnostic tools at the local hospitals. It is thus possible that informants – particularly those working at poorly equipped district hospitals – exaggerated the problems with postinjury malaria in order to please their supervisors and gain material benefit for their hospitals. However, the lively medical discussions in the focus group and the unanimous agreement on reduced prevalence of postinjury malaria indicate that this bias did not seriously affect the reliability of the data.
3. Cross-cultural research always implies a risk of conceptual confusion. Terms like "fever", "pain" and "depression" do not necessarily carry the same meaning in the European and Khmer medical tradition. The translators were "village boys" themselves, knowing the local popular medical terms, and had later been trained by teachers belonging to the Western medical tradition. By continuous careful discussions in the research team ("what does this really mean?"), the risk of terminological misunderstanding in translation of questions and information was reduced to a minimum.

Conclusion

In the areas where Falciparum malaria is endemic, postinjury malaria seems to be a common complication after trauma. The complication is normally not fatal if treated on ready indications, but it is reported to increase the risk of wound infection and considerably delay recovery after surgery. Postinjury malaria thus increases the burden of the trauma on the patient and the patient's family. Similar studies should be conducted to find out if our results are valid also for other countries and populations suffering from Falciparum malaria.

These results suggests that one should investigate efficient ways of preventing this complication. One can imagine that a routine dipstick test for malaria at admission for all high-risk patients is one way of reducing the morbidity.

The study confirms that the knowledge of postinjury malaria is non-institutional and maybe neglected by the medical academy; also in a country severely affected such as Cambodia, the insight and treatment skill is so far based on the rural doctor's personal experiences.

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