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Short Research Communications

Study of clinical profile of acute respiratory distress syndrome and acute lung injury in *Plasmodium vivax* malaria

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Malaria is a common infection in many parts of India. *Plasmodium vivax* accounts for more than half of all malaria cases in Asia[1]. Severe malaria is typically caused by *Plasmodium falciparum* and it is manifested by various organ involvements; for example, kidney, lung or CNS. *Plasmodium vivax* malaria usually presents as a benign acute febrile disease. Severe *P. vivax* malaria was first reported by Kocher *et al*[1], from Bikaner in northwest India. In this study *P. vivax* monoinfection, *i.e.* absence of *P. falciparium* coinfection, causing severe disease was proven by PCR test[1–2]. In a study done at our institute in 2009, various complications like thrombocytopenia, acute kidney injury, hepatic involvement, anaemia, ARDS/ALI, cerebral involvement and shock were observed with *P. vivax* malaria. Analysis of deaths in these patients has shown that the lung complications in form of ARDS/ALI were present in almost all the patients who succumbed to death[3]. Hence, we did this study to throw more light on the clinical profile of ARDS/ALI in *P. vivax* malaria. Sporadic cases of *P. vivax* causing severe malaria and ARDS have been reported in the last 30 years. Acute respiratory distress syndrome (ARDS) as a complication of *P. vivax* infection was reported in a traveller, with low immunity against malaria, returning from Venezuela[4] and from Gujarat, India[5]. In all of these cases the symptoms developed after commencement of antimalarial therapy indicating inflammatory response to parasite killing.

The present study was undertaken to study the clinical profile of ARDS/ALI in *P. vivax* malaria including the demographic profile, other system complications due to malaria, mortality, risk factors for mortality; to compare mortality in vivax malaria and ARDS with falciparum malaria and ARDS and to confirm the temporal association of antimalarial therapy with onset of ARDS/ALI.

It was a retrospective observational study done in a medical ICU of a tertiary care public hospital in Mumbai. Duration of study was from January 2011 to June 2013 (two and a half years). The study commenced after obtaining approval from Institutional Ethics Committee.

All adult patients admitted in medical wards and MICU who were positive for *P. vivax* malaria either on peripheral smear or malaria antigen test or both and also having ARDS or ALI were included in the study. ARDS was defined as $PaO_2/FiO_2<200$, diffuse pulmonary infiltrates on chest radiograph and normal left atrial pressure. Acute lung injury (ALI) was defined as PaO_2/FiO_2 200–300, diffuse pulmonary infiltrates on chest radiograph and normal left atrial pressure. All patients who had *P. falciparum* or mixed malaria or dengue or leptospirosis or any other alternative diagnosis were excluded from the study. The data were obtained from medical records of the hospital.

Following data were noted in each case: the demographic profile of these patients; reports of peripheral smear, malarial antigen test, ABG analysis, chest radiograph findings; whether antimalarial therapy was started before the onset of breathlessness; therapeutic intervention in the form of high flow oxygen or invasive or non-invasive ventilation, antimalarials used; other complications associated with malaria like anaemia, thrombocytopenia, acute kidney injury, hepatic involvement, shock and cerebral involvement; comorbid conditions like diabetes mellitus, hypertension, asthma, chronic obstructive pulmonary disease (COPD), ischemic heart disease, HIV infection; ventilator associated complications and death or survival.

Data were analysed using Student's *t*-test and Fischer's exact test as the sample size was small (30).

Thirty patients satisfied both inclusion and exclusion criteria and were included in the study. Twenty-eight had peripheral smear positive for vivax malaria; 13 had malaria antigen test positive and 11 had both the tests positive. Twenty two (73.3%) were males and 8 (26.67%) were females. The age of patients ranged between 13 and 82 yr with mean age of 35.18 yr. Comorbid conditions were present in four patients; two had diabetes mellitus

and hypertension and two had COPD; all of these patients were older than 40 yr of age and all succumbed.

Overall mortality in our study was found to be 60% (*i.e.* 18 out of 30 patients died). We compared the mortality of patients having vivax malaria and ARDS with mortality of patients suffering from mixed malaria with ARDS (59.2%, *i.e.* 19 out of 32 died) and falciparum malaria with ARDS (50%, *i.e.* 24 out of 48 died) admitted in our hospital during the same period. The difference was not statistically significant (p =1 and 0.48, respectively).

Mean age of patients who succumbed was 44.61 yr whereas that of patients who survived was 25.75 yr. The difference was statistically significant (p = 0.003).

Before the onset of symptoms of ARDS antimalarial drug therapy had been received by 13 (43.3%) patients, and eight had received artesunate; two had received artesunate + clindamycin; two had received chloroquine; and one had received chloroquine + artesunate and 17 (56.67%) patients had not received any antimalarial drug before the onset of symptoms of ARDS. Amongst 18 deaths, seven patients had received antimalarials before onset of breathlessness (39%), whereas amongst survived patients six had received antimalarials before onset of breathlessness (50%). The difference was not statistically significant (p = 0.71). Mortality was not affected with early institution of antimalarial drug therapy.

In all, 21 patients required invasive ventilator and nine could be managed on high flow oxygen therapy. The indications for providing ventilator support were predominantly clinical. The patients requiring invasive ventilator support had severe and persistent hypoxia (PaO_2/FiO_2 <200) and peripheral capillary oxygen saturation < 90%, not improving with high flow oxygen inhalation and severe tachypnoea. A low tidal volume (6–7 ml/kg of body weight) ventilation strategy was followed in invasive ventilation. FiO_2 and positive end-expiratory pressure (PEEP) were adjusted to maintain peripheral capillary oxygen saturation >90%. Maximum PEEP values needed varied from 8 to 12 in different patients with mean of 9.33. Mean age of patients requiring ventilator support (41.62 yr) was significantly greater than that of patients managed without ventilator (26.44 yr) (p = 0.031). Patients requiring ventilator support also had significantly more number of other complications of malaria (mean = 3.43) than those who could be managed without ventilator (mean = 2) (p = 0.013).

All the patients (9) who could be managed on oxygen inhalation therapy survived. Amongst them five patients had PaO_2/FiO_2 persistently within 200 to 300. These cases of acute lung injury were managed on inhaled oxygen and all survived. Four patients had PaO_2/FiO_2 < 200 on admission satisfying definition of ARDS which subsequently improved with inhaled oxygen along with antimalarial and supportive treatment.

ARDS was present in 25 patients; of which 21 required invasive ventilator support and of these only three survived (mortality 85.7%). Low PaO_2/FiO_2 (<200) and low peripheral oxygen saturation was present in all patients requiring invasive ventilation. In 15 patients, it was present from the time of admission to ICU, whereas six patients had higher PaO_2/FiO_2 and percent oxygen saturation at the time of admission and were initially offered oxygen inhalation therapy. However, they required invasive ventilation after 24 h due to progressive hypoxia. The incidence of low PaO_2/FiO_2 was significantly higher (100%) in patients who succumbed as compared to patients who survived (58.33%) (p = 0.0056). The proportion of patients requiring invasive ventilation was significantly higher in death group (100%) as compared to survival group (25%) (p < 0.0001).

Ventilator associated complications were seen in six patients including ventilator associated pneumonia (VAP) in five, difficult weaning in two and pneumothorax in one. One patient with ventilator associated pneumonia and difficult weaning was successfully treated and later discharged; while four patients with VAP expired. Patient having pneumothorax also had acute kidney injury, hepatic involvement and thrombocytopenia along with ARDS and he succumbed.

Other complications of malaria in the study population included thrombocytopenia (platelet <1,00,000/mm^3) in 26 patients, acute kidney injury (serum creatinine >3 mg/dl) in 17 patients, hepatic involvement (serum bilirubin >3 mg/dl) in 14 patients, shock (SBP <90 mmHg) in eight patients, anaemia (Hb <5 g%) in six patients and cerebral malaria (unconsciousness and convulsion) in one patient. Thirteen patients had three or more complications. Mean number of other complications was 3.67 in death group and 1.92 in survival group. The difference was statistically significant (p = 0.0013). The risk factors of mortality in *P. vivax* related ARDS are shown in Table 1.

The onset of fever preceded the onset of breathlessness in all the patients except two; the interval varying widely from 0 to 10 days with mean interval of 3.33 days. The mean interval between onset of fever and onset of breathlessness was not significantly different in death and survival groups (3.61 *vs* 2.92; p = 0.43).

ARDS is the most severe pulmonary manifestation of severe malaria. ARDS/ALI may occur as a part of multiorgan failure or it may be the only complication. The pathophysiology of ARDS centres on inflammatory-mediated increased capillary permeability or endothelial dam-

Table 1. Risk factors for mortality in *P. vivax* malaria with ARDS or ALI

Factor	Death group (n=18)	Survival group (n=12)	*p*-value
Mean age (yr)	44.61	25.75	0.003*
Requirement of invasive ventilation	18 (100%)	3 (25%)	<0.0001*
Mean number of other complications	3.67	1.92	0.0013*
PaO_2/FiO_2 <200	18 (100%)	7 (58.33%)	0.0056*
Early intake of antimalarial drugs	7 (39%)	6 (50%)	0.71†
Mean interval between onset of fever and onset of dyspnoea (Number of days)	3.61	2.92	0.43†
Gender	Males: 12 Females: 6	Males: 10 Females: 2	0.42†

*Significant; †Non-significant.

age leading to diffuse alveolar damage that can continue after parasite clearance. The role of parasite sequestration in the pulmonary microvasculature is unclear, because sequestration occurs intensely in *P. falciparum*, and has not been shown convincingly in *P. vivax*[5]. Recent *in vitro* trials suggested that *P. vivax* infected red cells may cytoadhere to the endothelial cell ligand chondroitin sulphate A which is present in the human lung and brain, thus, explaining the occurrence of ARDS/ALI in *P. vivax* malaria[1, 4–6].

Anstey *et al*[7], demonstrated the sequestration of parasite infected RBCs in pulmonary vasculature. Few studies also demonstrated that different clinical presentations of vivax malaria infection are strongly associated with a potent activation of pro-inflammatory responses and cytokine imbalance[8–11].The sequestration of parasitized RBCs in the pulmonary microcirculation may initiate lung damage via direct endothelial activation and recruitment of host inflammatory responses, which can continue after treatment with antimalarial drugs. The occurrence of ARDS/ALI when a parasite is declining or has been cleared suggests a post-treatment inflammatory effect as a contributory cause. The parasite products such as malaria hemozoin pigment can persist in the vessels either bound to endothelial cells or phagocytosed by host leukocytes.

The histopathological findings of a *P. vivax*-infected patient who died with rapidly progressive breathlessness have been published[12–13]. *P. falciparum* was excluded by light microscopy and polymerase chain reaction. The main findings were heavy (mean, 470 g) edematous lungs, congestion of alveolar capillaries with mononuclear cells, mostly CD68-positive monocytes/macrophages, and CD3-positive T-cells, with some containing phagocytosed pigment and few neutrophils. There were early signs of diffuse alveolar damage and focal areas of hyaline membrane formation. Scanty packed red blood cells (PRBCs) were seen, but there was no cytoadherence. The findings in this patient overlap with those found in falciparum-infected patients, but the lack of cytoadherence stands in contrast.

Pulmonary edema in *P. vivax* has been documented at presentation and up to 4-days post-treatment. Though many case reports have recorded the onset of symptoms of ARDS after starting antimalarial therapy, 56% patients in our study had not received antimalarial therapy before the onset of breathlessness. Also the timing of institution of antimalarial drug therapy did not make any difference in terms of survival.

We observed that the patients who could be managed on high flow oxygen and non-invasive ventilation had a favourable outcome as compared to those who required invasive ventilation. Agarwal *et al*[5] in a systematic review of case reports noted that use of NIV in a vivax malaria related ALI/ARDS in associated with a good outcome. ALI carries a good prognosis but development of ARDS and need for invasive ventilation have grave prognosis.

We observed that the requirement of invasive ventilation and mortality were significantly higher in older patients. This was is concordance with other studies[1]. The possible explanation can be the presence of comorbid conditions like diabetes mellitus, hypertension, COPD or more susceptibility to ventilator associated pneumonia, acute kidney injury and bacteraemia[1–2].

We found that the association of ARDS with other complications of malaria like hepatic and renal involvement and shock has a poorer outcome. Similar findings were noted in the study by Kochar *et al*[1].

The mortality rate of ARDS was not different in vivax, falciparum or mixed malaria when treated in the same setting. However, the total number of patients of falciparum and mixed malaria having ARDS admitted during the same time period (80) was much more than that of vivax malaria and ARDS (30).

Small sample size was one of the limitations in our study. However considering rare occurrence of the condition we believe that it is a significant sample size. Also being a retrospective study it was impossible to get PCR test for confirmation of *P. vivax* infection as it is not done routinely while managing patients.

CONCLUSION

ARDS in *P. vivax* malaria has high mortality rate (60% in our study). The risk factors for mortality were:

older age, requirement of invasive ventilation, severe hypoxia (PaO_2/FiO_2<200), presence of other complications of malaria especially renal and hepatic involvement and presence of comorbid conditions. Temporal association of antimalarial therapy with onset of ARDS was not found in our study.

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