

The effect of regularly dosed paracetamol versus no paracetamol on renal function in Plasmodium knowlesi malaria (PACKNOW): a randomised controlled trial.

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Background:

Acute kidney injury (AKI) is a frequent complication of Plasmodium knowlesi malaria; the commonest cause of malaria in Malaysia and an increasing public health concern in regions of Southeast Asia aiming to eliminate falciparum and vivax malaria. Intravascular haemolysis and subsequent oxidative damage and lipid peroxidation from cell-free haemoglobin (CFHb) is thought to be a major mechanism of AKI in malaria. Paracetamol inhibits CFHb-induced lipid peroxidation and has been demonstrated to improve renal function in a pilot study in severe falciparum malaria. The renoprotective effect of paracetamol in knowlesi malaria has not been evaluated.

Methods:

PACKNOW was a two-arm open-label randomised controlled trial of regularly-dosed paracetamol (1g 6-hourly for 72 hours) versus no paracetamol in Malaysian patients aged ≥ 5 years with microscopy-diagnosed knowlesi malaria treated with standard antimalarial therapy. The primary endpoint was change in creatinine at 72 hours. Secondary endpoints included longitudinal changes in creatinine in patients with severe malaria and AKI.

Results:

During 2016-2018, 396 patients were randomised to receive paracetamol (n=199) or no paracetamol (n=197). The primary endpoint did not differ between arms, with creatinine falling by a mean 15% (95%CI:12%-17%) in both arms. In patients with severe malaria (n=19), creatinine decreased by a mean 38% (95%CI:20-57%) at 7 days in the paracetamol arm compared to 9% (95%CI:-13 to 30%) in the control arm (p=0.04), and in those with AKI (n=71), by a mean 36% (95%CI:31-42%) in the paracetamol arm compared to 29% (95%CI:24-35%) in the control arm (p=0.067). In both subgroups, this effect was more pronounced in those with hemolysis, with creatinine falling by a mean 45% (95% CI 34-58 %) over 7 days in the paracetamol arm compared to 15% (95% CI -5 to 34%) in the control arm (p=0.022) in those severe malaria and haemolysis (n=11) and by a mean 43% (CI 38-49 %) over 7 days in the paracetamol arm compared to 26% (95% CI 21-32 %) in the control arm (p<0.001) in those with AKI and haemolysis. In the subgroup of patients with severe malaria and hemolysis, proteinuria was detected at 28 days in 60% (3/5) in the control arm and no patients (0/7) in the paracetamol arm (p=0.045) No patient met criteria for Hy's law of hepatotoxicity.

Conclusions:

These findings support the hypothesis that paracetamol inhibits CFHb-mediated oxidative damage. Regularly dosed paracetamol improves renal function in patients with severe knowlesi malaria, and in those with AKI, with this effect more pronounced in those with intravascular hemolysis. Use of adjunctive

paracetamol as a renoprotective agent should be considered in these groups and warrants further investigation in other disease states with circulating free haemoproteins.