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Safety and efficacy of artesunate-amodiaquine combined with either methylene blue or primaquine in young children with falciparum malaria in Burkina Faso: a non-inferiority randomised controlled trial

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The development and spread of artemisinin resistance are major threats to the global malaria control and elimination efforts. Primaquine and methylene blue are gametocytocidal drugs that can be combined with an artemisinin-based combination therapy to reduce malaria transmission, including the spread of resistant strains.

Children (6-59 months old) with uncomplicated falciparum malaria attending the Nouna Hospital, Burkina Faso, were treated with artesunate-amodiaquine and randomised 1:1 to either methylene blue (15 mg/kg/day for three days) or primaquine (0.25 mg/kg at D2). The primary outcome was the haematological recovery at D7 and the trial was designed as a non-inferiority randomised clinical trial.

Methylene blue-artesunate-amodiaquine could not be shown to be non-inferior to primaquine-artesunate-amodiaquine, however, haemoglobin recovery following treatment was similar in both study arms (D7: mean 0.2±1.4 g/dl vs. 0.5±0.9 g/dl; p=0.446). Adverse event rates were alike in the two study arms, except for vomiting, which was more frequent in the methylene blue arm than in the primaquine arm (20/50 vs 7/50; p=0.003). Adequate clinical and parasitological response was above 95% with both treatments, but the clearance of asexual parasites was significantly faster in the methylene blue arm when compared to the primaquine arm (D1: 48/50, 96%, vs 40/50, 80%; p=0.014). Furthermore, *P. falciparum* gametocyte prevalence and density were consistently lower in the methylene blue arm than in the primaquine arm during follow-up, which reached statistical significance on D2 (prevalence: 2/50, 4%, vs 15/49, 31%; p<0.001; density: 9.6 vs 41.1/µl; p=0.024).

Methylene blue combined with an artemisinin-based combination appears to be an alternative to primaquine combined with an artemisinin-based combination for the

treatment of falciparum malaria in Africa. Despite the need to further improve its formulation, methylene blue combined with an artemisinin-based combination may already be considered useful to increase treatment efficacy, reduce falciparum malaria transmission intensity, and consequently reduce the risk for resistance development and spread.

Trial registration: ClinicalTrials.gov; Identifier: NCT02851108; Registered 1st of August 2016; https://clinicaltrials.gov/ct2/show/NCT02851108