Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperaquine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial


Summary

Background  Ivermectin is being considered for mass drug administration for malaria due to its ability to kill mosquitoes feeding on recently treated individuals. However, standard, single doses of 150–200 μg/kg used for onchocerciasis and lymphatic filariasis have a short-lived mosquitocidal effect (<7 days). Because ivermectin is well tolerated up to 2000 μg/kg, we aimed to establish the safety, tolerability, and mosquitocidal efficacy of 3 day courses of high-dose ivermectin, co-administered with a standard malaria treatment.

Methods  We did a randomised, double-blind, placebo-controlled, superiority trial at the Jaramogi Oginga Odinga Teaching and Referral Hospital (Kisumu, Kenya). Adults (aged 18–50 years) were eligible if they had confirmed symptomatic uncomplicated Plasmodium falciparum malaria and agreed to the follow-up schedule. Participants were randomly assigned (1:1:1) using sealed envelopes, stratified by sex and body-mass index (men: <21 kg/m²; women: <23 vs ≥23 kg/m²), with permuted blocks of three, to receive 3 days of ivermectin 300 μg/kg per day, ivermectin 600 μg/kg per day, or placebo, all co-administered with 3 days of dihydroartemisinin-piperaquine. Blood of patients taken on post-treatment days 0, 2 + 4 h, 7, 10, 14, 21, and 28 was fed to laboratory-reared Anopheles gambiae sensu stricto mosquitoes, and mosquito survival was assessed daily for 28 days after feeding. The primary outcome was 14-day cumulative mortality of mosquitoes fed 7 days after ivermectin treatment (from participants who received at least one dose of study medication). The study is registered with ClinicalTrials.gov, number NCT02511353.

Findings  Between July 20, 2015, and May 7, 2016, 741 adults with malaria were assessed for eligibility, of whom 141 were randomly assigned to receive ivermectin 600 μg/kg per day (n=47), ivermectin 300 μg/kg per day (n=48), or placebo (n=46). 128 patients (91%) attended the primary outcome visit 7 days post treatment. Compared with placebo, ivermectin was associated with higher 14 day post-feeding mosquito mortality when fed on blood taken 7 days post treatment (ivermectin 600 μg/kg per day risk ratio [RR] 2·26, 95% CI 1·93–2·65, p<0·0001; hazard ratio [HR] 6·32, 4·61–8·67, p<0·0001; ivermectin 300 μg/kg per day RR 2·18, 1·86–2·57, p<0·0001; HR 4·21, 3·06–5·79, p<0·0001). Mosquito mortality remained significantly increased 28 days post treatment (ivermectin 600 μg/kg per day RR 1·23, 1·01–1·50, p=0·0374; and ivermectin 300 μg/kg per day RR 1·21, 1·01–1·44, p=0·0337). Five (11%) of 45 patients receiving ivermectin 600 μg/kg per day, two (4%) of 48 patients receiving ivermectin 300 μg/kg per day, and none of 46 patients receiving placebo had one or more treatment-related adverse events.

Interpretation  Ivermectin at both doses assessed was well tolerated and reduced mosquito survival for at least 28 days after treatment. Ivermectin 300 μg/kg per day for 3 days provided a good balance between efficacy and tolerability, and this drug shows promise as a potential new tool for malaria elimination.

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Introduction

Ivermectin, a broad-spectrum antiparasitic endectocide used for onchocerciasis and lymphatic filariasis control,1 also kills malaria mosquitoes (Anopheles spp) that feed on recently treated individuals and has been proposed as a potential novel method to reduce malaria transmission.2 Ivermectin has a different method of action from other insecticides, and might be effective against mosquito populations that rest and feed outdoors, which have escaped the killing effects of contact insecticides deployed on long-lasting insecticidal nets and through indoor residual spraying. Ivermectin could also be effective against mosquitoes that are resistant to insecticides used for long-lasting insecticidal nets and indoor residual spraying.3 However, several entomological studies have shown that the mosquitocidal effects of standard 150–200 μg/kg doses...
of ivermectin are short-lived (<7 days). Population-level modelling suggests higher doses of ivermectin, resulting in longer lasting mosquitocidal activity, could provide a substantial boost to the effects of mass drug administration with the antimalarial dihydroartemisinin-piperaquine, a strategy that is being deployed for malaria transmission reduction and elimination. 6, 11

Ivermectin has an excellent safety profile. More than 2.5 billion treatments have been distributed as part of mass drug administration for onchocerciasis and lymphatic filariasis control. A single dose of 300–400 μg/kg is recommended when these mass drug administrations are done yearly, 13 a dose of 400 μg/kg repeated after 1 week has been shown to be safe and effective in children with head lice, 14 and doses of 800 μg/kg repeated every 3 months were safely tested in hundreds of volunteers had an effect for 2 weeks after treatment, but subsequent trials with a single dose of ivermectin 200 μg/kg showed no effect on mosquito survival at 14 days after treatment and a repeated dose of 200 μg/kg given on days 0 and 2 showed only a modest effect on survival 7 days after treatment. Population modelling predicted that the mosquitocidal effects found in these trials would only have a modest effect on reduction of malaria prevalence if distributed in mass drug administration with dihydroartemisinin-piperaquine, although higher doses of ivermectin were predicted to have a greater and longer-lasting effect.

Methods
Study design and participants
We did a randomised, double-blind, placebo-controlled, parallel three arm, superiority trial at the Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH; Kisumu, Kenya). Since mosquito feeding involved around 150 mosquitoes (Anopheles gambiae sensu stricto) per feed, the study had a clustered design, with the patient as the unit of randomisation and the mosquito as the unit of analysis. Details of our study design and procedures have been published elsewhere. 21

This study was approved by the ethics committees of JOOTRH, the Kenya Medical Research Institute (KEMRI), the Liverpool School of Tropical Medicine, and the US Centers for Disease Control and Prevention (CDC), with the CDC approving reliance on KEMRI’s ethics committee.

Evidence before this study
We searched PubMed on Nov 15, 2017, for studies assessing Anopheles spp mortality following feeding on blood of human beings treated with ivermectin, using the search terms “ivermectin” AND (“anopheles” OR “malaria”) AND “clinical trial” [publication type]. The search was unrestricted by language or publication date. Using this search and by scanning reference lists of articles and trial registers, we identified three publications in peer-reviewed journals. An early study found that a single dose of ivermectin 250 μg/kg in a human volunteer had an effect for 2 weeks after treatment, but subsequent trials with a single dose of ivermectin 200 μg/kg showed no effect on mosquito survival at 14 days after treatment and a repeated dose of 200 μg/kg given on days 0 and 2 showed only a modest effect on survival 7 days after treatment. Population modelling predicted that the mosquitocidal effects found in these trials would only have a modest effect on reduction of malaria prevalence if distributed in mass drug administration with dihydroartemisinin-piperaquine, although higher doses of ivermectin were predicted to have a greater and longer-lasting effect.

Added value of this study
We present the first trial assessing the safety, tolerability, and mosquitocidal efficacy of repeated high doses of ivermectin on mosquito mortality. Our findings show that ivermectin 600 μg/kg per day and 300 μg/kg per day for 3 days was well tolerated and increased mosquito mortality for at least 28 days after treatment, making ivermectin a promising new tool for malaria elimination. Using population-level modelling, we also showed that adding ivermectin 600 or 300 μg/kg per day for 3 days to mass drug administration with dihydroartemisinin-piperaquine reduced malaria prevalence by an additional 56% (600 μg) and 44% (300 μg) in low prevalence areas (10%), and 61% (600 μg) and 54% (300 μg) in high prevalence areas (30%).

Implications of all the available evidence
Mass drug administration and seasonal malaria chemoprevention are being deployed in countries across the globe. Adding high dose ivermectin to mass drug administration and seasonal malaria chemoprevention could substantially boost effects on malaria transmission reduction.

Additional Reading
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We aimed to establish the safety, tolerability, and mosquitocidal efficacy of 3 day courses of ivermectin 600 μg/kg per day or 300 μg/kg per day, co-administered with a standard 3 day course of dihydroartemisinin-piperaquine, to identify safe and practical regimens for malaria elimination.

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