Chloroquine as a therapeutic option for the mild post malaria anaemia – A proposed RCT

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Background

- Malaria is pro-inflammatory and can cause the release of various cytokines, contributing to the development of anaemia
- Absolute and relative concentrations of the cytokines determine level of anaemia
- Released cytokines enhance macrophageal erythrophagocytosis & increases iron sequestration
- Inflammatory response impedes macrophageal iron release causing considerable iron delocalisation within the Reticulo-endothelial system and causes hypoferaemia
- Increased serum levels of TNF-α, IFN-γ and nitric oxide depress erythropoiesis via bone marrow depression, dyserythropoiesis and erythrophagocytosis
- Continuing inflammation after a malarial event may contribute to the slow resolution of anaemia

CQ & erythropoietic response to malaria

- **Chloroquine (CQ) may**
  - block the acute incorporation of iron into reticuloendothelial macrophages during clinical malaria associated with haemolysis and iron delocalization.
  - have an anti-inflammatory effect might be a useful adjunctive therapy to continue to utilize after its initial antimalarial effect.
  - have a continuing direct anti-malarial effect to both clear microscopically undetectable persistent infection and prevent further episodes until haematological recovery is optimized

Aim & Hypothesis

Aim:

To explore the effect of CQ on mild post malaria anaemia (MA) after standard treatment, and after co-artemether treatment

Hypothesis:

The anti-inflammatory, anti-malarial and anti-macrophageal iron loading effects of CQ could make it a useful drug in the management of mild post malaria anaemia

Study Design

- RCT in 13 villages in West Kiang (Gambia) between July 2007 and April 2008 in children aged 12 - 72 months
- Children with malaria (subjects) identified through active and passive surveillance
- Subjects randomised at day 0 to receive either CQ + fansidar or co-arthemeter
- Subjects with cleared parasitaemia at day 3 + day 3 Hb $\geq$70 & <110g/L randomised again to either weekly CQ or weekly placebo.
- Subjects followed up till day 90 (seen a total of 8 times)

Outcome Measures

- **Primary outcome measures**
  - change in Hb from day 3 post treatment to day 90 in the weekly CQ and placebo arms

- **Secondary outcome measures**
  - Curve of Hb change from day 3 post treatment to day 30 in the two placebo arms
  - Change in markers of iron status, and erythropoietic response between day 3 and day 30, and between day 3 and day 90
  - Changes in measures of inflammation between day 3 and day 30, and between day 3 and day 90

Laboratory Methods

- Hb & other red cell indices – all time points
- Zinc protoporphyrin – all time points
- Pro- & anti-inflammatory cytokines – days 3 & 45, using both Peripheral Blood Mononuclear Cell culture and multiplex assay
- Malaria parasite – thick & thin blood films + qPCR (day 0 & 90) & nested PCR (all other time points)
- Urine neopterin & hepcidin (days 3, 15 & 30)

Implications of Project

- Exploits the multifarious actions of CQ to enhance malaria management
- Positive outcome will have important public health implications for the management of MA
- Could provide an alternative to iron in the management of mild MA
- Project will also advance knowledge of the pathogenesis of MA