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Prophylactic effect of artemether on human schistosomiasis mansoni among Egyptian children: A randomized controlled trial

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This paper is dedicated to Professor Rashida Barakat, who not only inspired our team but a generation of scientists committed to better health and well-being for all.

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ABSTRACT

A double-blind, randomized controlled trial was conducted in an endemic focus for *Schistosoma mansoni* in Kafr El-Sheikh Governorate, Northern Nile Delta, Egypt, to evaluate the prophylactic effect of artemether (ART) given in conjunction with praziquantel (PZQ). The study encompassed 913 primary school children randomly assigned to two treatment groups PZQ/ART and PZQ/ART-placebo. At baseline, both groups received 40 mg/kg body weight of PZQ twice four weeks apart, after which one group received 6 mg/kg body weight of ART every 3 weeks in 5 cycles during the transmission season and the other group received ART-placebo. At the end of the study, prevalence of infection among the PZQ/ART was approximately half that of the PZQ/ART-placebo group, i.e. 6.7% versus 11.6%, and incidence of new infections for the PZQ/ART was 2.7% versus 6.5% for the PZQ/ART-placebo. In conclusion, PZQ/ART combined therapy might be considered as an adjunct measure against human schistosomiasis, by specifically reducing transmission and therefore contribute to disease elimination.

1. Introduction

Schistosomiasis is a neglected tropical disease (NTD) that remains one of the most prevalent parasitic infections in the humid tropics ranking second only after malaria in terms of gravity and public health importance (Chitsulo et al., 2000). The estimated global burden of the three most common schistosome species, *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum* has been reported to be 4–5 million disability-adjusted life years (DALYs) (World Health Organization, 2002) but would be considerably higher if subtle morbidities were included. The great majority of the world's burden of schistosomiasis is concentrated in the African continent with an overall estimated average prevalence of approximately 10% (Steinmann et al., 2006; Utzinger et al., 2009). In Egypt, both *S. mansoni* and *S. haematobium* species are endemic. Currently, the number of infections due to *S. mansoni* exceeds that of *S. haematobium* due to ecological changes influenced by the shift in irrigation system from basin to perennial following the construction of the Aswan High Dam (Dazo and Biles, 1972; Malek, 1975). In Egyptian hyper-endemic foci of *S. mansoni* infection, the prevalence even approaches 70% and the percentage of heavily infected

Abbreviations: PZQ, praziquantel; ART, artemether; NTD, neglected tropical disease; DALYs, disability adjusted life years; EPG, eggs per gram; WHO, World Health Organization; MDA, mass drug administration; MOHP, the Egyptian Ministry of Health and Population; UNDP, United Nations Development Program; USAID, United States Agency for International Development; KES Governorate, Kafr El Sheikh; GMEC, geometric mean egg count; Swiss TPH, the Swiss Tropical and Public Health Institute; RHU, Rural Health Units; CI, confidence interval; ACTs, artemisinin-based combination therapies.

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individuals, i.e. those excreting more than 400 eggs per gram (EPG) of faeces accounts for 20% of those infected (Barakat et al., 2000).

The World Health Organization (WHO) recommends schistosomiasis control through large-scale mass drug administration (MDA) with PZQ, a key anti-morbidity strategy that remains in place to date (World Health Organization, 1983, 2011). Chemotherapy as a measure of control is feasible and sustainable if distributed repeatedly according to defined, long-term schedules (World Health Organization, 2011). The Egyptian Ministry of Health and Population (MOHP) has implemented a large-scale control programme since the early 1980s supported by international agencies including the United Nations Development Program (UNDP) and the United States Agency for International Development (USAID). The outcome was excellent during the first implementation phase with prevalence rates falling throughout the country (Barakat et al., 2014). However, shortly after cessation of control measures, infection indices increased drastically exceeding baseline levels. In addition, new infection foci appeared in areas claimed to have been secure (Talaat et al., 1999; El-Khoby et al., 2000; Barakat, 2013; Abdel-Wahab et al., 2000). It was also noticed that the age pattern had shifted in the direction of more infections among children and occurring at a younger age (Barakat et al., 1998).

In the late 1990s, the MOHP followed up with more vigorous control strategies based on MDA and providing chemotherapy to all individuals in hyper-endemic foci annually regardless of infection status. However, transmission continued unabated as snail control had been abandoned and PZQ does not affect the immature stages of the parasite leaving new infections to mature and start egg production (World Health Organization, 2011; Cioli and Pica-Mattoccia, 2003; Pica-Mattoccia and Cioli, 2004). Although snail control measures affect disease transmission, application is not always feasible due to the high cost of molluscicides and their broad-spectrum effect on the fauna, e.g. fish, as well as administrative and logistic limitations of its use, particularly as preventive chemotherapy is now the recommended main approach (Taylor, 2008).

Artemether (ART), a methyl-ether derivative of dihydroartemisinin (Li and Wu, 2003), in addition to its excellent anti-malarial properties, also exhibits activity against the immature stages of *Schistosoma* spp. (Shuhua et al., 2000; Utzinger et al., 2001, 2000; Utzinger and Keiser, 2004; Xiao et al., 2002; Bergquist et al., 2004; N'Goran et al., 2003). The administration of a dose of 6 mg/kg once every 2–4 weeks, reduces the incidence of schistosome infection significantly (Utzinger et al., 2001; Utzinger and Keiser, 2004). Peak efficacy of the drug varies from two weeks after cercarial skin penetration for *S. japonicum* to four weeks for *S. haematobium*. ART complements PZQ as its effect is focused on the juvenile stage, thereby blocking the development of new adult stages (Shuhua et al., 2000; Utzinger et al., 2001; Utzinger and Keiser, 2004; Xiao et al., 2002). Theoretically, combined drug therapy should completely wipe out schistosome infection in the human host as there would be no replacement of the adult worms by those maturing, as is the case after exclusive PZQ treatment. This type of combined treatment should ultimately impact transmission by reducing overall egg excretion from the human host. It is worth noting that ART treatment might also have an effect comparable to a vaccine as shown in a previous experimental study, where ART treatment in the second and third week after infection resulted in immune responses that protected mice at the level of 58% and 81% respectively (Bergquist et al., 2004).

After initial Chinese trials of artemisinin derivatives for prevention of *S. japonicum* infection (unpublished in the international literature), several clinical trials have confirmed the effect of ART against the three most common species (Utzinger et al., 2000; N'Goran et al., 2003; Li et al., 2005). A comprehensive meta-analysis from 2011, refers to 52 trials and 38 articles on the antischistosomal efficacy of different medication strategies with various artemisinin derivatives including combination therapy with PZQ (Liu et al., 2011). According to this systematic review, it is preferable to use complementary treatment regimen which includes PZQ and multiple doses of ART or artesunate (Liu et al., 2011). Given these facts and since field studies evaluating the ART effect on Egyptian *Schistosoma* species do not exist so far, we set the following objectives:

1. Evaluate the prophylactic effect of ART chemotherapy on schistosomiasis mansoni in a double-blind randomized controlled trial.
2. Assess the safety and efficacy of combined PZQ and ART versus PZQ only.

2. Methods

2.1. Ethical approval and financial support

The study protocol was approved by the Ethical Review Board, Ministry of Health and Population (MOHP), Egypt. Before the implementation of the study, written informed consents were obtained from the guardians of the children. The study was funded by the Special Programme for Research and Training in Tropical Diseases (TDR) (ID No.: SGS02/39).

2.2. Study area

The study was conducted in a hyper-endemic area for *S. mansoni* in the north-western region of the Metobas District, Kafr El-Sheikh Governorate (KES), which is located in the northern part of the Nile Delta (Fig. 1). It is bordered by the Mediterranean Sea to the north, the Rosetta Nile Branch to the west, the Dakahleya Governorate to the east, and the Gharbeya Governorate to the south. One of the main geographical features of the coastal area of KES is the El-Borolos Lake which is located in the northern part of the Nile Delta and connected to the Mediterranean Sea by the Boghase-El-Borolos canal. The whole study area is free from malaria.

2.3. Study design and study sample

A randomized, double blind controlled trial was conducted during the period 2003–2005. The study encompassed a total of 913 primary school children attending grades 1–5, aged 6–11 years. The children were randomized into two treatment groups using a computer generated random list. The PZQ/ART-placebo group included 453 children, and the combined-therapy group (PZQ/ART) included 460 children. Both the investigators and the study participants were blinded as to which participants were given ART or ART-placebo. Considering an attrition rate of 10%, the sample size was estimated to give the study at least 80% power at 0.05 level of significance to detect the difference between the two treatment groups.

2.4. Socio-demographic data

The data form contained the following personal information: name, class, identification number, gender, residence, body weight, compliance to stool sample collection and treatment and results of stool sample analysis. The investigators dealing with the data were unaware about the group identity of the study subjects until the final analysis of data at the end of the study.

2.5. Stool sample evaluation

Since the most intense schistosomiasis transmission in Egypt is from April through October, the study was started in the former month, when stool samples were collected to determine baseline prevalence and intensity of infection. For the assessment of PZQ