

Original Article

Treatment of pre-school children under 6 years of age for schistosomiasis: safety, efficacy and acceptability of praziquantel

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Abstract

Background

The World Health Organization (WHO) recommends praziquantel for the control and treatment of schistosomiasis, with no real alternative. Pre-school children are excluded from population treatment programs mainly due to paucity of safety data on this age group.

Objectives: This study investigated safety, efficacy and acceptability of praziquantel for the treatment of *S. haematobium* and *S. mansoni* infections among pre-school children aged <6years. The study also investigated the burden of schistosomiasis in this age group.

Methods: Pre-school children (n=188) from Sudan were included in the study. The children were treated with praziquantel tablets at a single dose of 40 mg/kg body weight. Adverse events were assessed at 24 hours and 7 days later, via questionnaire administration to parents and guardians. Efficacy of treatment was assessed at 1, 3 and 6 months by examining stool and urine samples for schistosome eggs. Acceptability was determined by the number of children spitting or vomiting during administration of the drug.

Results: The burden of schistosomiasis among pre-school children aged <6 years was high (31.1%), and this was comparable to that observed among school children-aged ≥6 years (32%). Praziquantel treatment achieved high cure rates (egg negative) for both *S. haematobium* and *S. mansoni* infections when assessed at 1 month after treatment (89.6-92.1%) and remained high for *S. haematobium* (89.6-100%) up to 6 months. However, cure rate dropped from 90.5% at one month to 58.8% and 69.2% at 3 and 6 months among *S. mansoni*-treated children. Praziquantel treatment decreased egg counts considerably with post-treatment geometric mean egg reductions rates ranging from 96.4% to 99.4% at 1 month. Acceptability of praziquantel treatment was high, only for one child the dose had to be repeated after initial spitting. Treatment resolved haematuria and improved weight of the children. There were no drug-related adverse events in all the treated children during follow-up at 24 hours and 7 days.

Conclusions: Praziquantel is safe, effective and acceptable among children aged <6 years. Pre-school children represent a high risk group for schistosomiasis and should be included in population treatment programs.

Keywords: Schistosomiasis, Praziquantel, Safety, Young Children.

Schistosomiasis can lead to significant ill-health and economic burden^{1,2}. Two main species, *Schistosoma mansoni*

(causing intestinal schistosomiasis) and *S. haematobium* (causing urogenital schistosomiasis) are endemic in Africa and

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account for about 85% of the global burden of the disease^{1, 2, 3}. In most African countries, there is an overlap of the two schistosome species resulting in mixed infections⁴. Continuous exposure to contaminated water causes repeated infections during childhood but severe-chronic disease appears later in life. Other, more subtle, effects of the infection in school children include short-term memory loss, slower reaction time, lower scores in some tests of cognitive ability, and poor growth^{5,4}. Anaemia and other nutritional deficiencies have also been linked with the infection⁶.

The disease can be prevented or the underlying pathology reversed by treatment with praziquantel, the anti-schistosomal drug of choice^{7,-13}. With the high price of praziquantel following its discovery in the late 1970s, experts suggested that selective treatment i.e. identification of high prevalence communities, screening the people and treating those identified to have the infection would be more cost-effective¹⁴. Also, intensity of infection is highest in children and adolescents, hence treatment should be targeted to school-aged children^{15,4,10}. Within this approach the standard single dose of 40 mg/kg of praziquantel is recommended^{14, 4}. In parts of sub-Saharan Africa, population-based treatment campaign programs remain the only option for most individuals suffering from schistosomiasis to receive treatment⁹.

Since the early millennium, however, praziquantel use has increased considerably mainly due to the sharp fall in price^{16, 17}. The finding of a meta-analysis that first suggested that although emergence of clinical resistance could not be ruled completely out, there was no eminent threat to praziquantel, contributed to the adoption of the policy for mass distribution of this drug to endemic countries¹⁸. A recent study also concluded that there is no evidence to suggest that resistance against praziquantel has emerged, or is emerging¹⁷. The 54th World Health Assembly endorsed mass drug distribution and treatment of at least 75% of school-aged children and other high-risk groups with

praziquantel by 2010⁴. The Schistosomiasis Control Initiative (SCI), started in 2003 and supported by Bill and Melinda Gates, has been in the forefront of these large-scale control programs across selected countries in sub-Saharan Africa^{16, 19}. However, pre-school children under 5 five years have been excluded from population treatment programmes²⁰. There is emerging evidence that the burden of schistosomiasis is high in pre-school children and the World Health Organization (WHO) is considering a recommendation that will include pre-school children and infants in population treatment programs. However, there is paucity of safety and efficacy data on praziquantel in pre-school children aged <5 years²¹. In order to contribute evidence to inform treatment policies, this study was sponsored by WHO to assess safety, efficacy and acceptability of praziquantel among pre-school children in schistosomiasis endemic area along the Gezira Irrigation Scheme in Sudan. The study was also to document the extent of schistosomiasis burden in pre-school children by determining prevalence and intensity of *S. haematobium* and *S. mansoni*; to describe morbidity related to schistosomiasis from micro and macro haematuria. With most population treatment administered without prior diagnosis in the approach termed 'preventive chemotherapy' - the control strategy currently recommended by the WHO and applied in many endemic countries^{4,22}, this study also assessed age-specific prevalence rates within this age group to inform on the age at which treatment should best be initiated.

Materials and Methods

Ethical clearance

Ethical clearance for the study was obtained from WHO's Research Ethics Review Committee, National Ministry of Health and Ahfad University for Women in Sudan. Parents and guardians were adequately informed about the treatment and possible treatment-related side-effects and what they should do in the event of side effects. Written consent of a child to

participate in the study was obtained from household heads, parents or guardians.

Study area and population

This study was conducted in Hassaheba and Kamlin localities in the Gezira Irrigation Scheme, Gezira State, Sudan. The Irrigation Scheme was initiated in 1924 and located between the Blue and White Niles, South Khartoum. The scheme provides over 800,000 hectares of farm land intended to boost agricultural production, but this in turn has favoured breeding of the intermediate host snails responsible for transmission of schistosomiasis. The inhabitants in this area are mainly Arab tenants who live with their families, but there are also non-tenant Arabs. Outside of Arab villages there is scattered population of workers from west Sudan and migrants from neighboring countries who live either in camps or in unregistered villages without health services, electricity clean piped water supply or schools. The children can attend the nearest primary school and some immigrants make use of the nearby dispensary or dressing station. In 1985 the total permanent and migrant population was estimated to be 2 million²³. The estimate of the population of the Gezira State in 2009 was over 3.6 million²⁴. A detailed description of the Gezira Irrigation Scheme has been reported elsewhere²⁵.

School surveys

Surveys were conducted in primary schools to identify villages with schistosomiasis prevalence rates greater than 40%. On the basis of the prevalence in the school surveys, 10 villages were further surveyed for schistosomiasis in pre-school children aged <6 years. Three villages namely, Hilat Daoud, Branco and Hamad Alla were then selected. *S. haematobium* is the predominant species in Hilat Daoud and Branco whilst Hamad Alla is mainly endemic for *S. mansoni*.

Parasitological diagnosis of the infection

The Kato-Katz method²⁶ was used for parasitological diagnosis of the infection and egg count was expressed as eggs per gram (epg) of stool. Three slides were examined from a single stool sample. *S. haematobium*

was diagnosed by the urine filtration technique and egg count expressed as eggs per 10 ml of urine²⁷. The intensity of infection was categorized according to the WHO classification as light infection (1 to 99 epg) moderate (100 to 399 epg) and heavy (≥ 400 epg) for *S. mansoni* and for *S. haematobium*, light infection was (≤ 50 eggs/10ml urine) and heavy was (≥ 50 eggs/10 ml).

Clinical examination

All the children underwent clinical examination before treatment was given. Urine samples of participating children were examined and 103 (74.6%) had abnormal urine color, mainly blood in urine (haematuria). Abdominal pain was also prevalent among these children and infants (n=78; 56.5%). Only three children (2.2%) reported general fatigue. General physical examinations and anthropometric measurements revealed that 11 patients (8%) had stunted growth (Height-for-age <3rd percentile); 9 patients (6.5%) were under weight according to Welcome classification of malnutrition. Hepatosplenomegaly was not common among these children but in case it was detected the affected child was referred to the district hospital for further evaluation and management. Children with umbilical hernias were also referred. The children with vitamin A deficiency were given therapeutic doses of vitamin A. Children with other minor infections were treated with the appropriate medication.

Treatment

Praziquantel tablets (Distocide, Batch No. DISTT 4010) made in Korea, and provided by the WHO was used for treating the pre-school children in this study. Each child was weighed using a calibrated weighing scale and a single dose of 40 mg/kg praziquantel was administered. For children aged 1-3 years, their weight ranged from 6-20 kg (mean, 13 kg), and the corresponding mean dose administered was 518 mg with the number of tablets a child received ranging from 1/3 -1 1/3 (mean, 1 tablet). Children aged 3-5 years had weight ranging from 12-28 kg (mean, 18.6 kg) and the mean dose was 740 mg, with the number of tablets ranging from

1-2 (mean 1¼ tablet). The 5-6 year old children had weight ranging from 17.5-33 kg (mean, 24.5kg), mean dose (977 mg) and the corresponding number of tablets ranging from ¼-2¼ (mean, 1⅓ tablet). The praziquantel tablets were broken into pieces before administration. For children who could not swallow, the tablets were crushed and administered with honey to decrease the bitter taste. The drug administration was supervised using a modified Direct Observation Therapy (DOT). All the children included in the study received a snack before the drug was administered. The mothers or guardians of the treated children were interviewed 24 hours and 7 days post treatment by the clinician using structured questionnaire for episodes of treatment-related side effects. The children were followed (less actively) until 6 months to record adverse events. At each of the visits, specific signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, anorexia, fever, headache, dizziness and fever) were evaluated. Other symptoms reported by parents or guardians were also recorded. Each symptom was classified according to severity as mild, moderate, severe or life-threatening; seriousness was assessed using a grading scale. The symptoms were graded as not related, unlikely, possible, probable, most probable or insufficient data to enable adequate assessment. The efficacy of praziquantel was assessed at one, three and six months using the same diagnostic criteria as baseline. Any treated child presenting stool sample from which three slides were free for schistosome eggs or no eggs found in 10 ml of urine was considered to be cured. In this study treatment acceptability was defined as the number of children spitting or vomiting during administration of the drug, and it was assessed by direct observation therapy (DOT). The weight of children was measured using a calibrated weighing scale; heights were measured using a stadiometer with a flat wooden base.

Inclusion and exclusion criteria

Pre-school children under six years of age with confirmed schistosomiasis by microscopy were eligible for inclusion in the

study. Seriously ill children; or children reporting a history of epilepsy, other signs of potential central nervous system involvement such as subcutaneous nodules suggestive of cystercosis; or have previously suffered one of the rare serious adverse events such as Stevens-Johnson syndrome, were excluded. These criteria were based on the World Health Organization (WHO) Manual of Preventive Chemotherapy²². Over all, one hundred and eighty-eight pre-school children were included in the study.

Results

Overall, prevalence of schistosomiasis among pre-school children in the three selected study villages (n=604) was high (31.1%). Urine examination revealed that in Branco a high number of pre-school children were infected with *S. haematobium* (43%); this was 22% in Hilat Daoud. The prevalence of *S. mansoni* in Hamad Alla was also high (44%). Age-specific prevalence rates in the three villages have been reported in (Table 1). There was no significant difference across age-specific categories in this group in Hilat Daoud and Branco, but differences were observed in Hamad Alla ($p \leq 0.005$). Strikingly, the rates of infection with schistosomiasis in pre-school children aged <6 years was comparable to that observed among school children aged ≥ 6 years in the 26 primary schools surveyed (n=1,427): 31.1% versus 32%, respectively.

In this study praziquantel treatment achieved high cure rates (egg negative rates) for both *S. haematobium* and *S. mansoni* infections at 1 month and remained high for *S. haematobium* at 3 and 6 months (Table 2). Fifty-nine of 77 (76.6%) children assessed at baseline who were found with *S. haematobium* were available for treatment in Hilat Daoud with a respondent rate of 76.6%. Of these 48 (81%) children were available at one month's follow-up, 36 (61%) at three months and 29 (49%) at six months. The overall cure rate was 89.6%, 91.6% and 100% at one month, and three and six months, respectively. In Branco, 50 of 64 (70.1%) children were available for treatment and 38 (76%) children were available at one month's follow-up, 35

(70%) at three months and 36 (72%) at six months follow-up. The cure rates were 92.1% at one month, 91.4% at three months and 91.7% at six months. In Hamad Alla 29 of 47 (61.8%) children found to have *S. mansoni* infection were available for treatment. Of these 21 (72%) children attended for follow-up assessment at one month, 17 (59%) children at three months and 13 (45%) children at six months. The cure rate was 90.5% at one month, but this dropped to 58.8% at 1 month and 69.2% at 6 months. Instability and lack of cooperation of the inhabitants contributed to the low turn out rate at follow-up in this village.

For the two villages investigated for *S. haematobium* infections, the geometric mean egg count was higher for children in Hilat Daoud (166.1 eggs/10ml) than in Branco (28.2 eggs/10ml). Egg reduction rates were very high one month after treatment: in the children from Hilat Daoud egg count reduced to 1.5 eggs/10ml (a reduction of 99.4%) and in Branco to 1.3 eggs/10ml (a reduction of 96.4%). The pretreatment geometric mean

egg count for *S. mansoni* infection in the children from Hamad Alla was 97.8 epg and reduced to 1.5 epg after one month after treatment leading to a reduction rate of 99.0% (Figure1).

All children accepted the drug without spitting or vomiting except for one child aged 1½ years for whom the dose was repeated. However, dose determination, preparation and administration of the medication in this study were cumbersome. During post-treatment follow-up visits and contacts after 24 hours and 7 days, when the children and their parents or guardians were asked about drug related side effects including gastro intestinal symptoms, skin manifestations, bleeding episodes, dizziness, general fatigue or change in gait or behaviour, no side effects were reported in all the treated children. Also, during the less active follow-up at 3 and 6 months, no events were recorded.

For anthropometry measurements, a significant increase in weight in children from Hilat Daoud ($P \leq 0.005$) was observed one month after treatment (Figure 2).

Table 1. Prevalence of schistosomiasis among pre- school children in the three study villages.

Village	Species	Age-group			Total
		1-3	>3-5	>5-6	
Hilat Daoud	<i>S. haematobium</i>				
No. Examined		94	176	80	350
No. positive		21	32	24	77
Prevalence		22.3%	18.2%	30%	22%
Branco	<i>S. haematobium</i>				
No. Examined		43	82	23	148
No. positive		14	36	14	64
Prevalence		32.6%	43.9%	60.9%	43.2%
Hamad Alla	<i>S. mansoni</i>				
No. Examined		33	54	19	106
No. positive		6	29	12	47
Prevalence		18.2%	53.7%	63.2%	44.3%
Total positive		41	97	50	188
Prevalence		24.1%	31%	41%	31.1%

Table 2. Results of follow-up urine and stool examinations.

Village	No. treated	Follow-up examinations								
		One month			Three months			Six months		
		No followed	No. cured	% cured	No followed	No. cured	% cured	No followed	No. Cured	% cured
Hilat Daoud	59	48	43	89.6	36	33	91.6	29	29	100
Branco	50	38	35	92.1	35	32	91.4	36	33	91.7
Hamad Alla	29	21	19	90.5	17	10	58.8	13	9	69.2

Discussion

This study revealed that the prevalence of schistosomiasis in pre-school children from the three selected villages was high (31.1%), comparable to that observed among school children aged ≥ 6 years (32%) in the 26 primary schools surveyed (n=1,427). The findings are consistent with emerging evidence that the burden of schistosomiasis is high in pre-school children²¹. In Ghana, a study investigating the extent of schistosomiasis in pre-school children and infants found prevalence of 11.2% for *S. haematobium*, with the highest egg count detected in a 4-month old infant²⁸. In a rural endemic area in Nigeria, prevalence of 58.1% was reported for *S. haematobium* in children aged 1-6 years²⁹, whereas in Niger, rates of the infection among infants and their mothers were 61% and 72%, respectively³⁰. Similar findings have emerged from Mali where prevalence of *S. haematobium* among pre-school children aged 1-4 years was found to be 51.2%³¹. In Uganda nearly 50% of children less than three years of age living along the northern shoreline of Lake Victoria had *S. mansoni* infections³². A recent study from the shoreline villages of Lakes Albert and Victoria in Uganda found even higher prevalence of *S. mansoni* (62.3%) in pre-school children³³. In Sudan, an earlier study found high prevalence of schistosome infection (40%) among pre-school children in the Gezira Irrigation Scheme³⁴. The common feature associated with infection in these children from the various settings is that the children and their caregivers (parents or

guardians) have high levels of water contact and thus intense exposure to the infective parasite.

The implications of these findings are serious in the sense that since the advent of safe and efficacious drugs that shifted the focus of schistosomiasis control to individual or population-based chemotherapy, pre-school children have been excluded from such interventions mainly due to paucity of data to document the safety of praziquantel in this age group⁴. Other reasons for excluding pre-school children from population chemotherapy programs include the following: these children cannot swallow praziquantel tablets and when the tablets are broken or crushed they reject it mainly because of the bitter taste; syrup formulations are not readily available; and the WHO recommended dose-pole for determining dose of praziquantel applied in control programs only works for children of height $>94\text{cm}$ ²⁰. Therefore, the suggestion was that pre-school children and infants should seek treatment in the regular health service or clinics. These facilities on the other hand deal with symptomatic cases and only the children presenting with symptoms would obtain treatment, which also is dependent on whether their parents or guardians would send them to health facilities at all. It means that even if a child has heavy worm burden but does not show symptoms, he/she is unlikely to receive treatment. However, without early treatment, schistosomiasis in children often leads to serious health consequences including nutritional deficiencies,

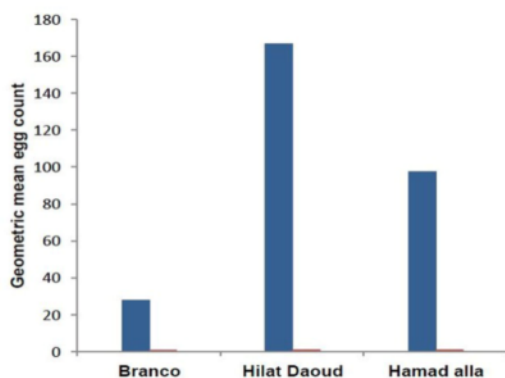


Fig.1. Geometric means of egg counts in Hilat Daoud, Branco and Hamad Alla before and one month after treatment

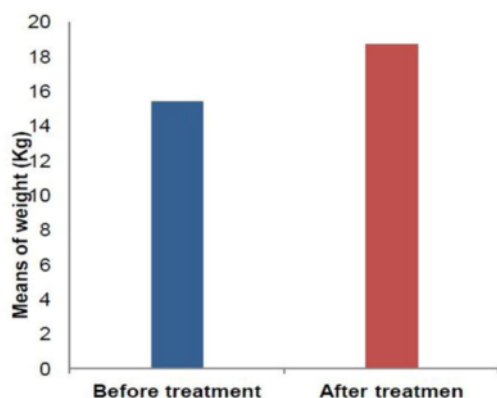


Fig.2. Means of weight in Hilat Daoud before and one month after treatment.

retarded growth, reduced physical activity, and impaired cognitive function^{35,4}. Another concern is that schistosomiasis is associated with rural dwelling^{36,37} and in such settings the peripheral health facilities where parents would send their children for treatment for schistosomiasis are mostly not available or nonfunctional. Even if available, these peripheral health facilities are faced with difficulties from lack diagnostic capacity and availability of praziquantel making it less likely for infected children to obtain the much needed intervention^{38,39}. Also, whereas population-based schistosomiasis chemotherapy interventions delivered through vertical programs are free of charge⁴⁰, visiting regular health care facilities is not free and the money charged may deter parents and guardians from seeking treatment from these facilities. Perceived seriousness of

schistosomiasis-related symptoms which is usually underestimated at the community level may decrease the tendency for obtaining treatment for these vulnerable children⁴¹. Therefore, for some who are unable to seek health care from the regular health facilities, their disease-related morbidity has not been averted raising serious public health concern for leaving pre-school children out of population-based chemotherapy campaign programmes⁴². Results of recent Cochrane systematic review showed that treatment with the standard dose of praziquantel (40 mg/kg) generally results in cure rates of $\geq 80\%$ 1-3 months after treatment⁴³. In this study praziquantel achieved high cure rates of 89.6–91.4% against *S. haematobium* and 90.5% against *S. mansoni* infections 1 month after treatment. Strikingly, cure rate from *S. haematobium* treatment rose to 100% at 6 months but that of *S. mansoni* dropped to 58.8% at 3 months and 69.2% at 6 months. This observation, particularly the former, calls for caution when interpreting these findings as high losses to follow-up were experienced in the study mainly as a consequent of civil disturbances in the study setting at the time of the trial. The drop in cure rate over time for *S. mansoni* infection may be explained by factors such as rapid re-infection rate after treatment, high pretreatment worm load that could not be completely cleared by the treatment that remained in the treated children and started producing eggs, and the presence of high numbers of immature worms less sensitive to praziquantel that escaped drug action and matured to egg producing worms during subsequent follow-ups¹⁸; praziquantel is refractory against immature worms⁴³. The effect of treatment in terms of egg reduction rates ranging from 96.4–99.4% was high and supported by evidence of Cochrane systematic review⁴⁴.

No drug-related adverse events were recorded or reported for the treatment of pre-school children with praziquantel during follow-up visits at 24 hours and 7 days. Possible bias could not be ruled as parents or guardians

reported side-effects on behalf of their preschool children who could not speak for themselves. However, in other studies involving pre-school children, minor and transient side-effects 24 hours after treatment were reported in Uganda³³, in Zimbabwe⁴⁵ and in Mali³¹ in accordance with established evidence that praziquantel is associated with minor and transient adverse events^{46,47}.

Conclusions and recommendations

The results of this study shows that chemotherapy with praziquantel against *S. haematobium* and *S. mansoni* in pre-school children aged <6 years is safe, effective and acceptable. Therefore, these young children should be included in the national treatment control programs in order to prevent long-term chronic ill-health or schistosomiasis-related complications later in life. Given the cumbersome nature of dose determination, preparation and administration, it is important for manufacturers to come with smaller or easy to break tablets.

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The authors declare that they have no competing interests.

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