Comparison of praziquantel efficacy at 40 mg/kg and 60 mg/kg in treating *Schistosoma haematobium* infection among schoolchildren in the Ingwavuma area, KwaZulu-Natal, South Africa

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Background. The World Health Organization recommends praziquantel (PZQ) (40 mg/kg body weight) for treating schistosomiasis. However, drug failure has been reported, prompting use of 60 mg/kg, for which results have been inconsistent.

Objectives. To compare the efficacy of PZQ 40 mg/kg and 60 mg/kg in treating schoolchildren infected with *Schistosoma haematobium*.

Methods. The study was conducted during November 2017 - August 2018 in the Ingwavuma area, uMkhanyakude District, KwaZulu-Natal Province, South Africa. Children aged 10 - 15 years were screened for *S. haematobium* using a filtration technique. Infected children were randomly assigned to a dose of PZQ of 40 mg/kg or 60 mg/kg. Side-effects were recorded within 24 hours after treatment using questionnaires and direct observation. Four weeks after treatment, participants were retested for *S. haematobium* infection. Baseline and post-treatment mean egg counts were calculated. Cure rate (CR) and egg reduction rate (ERR) were used to determine PZQ efficacy, while repeated-measures analysis of variance determined the effect of both doses on infection intensity. A χ^2 test was used to determine the association of side-effects with treatment, with a p-value ≤0.05.

Results. Forty-three and 36 children were treated with PZQ 40 mg/kg and 60 mg/kg, respectively. The 40 mg/kg group had a CR of 79.0% and an ERR of 97.2%, and the 60 mg/kg group a CR of 83.0% and an ERR of 98.3%. The effect of dose on infection intensity was not significantly different between the two groups (p>0.05). Abdominal pains, dizziness and fatigue were common among children who received PZQ 40 mg/kg, while headache, dizziness and nausea were common in the 60 mg/kg group.

Conclusions. The efficacy of PZQ at 60 mg/kg was similar to that at 40 mg/kg. A dose >40 mg/kg therefore does not add value in treating *S. haematobium* infection. Transient side-effects (mostly dizziness) were observed more in the 60 mg/kg group than in the 40 mg/kg group. We recommend continued use of 40 mg/kg body weight for treating schistosomiasis.

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The recommended drug for treating schistosomiasis is praziquantel (PZQ) at a dose of 40 mg/kg.[1] While 60 mg/kg has been used in some countries,[2] it has not been adopted for wide use in current schistosomiasis control programmes. In sub-Saharan Africa, which carries 90% of the global burden of schistosomiasis, PZQ has been used in mass drug administration,[3] resulting in a drastic decrease in morbidity and transmission of the disease. High cure rates (CRs) and satisfactory egg reduction rates (ERRs)[4-7] have been achieved in schoolchildren treated for schistosomiasis using a single or repeated dose of PZQ 40 mg/kg.

Although the 40 mg/kg body weight dose of PZQ reduces the schistosomiasis burden, cases of failure/resistance have been reported, prompting the possibility of using repeated doses. It was reported that repeating the standard dose of 40 mg/kg was more efficacious than a single dose,[8] although cases of failure were still observed.[9,10] Use of PZQ at 60 mg/kg body weight has therefore been suggested to prevent failure. Comparisons of the efficacy of PZQ given at the standard dose of 40 mg/kg v. 60 mg/kg as a split dose[11,12] have shown differing outcomes. Moreover, a study that compared the efficacy of a higher dose of PZQ (80 mg/kg) v. 40 mg/kg found no difference between the doses.[13] For *Schistosoma mansoni*, both regimens had similar efficacy, although the 60 mg/kg dose was associated with more side-effects.[11] In contrast, improved efficacy was reported for the 60 mg/kg regimen compared with 40 mg/kg. Factors such the parasite species,[8] parasite stage[14] and intensity of the infection affect PZQ treatment outcomes (CR and ERR). Low CRs have been reported for mixed infections of *S. haematobium* (37 - 93%) and *S. mansoni* (42 - 79%) with PZQ 40 mg/kg.[8] PZQ does not kill immature worms,[15] and this has justified the use of a combination of PZQ with antimalarial drugs with anti-schistosoma properties such as artemether and artesunate to kill immature worms.[15,16] However, the outcomes of these trials have not been conclusive.

Since PZQ is the only drug recommended by the World Health Organization (WHO) for the treatment of schistosomiasis, it is crucial to monitor its efficacy constantly to prevent cases of treatment failure or eventual resistance. In sub-Saharan Africa, where *S. mansoni* and *S. haematobium* are endemic,[17] investigations of the influence of genetic variations on the severity of *S. haematobium* infection reported conflicting results.[18,19]

Objectives

Because of the lack of consensus on the efficacy of PZQ 40 mg/kg and 60 mg/kg in treating *S. haematobium* infection, we investigated the efficacy and evaluated the side-effects of PZQ at doses of 40 mg/kg and 60 mg/kg among schoolchildren in the Ingwavuma area of uMkhanyakude District, KwaZulu-Natal Province, South Africa (SA), where schistosomiasis is endemic.[20]

Methods

Study area

The study was conducted in seven local primary schools from seven villages (Emunywana, Madeya intermediate, Maphindela, Mpolimpolini, Mugedula, Mbadleni and Ziposheni), located in the north-western part of the Ingwavuma area. The study area has a subtropical climate, characterised by erratic rainy and dry seasons, a hot and humid summer from November to February, and a cooler and drier winter from June to August.[21] The area also has limited sources of water, so the population relies on water bodies such as ephemeral rivers and ponds for their daily needs, as described in our previous study.[22] The study area experienced an extended period of drought from 2015 to 2017.[23]

Study design and sampling

A cohort of 10 - 15-year-old schoolchildren was recruited between November 2017 and March 2018 in seven schools (Emunywana, Madeya intermediate, Maphindela, Mpolimpolini, Mugedula, Mbadleni and Ziposheni) in the Ingwavuma area. Schools with a prevalence of *S. haematobium* infection of at least 30% based on our previous study[10] were purposefully selected. The study population for the targeted age group in the schools was 534 after excluding children who had participated in previous surveys. Consent and assent forms were distributed to the 534 children, but only 442 brought signed forms back and hence became eligible to participate in the study. Eligible participants were screened for *S. haematobium* using the urine filtration methods as described by Cheesbrough.[24] The 111 children found to be infected were divided into two groups based on infection intensity: a group with heavy infection and a group with light infection, in accordance with WHO classification.[25] Of the 111 infected children, 87 were treated and constituted our study cohort. Seventy-nine were successfully followed up and were included in the data analysis. Participants in each group were randomly assigned a PZQ dose of either 40 mg/kg (n=43 participants) or 60 mg/kg (n=36). Treatment for the two groups was administered in June 2018 and follow-up screening was done after 28 days (4 weeks). Eight infected children who were absent during the first round of treatment were treated in July during the follow-up and assessed in August 2018. For the assessment of side-effects, only 54 participants responded successfully to the questionnaire. Those who were absent or could not provide urine samples 4 weeks after treatment were not included in the statistical analysis.

Data collection

Parasitology survey (collection of urine samples and processing)

Collection of urine samples for *S. haematobium* screening was done between 10h00 and 14h00, as recommended by the WHO.[25] Children were assigned an identification code by the research team members before being asked to provide a urine sample in a 90 mL plastic container labelled with a code. The containers were placed in a wooden box immediately after collection of the urine sample, and kept away from direct sunlight to avoid hatching of eggs. The urine samples were processed on the day of collection, using the recommended filtration technique.[24] Four weeks after treatment, the children were rescreened for *S. haematobium* infections, based on two urine samples collected on 2 consecutive days. Urine samples were collected and processed using the baseline technique to avoid any confounder effect on the post-treatment outcome.

PZQ treatment and post treatment monitoring

Before the start of the treatment process, a brief explanation about the side-effects of PZQ was given to participants by the research team nurse. Participants were also asked about any recent treatment they had taken. All infected children were weighed using a mechanical scale (786 seca, Germany) to determine weight for calculation of the treatment dose. They were given orange juice and four slices of bread spread with peanut butter before taking the drug. Treatment was administered in accordance with the dose (40 or 60 mg/kg body weight) for each randomised group. Treated children were observed for a minimum of 1 hour before being allowed to leave. Those who vomited after taking the drug were treated on the next visit to the area by the study team. All adverse events were recorded and appropriate care measures were taken. Twenty-four hours after treatment, a questionnaire related to any side-effects that had occurred since the treatment was administered using the KoBoCollect tool.[26]

Statistical analysis

Data were extracted from KoBoCollect[26] into an Excel spreadsheet, version 2016 (Microsoft, USA). Data analysis was done using Stata version 15 (StataCorp, USA). The means of egg counts were calculated at baseline (time 0) and at 4 weeks post treatment (time 1). For the assessment of PZQ efficacy, an average of egg counts for each child based on the urine samples collected on 2 consecutive days was calculated to represent the egg count after treatment (time 1). They were then log-transformed by adding 1 to allow the comparison of egg counts. Infection intensity was defined as 'light' for any number of eggs <50/10 mL of urine and 'heavy' for any number of eggs ≥50/10 mL.[27] Efficacy was defined as an absence of eggs in the urine specimen 4 weeks (28 days) post treatment. To assess the efficacy of PZQ, CR and ERR were used and the following formulae were applied:[28]

$$CR = \frac{\text{Number of negative children after treatment}}{\text{Number of positive children before treatment}} \times 100$$

$$ERR = \left(1 - \frac{\text{Arithmetical mean egg counts per 10 mL of urine after treatment}}{\text{Arithmetical mean egg counts per 10 mL of urine before treatment}}\right) \times 100$$

Repeated-measures analysis of variance was used to determine the effect of both dosage and gender on the change in the intensity of infection between baseline and follow-up (4 weeks post treatment). Descriptive analysis was used to determine side-effects that were most frequent. Cross-tabulation was also done for both regimens and side-effects of PZQ. The χ^2 test was used to determine the association of side-effects with the treatment regimen. A p-value ≤0.05 was considered significant. Children who were treated but were absent during the assessment of efficacy or did not respond to the questionnaire related to side-effects were excluded from the analysis.

Ethical considerations

Ethical approval was sought and granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ref. no. BE449/15). Gatekeeper permissions were obtained from the KwaZulu-Natal Department of Health, the traditional local leaders and local schools. Assent and consent were sought and obtained from

children and parents, respectively. Urine sample containers were coded for the purpose of confidentiality. All parents whose children were found to be infected were notified before treatment. At the time of writing, some of the participants had not been treated as they had moved from the area or changed schools.

Results

Infection patterns and efficacy of PZQ

Of the cohort of 87 infected children who were treated, 79 were successfully followed up. They provided two urine samples on 2 consecutive days 4 weeks after treatment. Of the 79 participants, 64 (81.0%) (38 female and 26 male) tested negative for *S. haematobium* and 15 (19.0%) (8 female and 7 male) tested positive, as shown in Table 1.

Of the 79 children who participated in the follow-up study, 43 were treated with PZQ 40 mg/kg and 36 received 60 mg/kg. The CR and ERR were 79.0% and 97.2%, respectively, for children who received 40 mg/kg and 83.0% and 98.3%, respectively, for those who received 60 mg/kg (Table 1). The CR and ERR for the PZQ 60 mg/kg dose were slightly higher than for 40 mg/kg, but the difference was not statistically significant. In the children who tested positive for *S. haematobium* 4 weeks after the administration of PZQ, infection intensity was light. The effect of the dose on infection intensity (egg count) showed that there was no significant difference between treatment outcomes for PZQ 40 mg/kg and 60 mg/kg ($p>0.05$).

Side-effects after treatment with PZQ

Of the 79 children who were successfully followed up, 54 responded to questions related to side-effects. Side-effects ranged from headache, dizziness, abdominal cramps, nausea, vomiting, fatigue and sweating to muscle pain, the most frequent being dizziness (n=25; 46%), fatigue (n=20; 37.0%), headache (n=16; 29.6%), nausea (n=12, 22.2%) and abdominal pains (n=11; 20.4%). Based on the PZQ treatment regimen, abdominal pains, dizziness and fatigue were more prevalent among participants who received PZQ 40 mg/kg, while dizziness, headache and nausea were more prevalent among those who received 60 mg/kg (Table 2). Dizziness was the most prevalent side-effect in both groups.

Discussion

We investigated the effect of two doses of PZQ, 40 mg/kg and 60 mg/kg, in schoolchildren. The CR and ERR were higher in the group that received PZQ at a dose of 60 mg/kg body weight than for the group treated with the same drug at 40 mg/kg. Nevertheless, the outcome indicates satisfactory efficacy of PZQ with both doses as per the WHO classification.[28] We did not establish any significant differences in the efficacy of the two doses. Our findings confirm those found in other efficacy studies.[2,11] Moreover, a study that compared higher doses of PZQ (50 mg/kg and 80 mg/kg) found similar results.[13] There are, however, other studies that used similar doses but reported lower cure rates against *S. haematobium*, and minor transient side-effects.[12,29] Efficacy of PZQ has been reported to increase with increased dose.[11] However, in another study testing escalating doses of PZQ (20 mg/kg, 40 mg/kg and 60 mg/kg), CR improved inversely to the dose.[30] A higher CR (85.7%) with PZQ 20 mg/kg than 40 or 60 mg/kg was also reported by Coulibaly *et al.*[30] In line with the above, PZQ 40 mg/kg showed a higher CR than 60 mg/kg.[29] These results may suggest that a high dose of PZQ (60 mg/kg) has no additional benefit in treating schistosomiasis compared with 40 mg/kg. The infection intensity (number of eggs per 10 mL of urine) has been shown to influence treatment outcome. Higher CRs and more satisfactory ERRs have been reported among children with light infection intensity than among those with heavy infection,[31] contrary to what was reported in Uganda, where the CR was independent of infection intensity.[32]

We found that dizziness was the most frequent side-effect among children treated with PZQ 40 mg/kg body weight, followed by abdominal pains/cramps and fatigue. For the 60 mg/kg body weight dose, the most observed side-effects were dizziness and headache, followed by nausea. However, more children treated with 60 mg/kg experienced dizziness compared with those who received 40 mg/kg. Similar observations of side-effects at high doses of PZQ have been made in other studies,[11,33] but their specificity has not been determined. In another study, contrary to our findings, side-effects were not dose dependent.[12]

Conclusions

We found that use of PZQ at a dose of 60 mg/kg did not offer any advantage compared with the standard dose of 40 mg/kg in the treatment of *S. haematobium* infection. Although we observed transient side-effects for both doses, with dizziness being the most common, few severe side-effects were reported in the group treated with 60 mg/kg.

Table 1. CRs and ERRs at PZQ doses of 40 mg/kg and 60 mg/kg in children with *Schistosoma haematobium* infection

	Gender, *n*					
PZQ regimen	Female	Male	Treated children, *n*	Cured children, *n*	CR, %	ERR, %
40 mg/kg	25	18	43	34	79.0	97.2
60 mg/kg	12	15	36	30	83.0	98.3

CR = cure rate; ERR = egg reduction rate; PZQ = praziquantel.

Table 2. Post-treatment side-effects related to PZQ 40 mg/kg and 60 mg/kg

	Participants, *n*			
Side-effects	PZQ 40 mg/kg (N=43)	PZQ 60 mg/kg (N=36)	χ^2	p-value
Headache	6	10	2.783	0.249
Dizziness	9	16	5.029	0.081
Fatigue	7	13	3.027	0.112
Abdominal pains	8	3	4.227	0.121
Nausea	4	8	3.078	0.215

We therefore recommend that PZQ at the standard dose should be used for treatment of *S. haematobium* infection, as recommended by the WHO.[28] However, efficacy should be monitored continually for early detection of possible resistance of *S. haematobium* to PZQ.

Declaration. None.

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Author contributions. MK, MJC and SM conceptualised the study. MK participated in the data collection and data analysis, and drafted the manuscript. MJC and SM participated in the conceptualisation of the manuscript and provided critical comments until final approval of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest. None.

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