



Full Length Research Paper

Comparative Cure Rates of Artesunate-Praziquantel Combination and Praziquantel Monotherapy in the Control of Urinary Schistosomiasis among ‘Almajiri’ School Children in Sokoto, Nigeria

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Abstract

Schistosomiasis is the third most devastating tropical disease in the world and about the most important of all water impounding diseases in the tropics. In the absence of vaccine for preventing the disease and the widely reported therapeutic failure with praziquantel monotherapy, identification of drug combinations with high therapeutic efficacy is crucial to protecting vulnerable populations such as ‘Almajiri’ children from the scourge of the disease. A randomized control trial was carried out in February and March 2014 to compare the cure rates of artesunate - praziquantel combination and praziquantel monotherapy among 70 children diagnosed with urinary schistosomiasis at the ‘Almajiri’ Integrated Model School, Sokoto, Nigeria. Urine samples were collected from the children and examined for ova of *Schistosoma haematobium* (microscopically by sedimentation technique) one month after drug administration. Mean age of participants was 11.9 ± 2.6 years. A significantly higher cure rate was recorded among the group on artesunate - praziquantel combination (85.7%) compared to the group on praziquantel monotherapy (51.4%), $\chi^2 = 29.109$, $p = 0.004$. Participants on artesunate - praziquantel combination were 5 times more likely to be cured than those on praziquantel monotherapy (Odds ratio (OR) = 5.426, $p = 0.002$, 95% Confidence Interval (CI) = 2.697 – 9.349). These findings underscore the need to adopt artesunate - praziquantel combination as the standard treatment for urinary schistosomiasis (instead of the currently used praziquantel monotherapy) particularly in populations at risk of repeated exposure to infected water, for prompt and effective treatment of those infected, and morbidity reduction in both the individual patients and the community.

Keywords: Comparative cure rates, artesunate, praziquantel, combination, monotherapy, urinary schistosomiasis.

INTRODUCTION

Schistosomiasis is the third most devastating tropical disease in the world and about the most important of all water impounding diseases in the tropics. Seven hundred and seventy nine million people in 76 tropical and sub-tropical countries are at risk of the disease. More than 200 million people are already infected globally (of whom about 85% live in sub-Sahara Africa, with annual mortality of 280,000), about 20 million people have

developed its sequelae, and about 120 million people are symptomatic (WHO, 2010).

Individuals become infected with schistosomiasis through contact with water contaminated with schistosome parasites while bathing, swimming, or performing daily chores (such as washing laundry, fetching water and herding animals). The deplorable water and sanitation patterns, and unhygienic water use

(including bathing or swimming in water containing larva form of the parasites) are believed to be key elements in the high risk of schistosomiasis infection in the tropical countries, particularly among children who suffer from both acute side-effects of the disease (such as anemia, malnutrition, learning difficulties, etc.), and other long term complications (such as bladder cancer, damage to intestines and liver, infertility, etc.) when they grow up and become adults (USAID, 2016).

Similar to the situation across Nigeria and other tropical countries endemic for the disease, previous studies in Sokoto (the study area) reported high prevalence of the disease ranging from 37.7% in Wurno (Bello et al., 2014), 38.3% in Wamakko (Kabir et al., 2013), 52.1% in villages around the Goronyo Dam (Bello et al., 2003) to 60.8% in riverine areas of Sokoto metropolis (Singh and Mudashiru, 2014).

Conspicuously, the pattern of disease at the Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria, showed high incidence of complications of schistosomiasis pari passu with the high prevalence of the disease in Sokoto. Of all cancers seen at UDUTH between January 1999 and December 2004, bladder cancer was the most common among men (15.7%), closely followed by prostate cancer with an incidence of 9.9% (Malami et al., 2007). Also, majority, 107 (80.5%) of the 133 cases of bladder cancer seen at UDUTH between January 1999 and December 2004 were farmers and fishermen from regions of the distribution of surrounding river or their small tributaries. About 65.1% of histologically verified cases were squamous cell carcinoma; of these, 50% show histological evidence of urinary schistosomiasis (Mungadi and Malami, 2007). Another study reported associated *Schistosoma haematobium* in 4.44% of cases of appendicitis seen at UDUTH between January 1997 and December 2002 (Mungadi et al., 2004). The burden of the disease and its complications in Sokoto, Nigeria, is evidently too high to ignore and a major public health challenge.

In the absence of vaccines for preventing the disease, control of schistosomiasis essentially relies on a combination of large scale treatment of at-risk population groups (preventive chemotherapy), access to safe water, improved sanitation, hygiene education and snail control. Perhaps cognizant of the prevalent inaccessibility to safe drinking water and basic sanitation particularly in many tropical countries endemic for the disease, the World Health Organization (WHO) strategy for schistosomiasis control focuses on morbidity control (reducing disease) through periodic targeted large-scale treatment (preventive chemotherapy) with praziquantel. (WHO, 2016a).

The target populations include school age children, adults considered to be special risk groups such as pregnant and lactating mothers, groups with occupation involving contact with infested water (fishermen, farmers,

irrigation workers, or women in their domestic tasks), or entire communities living in endemic areas (WHO, 2016b).

Although praziquantel monotherapy provides effective and safe single dose treatment with few side effects, thus making it ideal for use at the community level (WHO, 2016), the ineffectiveness of the drug against juvenile schistosome in early phase of infection (Katzung, 2012), and the high therapeutic failure rates reported in several studies from Kenya (Melman et al., 2009), Egypt (Botros et al., 2005), Brazil (Silva et al., 2005), Spain (Alonso et al., 2006), and United Kingdom (Lawn et al., 2002) among others, remain serious threats and called for its combined use with other anti-schistosomal agents.

Reports from several studies indicated significantly higher therapeutic efficacy with a combination of artesunate and praziquantel compared to praziquantel monotherapy in the treatment of schistosomiasis. A study conducted among 300 school children in Gabon reported 81% cure rate in the group on artesunate - praziquantel combination compared to 73% in the group on praziquantel plus placebo (Bormann et al., 2001). Another study by Clercq et al (2000) also reported significantly higher cure rate in the group on artesunate - praziquantel combination at 5 weeks post treatment compared to the groups on either praziquantel or artesunate monotherapy. The higher therapeutic efficacy with combination of the two drugs compared to monotherapy of either of the drugs is believed to be due to the fact that both drugs display broad-spectrum anti-schistosomal activities and act against different parasite stages; hence, the synergy in action as the combination covers all the stages of the parasite in its vertebrate host.

Almajirai (singular: Almajiri) is a Hausa word meaning immigrant children in search of Quranic education. In Nigeria, Almajirai are usually between the ages of seven and fifteen and mostly found in the Northern states of Nigeria. Almajiri children are known for roaming the streets, farm lands, waste dumping sites and swimming in dirty and contaminated water; they are therefore particularly at risk of urinary schistosomiasis. In view of the myriads of socio-economic and health problems confronting these children (Christian, 2010; Kabir et al, 2005), and the widely reported therapeutic failure with praziquantel monotherapy, identification of drug combinations with high therapeutic efficacy is crucial to protecting this vulnerable population from the scourge of the disease. This study on comparative cure rates of artesunate - praziquantel combination and praziquantel monotherapy in the cure of schistosomiasis among 'Almajiri' school children in Sokoto, Nigeria, was therefore conducted with a view to identifying the most effective treatment for the disease, particularly among this 'at risk' group.

MATERIALS AND METHODS

Study design and population

This was a randomized control trial conducted in February and March 2014 among 70 children diagnosed with urinary schistosomiasis in a cross-sectional survey that was carried out between December 2013 and January 2014 at the 'Almajiri' Integrated Model School, Tudun-Yandogo community, Dange –Shuni Local Government Area, Sokoto state, Nigeria. Most of the pupils were from the 23 Local Government Areas in Sokoto state, while a few came from the neighboring states. They were randomized into two treatment groups (artesanate – praziquantel combination group and praziquantel monotherapy group) using a computer based random numbers generation program; there were 35 study participants in each group. A proforma was used to obtain information on participants socio-demographic characteristics, treatment group and results of urine sample analysis. The identification numbers issued to the participants were also entered into the proforma.

Intervention (drug administration)

The intervention consists of oral administration of combination of artesunate (4mg/kg/day over 3 days) and praziquantel (40mg/kg once) to the first group; and praziquantel monotherapy (40mg/kg once) to the second group. The children's weight was measured with shoes off to the nearest 0.5kg using Seca optimal scale; it was validated with a standard weight and corrected for zero error. The drugs were administered to the study participants under direct observation to ascertain compliance. The children were monitored for development of side effects after the respective treatment regimens.

Post intervention urine sample collection and analysis

The post intervention urine sample collection and analysis was done 4 weeks after the drug administration. Terminal urine samples were collected between 10:00 and 14:00 hours, being the time of maximal egg output (Cheesbrough, 2005), into wide-mouthed, dry, sterile, clean bottles containing few drops of household bleach (as preservative), covered tightly and transported to the main microbiology laboratory of the Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria for analysis. The sample bottles were labelled using the identification number issued to the participants. The urine samples were examined for ova of *S. haematobium* (microscopically using standard sedimentation technique as described by Cheesbrough, 2005). Three laboratory technologists were recruited to assist in urine sample

collection after training them on the objectives and conduct of the study.

Data analysis

Data entry, processing and statistical analysis were done using IBM SPSS version 20 computer statistical software package after data cleansing. The cure rates in the two groups were expressed in percentages. The Chi-square and Fisher's exact tests were used for bivariate analysis involving categorical variables. Logistic regression analysis was used to predict the likelihood of cure in one group compared to the other. All levels of significance were set at $p < 0.05$.

Ethical consideration

Institutional ethical clearance was obtained from the Ethical Committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria. Permission to conduct the study was granted by the Sokoto state Ministry of Religious Affairs. The Principal of the school signed the parental informed consent on behalf of the children (and they also accented to participate in the study).

RESULTS

The age of the 70 children with urinary schistosomiasis that were enrolled into the study ranged from 6 to 18 years (Mean = 11.9 ± 2.6). Majority of participants were in the 10 to 14 years age category in both the artesunate - praziquantel combination group (74.3%) and the praziquantel monotherapy group (77.1%), and there was no significant difference in the age distribution of the participants in both groups (Fisher's exact $\chi^2 = 1.653$, $p = 0.516$) as shown in Table 1.

Cure rates of artesunate - praziquantel combination and praziquantel monotherapy

Table 2 shows the results of the cure rates of artesunate - praziquantel combination and praziquantel monotherapy. At 4 weeks after the drug administration, 30 (85.7%) of the 35 participants in the artesunate - praziquantel combination group had no ova of *S. haematobium* in their urine (cured) compared to 18 (51.4%) of the 35 participants in the praziquantel monotherapy group. The difference in the cure rates between the two groups was statistically significant ($\chi^2 = 29.109$, $p = 0.004$). In logistic regression analysis, participants on artesunate - praziquantel combination were 5 times more likely to be cured than those on praziquantel monotherapy (Odds ratio (OR) = 5.426, $p = 0.002$, 95% Confidence Interval (CI) = 2.697 – 9.349).

Table 1. Age distribution of study participants

Age categories (in years)	Artesunate - praziquantel combination group (n = 35) Number (%)	Praziquantel monotherapy group (n = 35) Number (%)	Test of significance
5 – 9	5 (14.3)	2 (28.6)	Fisher's exact $\chi^2 = 1.653$, p = 0.516
10 – 14	26 (74.3)	27 (77.1)	
15 – 19	4 (11.4)	6 (17.1)	

Table 2. Cure rates of artesunate - praziquantel combination and praziquantel monotherapy

Presence of ova of <i>S. haematobium</i> in urine	Artesunate - praziquantel combination group (n = 35) Number (%)	Praziquantel monotherapy group (n = 35) Number (%)	Test of significance
No (cured)	30 (85.7)	18 (51.4)	$\chi^2 = 29.109$, p = 0.004
Yes (not cured)	5 (14.3)	17 (48.6)	

The treatment regimens were well tolerated by the children, no side effect was reported.

DISCUSSION

A significantly higher cure rate was observed among the participants on artesunate - praziquantel combination (85.7%) compared to those on praziquantel monotherapy (51.4%) in this study. This is in agreement with the findings in a study by Bormann et al (2001) that reported 81% cure rate among participants on artesunate plus praziquantel compared to 73% cure rate among those on praziquantel plus placebo. Similar to the findings in this study, Inyang-Etoh and colleagues (2009) also reported a cure rate of 88.6% among participants on artesunate plus praziquantel compared to 72.7% among participants on praziquantel plus placebo. This could be due to a synergistic effect of two drug combination with different modes of action compared to a single drug therapy.

While the low cure rate (51.4%) observed among the participants on praziquantel monotherapy in this study differ from the findings in a study among preschool children by Coulibaly et al., (2012) that reported a high cure rate of 88.9%, it compares well with the findings in a study by Tchuente et al., (2004) that reported a low cure rate (of less than 50%) at 3 weeks post treatment. However, whereas the cure rate was low at 3 weeks post treatment, a high cure rate of 83% was reported at 9 weeks post treatment, and there was no significant difference in the cure rates or intensity of infection between the cohort that had a single dose of praziquantel, and cohorts who had two or three treatments with praziquantel at three weeks interval after the initial treatment (Tchuente et al., 2004). This could be due to the ineffectiveness of the drug against juvenile schistosome in early phase of infection (Katzung, 2012),

but since the drug is long acting, as the parasites mature, they are eventually killed. The findings in this study corroborate the submissions of Liu et al., (2011) that, while praziquantel monotherapy remains effective in schistosomiasis treatment, combination of artesunate and praziquantel perform better in treatment than praziquantel monotherapy, and they are especially suitable for treating patients with repeated exposure to infected water (similar to what obtains among the participants in this study).

CONCLUSION

This study demonstrated a significantly higher therapeutic efficacy with artesunate - praziquantel combination compared to praziquantel monotherapy among the study participants, and participants on artesunate - praziquantel combination were 5 times more likely to be cured compared to those on praziquantel monotherapy. These findings underscore the need to adopt artesunate - praziquantel combination as the standard treatment for urinary schistosomiasis (instead of the currently used praziquantel monotherapy) particularly in populations at risk of repeated exposure to infected water, for prompt and effective treatment of those infected, and morbidity reduction in both the individual patients and the community.

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