Efficacy of a single oral dose artesunate plus sulfalene/pyrimethamine versus praziquantel in the treatment of *Schistosoma mansoni* in Kenyan children: randomised, exploratory, open-label trial

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Research

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Abstract

Background: The global control strategy for schistosomiasis is the periodic administration of praziquantel. Schistosomes have developed reduced susceptibility to praziquantel. Artemisinin-based drug combinations are promising alternatives to praziquantel, but it is unclear whether a single dose of an artemisinin-based drug combination is as effective and safe as praziquantel. We assessed the efficacy and safety of a single oral dose of artesunate plus sulfalene/pyrimethamine in the treatment of schistosomiasis.

Methods: An exploratory, open-label randomized trial, was carried out in Rarieda sub-County, western Kenya to compare the efficacy of a single oral dose of artesunate plus sulfalene/pyrimethamine (12mg/kg of artesunate) to a standard single dose of praziquantel (40mg/kg) in the treatment of school children (aged 6 to 15 years) with *S. mansoni* infection.

The primary outcomes were cure and egg reduction rates on day 28 after treatment in the per-protocol population.

Results: A total of 73 *S. mansoni* infected children were included and randomized to receive either artesunate plus sulfalene/pyrimethamine (n=39) or praziquantel (n=34). 67 children completed the study. The cure rate was 69.4% (25/36) in the artesunate plus sulfalene/pyrimethamine group and 80.6% (25/31) in the praziquantel group (p=0.294). Egg reduction rates were 96.2% in the artesunate plus sulfalene/pyrimethamine group and 82.9% in the praziquantel group (p=0.339). Ten children treated with praziquantel developed adverse events compared with four in the artesunate plus sulfalene/pyrimethamine group. There was no serious adverse event.

Conclusion: A single oral dose of artesunate plus sulfalene/pyrimethamine was safe and as efficacious as praziquantel in the treatment of *S. mansoni* in Kenyan children. These results should be confirmed in larger randomized controlled trials. Combination treatment with praziquantel plus artemisinin-based combination therapies may be a potential alternative for improving praziquantel efficacy and transmission control.

Trial Registration: ClinicalTrials.gov, number NCT01054651.

Introduction

Human schistosomiasis is a chronic water-related parasitic disease that infects over 230 million people, globally, with a loss of 4.5 million disability-adjusted life-years, annually [1]. About 85% of people infected with schistosomiasis reside in sub-Saharan Africa, where *Schistosoma mansoni* and *S. haematobium* are endemic and the highest prevalence is in school-age children (5–16 years) [2]. The main global control strategy for schistosomiasis is a preventive treatment, using praziquantel [3]. However, reliance on a single drug for community-wide preventive treatment in endemic areas is likely to increase the risk of emergence of drug resistance or parasite tolerance [4–6]. Praziquantel is widely deployed because it is

effective against all the schistosome species that infect man, is administered as a single oral dose, and is relatively safe [7]. However, praziquantel is only effective against adult schistosome worms, is ineffective against the juvenile stages (schistosomula), is not 100% curative, and does not prevent re-infection. Schistosomes have developed reduced susceptibility to praziquantel, usually manifesting as low rates of cure and egg reduction rates [8, 9]. To achieve the global goal of schistosomiasis elimination, alternatives to praziquantel targeting all developmental stages of the parasite are required. This highlights the urgent need for research into the development or evaluation of new antischistosomal drugs. Currently, the drug development pipeline for schistosomiasis is almost empty [10]. In these circumstances, drug re-purposing may overcome the obstacles of cost and time needed to develop new drugs, by exploring new indications for available compounds used in the treatment of other conditions [11, 12]. Alternatives to praziquantel are scarce but include antimalarials, such as artemisinin-based drug combinations (ACTs) or mefloquine [13].

Artemisinin-based drug combinations (ACTs), are currently the most potent drugs for treating malaria but have demonstrated antischistosomal activities in animals and man [14]. World Health Organization (WHO) has recommended five ACTs for the treatment of malaria, including artemether-lumefantrine, artesunate plus mefloquine, artesunate plus amodiaquine, artesunate plus sulfadoxine/pyrimethamine and dihydroartemisinin-piperaquine [15]. Unlike praziquantel, artemisinin derivatives (artesunate, artemether) are effective against schistosomula [16]. The efficacy of ACTs has been evaluated in comparison to praziquantel in the treatment of schistosomiasis [17–20]. In these evaluations, ACTs were administered at a dosage of 4 mg/kg/day of artesunate over three days, the same dosage used for treating malaria. At this dosage, the efficacy of ACTs was significantly lower than that of praziquantel, in the treatment of schistosomiasis [21]. The efficacy of a single high dose of artesunate plus sulfalene/pyrimethamine (12 mg/kg/day of the artesunate component) was compared to 40 mg/kg of praziquantel for the treatment of *S. haematobium*, in Malian children. The cure rate was still significantly lower than praziquantel, 43.9% vs 54%, respectively [22]. There is no published study investigating whether a single oral dose of any of the ACTs is as effective and as safe as praziquantel in the treatment of *S. mansoni.*

Combination therapy using praziquantel plus ACTs has been suggested as a promising strategy to improve praziquantel efficacy, to interrupt the transmission of schistosomiasis infection and to accelerate the goal of schistosomiasis elimination [21]. The success of such combination therapy will depend on the synergistic activity of the components. Artemisinin derivatives are effective against juvenile stages of the schistosome while praziquantel is effective against the adult schistosome worms. Concurrent administration of combination therapy (praziquantel plus ACT) would be challenged by the timing of the doses. Currently, praziquantel is administered as a single oral dose, while for the treatment of malaria, ACTs are administered over three days.

We hypothesize that for treatment of schistosomiasis, ACTs may be more effective when the total artesunate dosage (12 mg/kg) is administered at weekly intervals as single oral doses rather than spread over three days. This study aimed to compare the efficacy and safety of a single oral dose of artesunate

plus sulfalene/pyrimethamine (12 mg/kg of the artesunate) compared to a single standard oral dose of praziquantel (40 mg/kg) in the treatment of school-aged children with *S. mansoni* in western Kenya.

Materials And Methods

Study site and participants

This study was conducted in primary schools located in the Lwanda Kotieno region in Rarieda sub-County, Siaya County, western Kenya. In the study area, more than 96% of the residents belong to the Luo ethnic group, and the majority of the adults are fishermen or small-scale subsistence farmers. Similarly, *S. mansoni* was the most prevalent schistosome species in school children, with a mean school prevalence of 16% (range 0–80%) [23].

School children were included if they were aged 6–15 years, appeared healthy at enrolment (as assessed by the study clinician), able to provide sufficient volume of a stool sample, had *S mansoni* infection (eggs excreted in stool), and could take oral treatment. We excluded children who weighed more than 50 kg, were pregnant or lactating (assessed by self-report), had co-infection with *P falciparum*, had severe illness (such as epilepsy), or had signs of severe malnutrition (MUAC < 11.5 cm). We also excluded children with a history of hypersensitivity to artesunate, sulfonamides or praziquantel, and those who had ingested another antimalarial or antischistosomal drug in 72hours before the study.

Study Design, Randomization, And Blinding

We conducted an exploratory open-label, randomized, controlled trial to evaluate the efficacy and safety of a single oral dose of artesunate plus sulfalene/pyrimethamine compared with a single oral dose of praziquantel in the treatment of children with *S. mansoni* in western Kenya. The randomization sequence was computer-generated by the study statistician. Eligible children were randomly assigned (1:1) to receive either artesunate plus sulfalene/pyrimethamine or praziquantel. The study nurse administered all the study medications after confirming the treatment allocation from the randomization sequence. The study nurse and study participants were aware of treatment assignment, but the laboratory technicians assessing study outcomes were masked to treatment assignment throughout the study.

Study Procedures

For screening, every child provided a fresh stool sample (about 5 g), which was used to detect the presence of *S. mansoni*, hookworms, *Ascaris lumbricoides*, and *Trichuris trichiura*. Children whose stools tested positive for *S. mansoni* eggs and who met all eligibility criteria were invited to participate in the study.

At enrolment, the study clinician took a standard baseline medical history and performed a clinical examination. Eligible children were sequentially assigned the next lowest study number, corresponding to the randomization list. Children who were assigned praziquantel (Biltricide, Bayer Healthcare, Leverkusen, Germany) received one dose of 40 mg/kg per day to the nearest half tablet (tablets of 600 mg). Children

who were assigned artesunate plus sulfalene/pyrimethamine (Co-Arinate Junior FDC [fixed-dose combination], Dafra Pharma, Turnhout, Belgium) received a single oral dose of 12 mg/kg per day to the nearest half tablet. Artesunate plus sulfalene/pyrimethamine is a fixed-dose combination of 100 mg artesunate with 250 mg sulfalene plus 12·5 mg pyrimethamine, packaged as three tablets per packet. All children received slices of bread and a glass of orange juice to improve bioavailability before drug ingestion. Children were observed for 1 h after taking the drug to ensure retention and to check for any immediate adverse events. If vomiting occurred within 1 h of drug ingestion, a second full dose was given. Children with repeated vomiting were withdrawn from the study. Adverse events were assessed on day 0 and day 1. If any children developed adverse events, they were followed up until the event resolved. Children with geo-helminthic infections were treated with 400 mg albendazole.

All the children were followed up for 28 days after treatment. At the follow-up visit on day 28 (range 26–30), children provided an early morning stool sample, and the study clinician took a medical history and performed a clinical examination. Participants who did not return for the scheduled follow-up visit were visited at home. Children who were not cured at the end of the study were treated using praziquantel.

Laboratory Procedures

Duplicate slides were prepared from stool samples using the Kato-Katz faecal thick-smear technique with a template containing about 41·7 mg of faeces when filled. The *S. mansoni* eggs were examined under a microscope independently counted by two experienced laboratory technicians. The mean number of *S. mansoni* eggs counted was multiplied by 24 to compute the eggs per gram (epg) of faeces. The intensity of infection was categorized based on the WHO classification as light (1–99 epg), moderate (100–399 epg), or heavy (≥ 400 epg) [24]. As a quality control measure to minimise interobserver variability, a third technician reread a random sample of 10% of slides and all slides for which the readings varied by more than 20% between the two technicians.

Statistical analysis

This exploratory study was designed to evaluate the feasibility of a novel treatment. WHO recommends the following formula for computing sample size in studies assessing the efficacy of anthelminthic drugs: N = 50/(0.8 X prevalence) [25]. Using a prevalence of 86% from our study at the same site [18], we calculated that we needed 73 children for this exploratory study. Data collected from participants were recorded on paper-based case report forms, entered into computers by use of Epi Info (version 3.2.2), and analyzed with SPSS for Windows (version 21.0).

The primary outcome was the proportion of participants cured between enrolment and day 28. The cure was defined as the proportion of children infected with *S. mansoni* at enrolment who were not excreting eggs on day 28 after treatment. Cure rates were compared between treatment groups by use of the Pearson χ^2 test for contingency tables and were summarised as risk difference (RD) with 95% CIs. In all comparisons, the praziquantel arm served as the control group. Secondary outcomes included the proportion of participants excreting *S. mansoni* eggs (egg reduction rate), the egg load (infection

intensity), and the incidence of adverse events in each treatment group. The egg reduction rate (ERR) was defined as the proportionate reduction of the geometric mean [GM] egg count among *S. mansoni* positive children after treatment, computed as:

$$\left(1 - \left[\frac{geometric\ mean\ egg\ count\ after\ treatment}{geometric\ mean\ egg\ count\ at\ enrollment}\right]\right) * 100$$

Changes in continuous variables between day 0 and day 28 were examined with student's *t*-test. Safety outcomes (adverse events) were analyzed for all participants who received at least one dose of the study drug regardless of whether they completed the study or not. Two-sided p values of less than 0·05 were regarded as statistically significant.

Results

The study was carried out between October and November 2010. A total of 100 school children were screened for eligibility, and 73 were enrolled and randomized to receive a single dose of artesunate plus sulfalene/pyrimethamine (n = 39) or a single dose of praziquantel (n = 34). The demographic and clinical baseline characteristics of the participants are summarized in Table 1. Treatment groups were balanced in terms of gender, age, and body weight.

Table 1
Baseline characteristics

Variable	Praziquantel	Artesunate plus sulfalene/pyrimethamine
Number enrolled	34	39
Male, N (%)	15 (44%)	19 (49%)
Mean Age (years) [SD]	11.4 [1.07]	11.4 [1.14]
Mean body weight [Kg] (SD)	34.8 (6.7)	34.4 (6.4)
Median body weight [Kg] (range)	34 (23 to 49)	33 (24 to 47)
Geometric mean egg count (95% CI)	272.8 (162.9 to 456.8)	529.6 (351.3 to 798.6)
S. mansoni intensity		
Light (1 to99 epg)	8 (23.5%)	4 (10.3%)
Moderate (100 to 399epg)	13 (38.2%)	9 (23.1%)
Heavy (≥ 400epg)	13 (38.2%)	26 (66.7%)

However, a higher proportion of children with heavy *S. mansoni* infection were randomized to the artesunate plus sulfalene/pyrimethamine arm compared to the praziquantel arm (66.7% [26/39] vs 38.2% [13/34], p = 0.015). This was reflected in a significantly higher geometric mean egg count at enrolment in the artesunate plus sulfalene/pyrimethamine arm compared to the praziquantel group (529.6 [95%CI 351.3 to 798.6] vs. 272.8 [95%CI 162.9 to 456.8]).

During follow up six children were excluded (3 were lost to follow-up in each treatment group). The treatment outcomes were known for 67 children (92%), whom we included in the per-protocol analysis: 31 (91.2%) in the praziquantel group and 36 (92.3%) in the artesunate plus sulfalene/pyrimethamine group (92.3%). The study flow diagram is shown in Fig. 1.

On day 28, the cure rate was 69.4% (25/36) in the artesunate plus sulfalene/pyrimethamine arm and 80.6% (25/31) in the praziquantel arm (see Table 2**)**. This means that the cure rate with artesunate plus sulfalene/pyrimethamine was 11.2% (95%CI -9.3–31.7%, χ^2 = 1.10, p = 0.294) lower compared to praziquantel group.

Table 2
Cure and egg reduction rates

	Praziquantel	**Artesunate plus sulfalene/pyrimethamine**	**P-value**
Number	31	36	
Overall cure [%] (95%CI)	25/31 [80.6%] (67.6–93.5%)	25/36 [69.4%] (54.3–84.5%)	0.294
Cure by initial *S. mansoni* intensity [%]			
Light	6/7 [85.7%]	2/3 [66.7%]	0.490
Moderate	9/11 [81.8%]	8/8 [100%]	0.202
Heavy	10/13 [76.9%]	15/25 [60.0%]	0.297
GMEC on day 28 (95% CI)	46.5 (12.74 to 169.6)	20.05 (12.05 to 33.37)	0.393
Egg reduction rate (95%CI)	82.9 (70.2 to 95.6)	96.2 (90.2 to 100)	0.339

A total of six children (4 had a light infection and 2 had a moderate infection) in the praziquantel group and 11 (10 had a light infection and 1 had a moderate infection) in the artesunate plus sulfalene/pyrimethamine group were still excreting eggs of *S. mansoni* on day 28. Pre-treatment, the geometric mean egg count (GMEC) in the praziquantel group was 272.8 epg and 529.6 epg in artesunate plus sulfalene/pyrimethamine group. On day 28 post-treatment the GMEC was 46.5 epg in the

praziquantel group and 20.05 epg in artesunate plus sulfalene/pyrimethamine group. This translates to egg reduction rates of 82.9% in the praziquantel group and 96.2% in the artesunate plus sulfalene/pyrimethamine group (p = 0.339).

The difference in cure rates was not significantly different between the treatment groups when stratified by the initial infection intensity. Over the follow up period the proportion of participants with negative infections increased, while light and moderate infections decreased, and heavy infections were cleared. On day 28, the proportion of participants with light intensity infections were 12.9% and 27.8%, in the praziquantel and artesunate plus sulfalene/pyrimethamine arms, respectively. Similarly, the proportion with moderate intensity infections were 0.5 and 2.8%, in the praziquantel and artesunate plus sulfalene/pyrimethamine arms, respectively. On day 28, heavy intensity infections were completely cleared in both treatment arms.

Table 3 is a summary of the reported adverse events by treatment group and severity. Overall, 14 children developed a total of 30 episodes of adverse events. Of these, 10 children were in the praziquantel group, while 4 were in the artesunate plus sulfalene/pyrimethamine group (p = 0.0387). The risk of developing an adverse event was significantly higher among those who received praziquantel compared to those who received artesunate plus sulfalene/pyrimethamine, 61.8% [21/34] vs. 21.1% [9/39]: risk difference 38.7, 95%CI 15.9 to 59.7, p = 0.0008.

Table 3
Incidence of adverse events and their severity

Adverse event	Severity	Praziquantel	Artesunate plus sulfalene/pyrimethamine
Abdominal pain	Mild	3	2
	Moderate	7	2
Headache	Mild	4	1
	Moderate	1	1
Nausea	Mild	2	0
	Moderate	2	1
Weakness	Mild	0	0
	Moderate	1	1
Skin rashes	Mild	1	0
	Moderate	0	1
TOTAL		**21**	**9**

All the adverse events were either mild (n = 13) or moderate (n = 17). Abdominal pain was the predominant adverse event reported by those who received praziquantel. The incidence of abdominal pain was significantly higher in the praziquantel arm compared to the artesunate plus sulfalene/pyrimethamine arm (29.4 [10/34] vs 10.3 [4/39], p = 0.039). None of the adverse events led to discontinuation of study treatment and there was no serious adverse event.

Discussion

We assessed the effect of a single large oral dose of artesunate plus sulfalene/pyrimethamine compared to a single standard dose of praziquantel in the treatment of Kenyan children with *S. mansoni*. We found that treatment with artesunate plus sulfalene/pyrimethamine was safer but on day 28 after treatment had comparable cure and egg reduction rates to praziquantel. These results suggest that artesunate plus sulfalene/pyrimethamine may be combined with praziquantel and may be administered on the same day or alternate days (due to the tablet load). However, it is not clear how the interaction between the two drugs may impact on safety.

For the treatment of *S. mansoni*, we found a cure rate of 69.4% with artesunate plus sulfalene/pyrimethamine, which was not consistent with 43.9% found when the same drug was used for treating children with *S. haematobium* in Mali [22]. We found egg reduction rate of 96.2% which was comparable to 92.8% found in the Malian study. In two randomized trials, artesunate plus sulfalene/pyrimethamine (according to current malaria treatment regimes) recorded significantly low cure rates compared to praziquantel in the treatment of children infected with *S. mansoni*, 58.7% vs 100% and 14% vs 65%, respectively [17, 18]. These low efficacies were partly explained by the administration of sub-therapeutic levels of artesunate when the total dosage was spread over 3 days. In this study, we investigated the effect of artesunate plus sulfalene/pyrimethamine, as a representative ACT. It is not clear whether any specific ACT is more effective in the treatment of schistosomiasis.

We found cure and egg reduction rates of 80.6% and 82.9%, respectively with praziquantel. This is consistent with a systematic review of praziquantel efficacy, that found a mean cure rate of 76.7% (95%CI 71.9 to 81.2%) and egg reduction rates of 86.3% (95%CI 81 to 91%) when the standard dose of 40 mg/kg bodyweight of praziquantel was used in the treatment of school-aged children with *S. mansoni* [26]. Current WHO guidelines recommend an annual, single dose of praziquantel for at-risk populations in high-risk (baseline prevalence ≥ 50%) endemic areas [3]. In the context of continued exposure to infection in high-risk areas, this treatment regime does not completely clear the infection, and re-infection is common, suggesting that annual large-scale targeted treatment alone is insufficient to reduce the prevalence and intensity of infection and to prevent re-infection in those settings [27, 28]. It is unclear whether more frequent praziquantel administration may be more effective compared with a single annual dose. The current utility of praziquantel is limited by its inactivity against juvenile schistosomes, which mature and start egg production after chemotherapy. A combination of artemisinin with praziquantel would be complementary, and potentially addictive, as it would target the parasite at two life cycle stages, thereby interrupting the transmission of infection.

Disease control programs are likely to be concerned about the safety of administering large single doses of artemisinin-based combination. In our study, safety was assessed by self-report, and a single dose of artesunate plus sulfalene/pyrimethamine appeared safer compared with praziquantel. We did not evaluate the safety of the artesunate plus sulfalene on liver and kidney functions. Participants on the artesunate plus sulfalene/pyrimethamine arm experienced significantly fewer adverse events compared to those on the praziquantel arm. This is consistent with previous studies that found artesunate plus sulfalene/pyrimethamine to be safer than praziquantel [17, 18, 22]. The most common adverse event on the praziquantel arm was abdominal pain, consistent with previous studies [29–31]. Future studies should assess the safety of ACTs in the preventive treatment of schistosomiasis.

A large geographical overlap exists in the endemic areas for schistosomiasis and malaria [32–34]. This may provide an opportunity for the integrated treatment of both parasites. ACTs are the mainstay of malaria control but have antischistosomial activity against schistosomulae and their combination with praziquantel may form a strong integrated preventive intervention for schistosomiasis transmission control. This combination is likely to prevent or delay the development of praziquantel resistance. A confirmation of the additional benefit of this combination therapy may contribute to the development of a potential innovative public health tool for improving child health and schistosomiasis control in endemic regions. However, the use of ACTs for preventive treatment of schistosomiasis raises concerns about safety and the possible selection for drug resistance to malaria. Currently, the use of ACTs should be restricted to the treatment of malaria. However, the risk of selecting for resistant malaria strains is likely to be low in schistosomiasis-malaria co-endemic areas if single curative doses of ACT are used. Combination therapy is likely to benefit patients with both schistosomiasis and malaria infections. Population-based surveillance systems should monitor for any benefits of ACT for schistosomiasis control in schistosomiasis and malaria co-endemic areas.

Our study has some limitations. It is an open-labelled study and was not adequately powered to detect significant differences in efficacy and safety. The duration of the study was short to assess any rare adverse events. This was an exploratory study and we did not assess the biological safety profiles of the investigational medicines.

Conclusions

Despite these limitations, we have shown that a single oral dose of artesunate plus sulfalene/pyrimethamine was safer and had comparable efficacy (measured by cure and egg reduction rates) to a standard dose of praziquantel in the treatment of children with *S. mansoni* infections. However, our results should be confirmed in well-designed larger trials in areas with other schistosome species.

Abbreviations

ACT Artesunate plus sulfalene/pyrimethamine

CI confidence interval

EPG eggs per gram

ERR egg reduction rate

FDC Fixed dose combination

GM Geometric mean

GMEC Geometric mean egg count

MUAC mid-upper arm circumference

RD Risk difference

SD Standard deviation

WHO World Health Organization

Declarations

Ethical approval and consent to participate

The study protocol was approved by the Ethics Review Committee based at the Kenya Medical Research Institute (KEMRI SSC number 1582). The trial described here is part of a larger trial that was registered with ClinicalTrials.gov (NCT01054651). Written informed consent was obtained from parents or legal guardians of potentially eligible children. Oral assent was obtained from children with parasitologically confirmed *S. mansoni* infection. The trial was conducted according to the Declaration of Helsinki and guidelines on Good Clinical Practice.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

CO initiated the idea and wrote the study protocol. CO, EMMO and VW supervised the data collection. CO and VW analyzed and interpreted the data. CO drafted the manuscript. All authors contributed to the writing of the paper and approved the final version.

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Figures

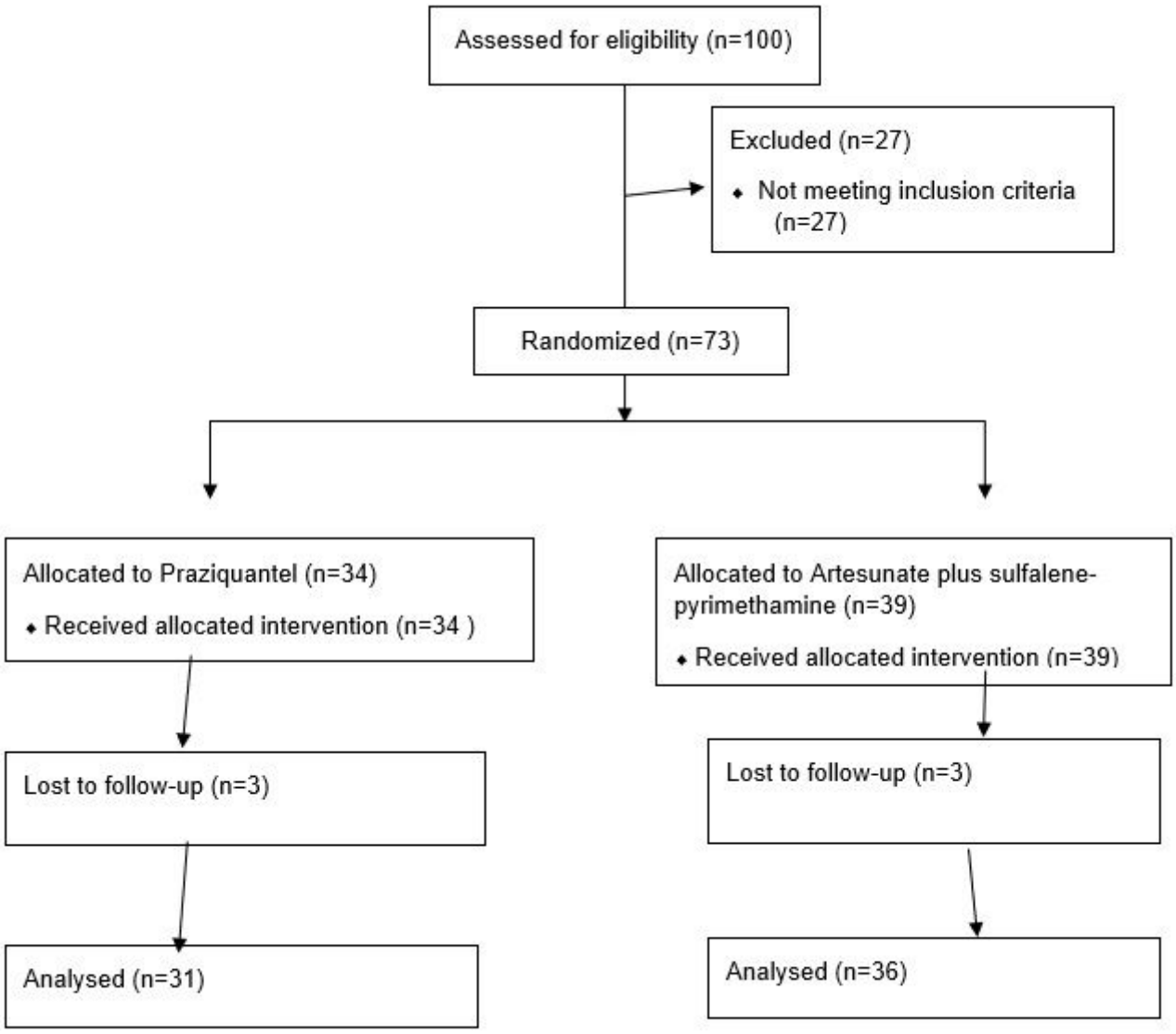

Figure 1

Study Flow chart