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Efficacy and Safety of Different Dosages of Praziquantel for the Treatment of *Schistosoma Japonicum*: A Systematic Review and Meta-Analysis

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Background: Praziquantel, an antischistosomal compound, is used as first-line drug for chemotherapy of Schistosoma japonicum since 1984. In this article, we conducted a systematic review and mete-analysis to evaluate the efficacy and safety of different dosages of praziquantel (PZQ) for treatment of *Schistosoma japonicum*.

Evidence Acquisition: A number of six articles published in peer-reviewed journals before December 2012 were selected for analysis after searching the following literature databases: PubMed/Medline, the Chinese WanFang Literature Database, China National Knowledge Infrastructure (1994-2012.12), and the Chinese Biomedical Literature (1978-2012.12).

Results: The meta-analyses showed that there is no statistically significant difference of the negative rate on the egg using 40 mg/kg compared to 60 mg/kg PZQ for S. japonicum treatment (RR 0.79, 95% CI 0.46 1.35; P < 0.39). The meta-analysis showed that there is no statistically significant difference of the side effects using 30 mg/kg compared with 40 mg/kg (RR 0.97, 95% CI 0.68 1.38; P = 0.87), 40 mg/kg compared with 60 mg/kg (RR 0.79, 95% CI 0.46 1.35; P = 0.39) and 50 mg/kg compared with 60 mg/kg (RR 0.89, 95% CI 0.56 1.42; P = 0.63).

Conclusions: According to the results, there is no statistically significant difference in different doses of PZQ for treating *S. japonicum*.

Keywords:Schistosomiasis Japonicum; Praziquantel; Meta-Analysis

1. Background

Schistosomiasis, an infectious disease caused by parasitic trematodes (schistosomes) dwelling in the host's mesenteric portal system, is a great public health problem in tropical and subtropical regions. The disease causes health and labor loss, and finally a significant reduction in socioeconomic benefits (1, 2). There are five Schistosoma species parasitizing in humans: *Schistosoma japonicum*, *S. mansoni*, *S. haematobium*, *S. mekongi*, and *S. intercalatum*. *S. japonicum* is transmitted by the amphibian snail Oncomelania and causes intestinal and hepatosplenic schistosomiasis in the People's Republic of China, Philippines, and Indonesia; *S. mansoni*, transmitted by Biomphalaria snails, causes intestinal and hepatic schistosomiasis in Africa, the Arabian peninsula, and South America; *S. haematobium*, transmitted by Bulinus snails, causes urinary schistosomiasis in Africa and the Arabian peninsula. *S. mekongi* and *S. intercalatum* are only of local importance (3-7). In the mid-1980s, the World Health Organization (WHO) recommended schistosomiasis control strategies for humans by focusing on the large-scale population-based and repeated chemotherapy, which is still the key strategy today (8). For schistosomiasis treatment, praziquantel (PZQ) has finally become the first-line medicine. Praziquantel proved to be free of major toxicity, and was well tolerated, highly effective, and easy to administer. Confirmation of results in extended trials may soon permit large-scale treatment (9).

In this article, we conducted a systematic review and mete-analysis to evaluate the efficacy and safety of different dosages of praziquantel (PZQ) for treatment of *Schistosoma japonicum*.

2. Evidence Acquisition and Analysis

2.1. Search Strategy and Data Sources

We searched the electronic database of PubMed (1966-2012), the Chinese WanFang Literature Database (1992-2012), China National Knowledge Infrastructure (1994-2012.12), and the Chinese Biomedical Literature (1978-2012.12) for all the randomized controlled trials evaluating the efficacy and the safety of PZQ with different doses for *Schistosoma japonicum* treatment. The Review Manager 5.1 software was used to Meta-analysis and using the Revised Jadad scale to access the quality of these studies. The terms and medical subject headings

(MeSH) used in retrieving citations were "*Schistosoma japonicum**" (*means the inclusion of all words with the preceding radical), "praziquantel". The retrieval formula was: *Schistosoma japonicum** and praziquantel .The searches were performed mainly in Chinese and English with a limitation to human participants.

2.2. Criteria of Inclusion and Exclusion

After training by a standardized evaluation method, literature were evaluated independently, and screened them in accordance with predetermined. Literature is screened independently by two reviewers. At first, we read the title and summary, and read the full text if the contents were related. All the literature was discussed by two evaluators, if different opinion raised, we discussed together or convinced by our tutor. The inclusion criteria were: (i) independent studies assessing the antischistosomal efficacy of different doses of PZQ, for human schistosomiasis treatment and prevention; (ii) the year of the study conducted or published was reported; (iii) the sample size was reported; (iv) the same drugs' efficacy evaluation indicators between experimental populations and control populations, i.e. reporting parasitological outcome eggs-positive or eggs-negative by Kato-Katz thick stool smears technique and/or miracidia hatching tests for detecting eggs of *S. japonicum*, *S. mansoni*, and *S. mekongi* or urine filtration for detecting eggs of *S. haematobium* after approximately 3-4 weeks post-treatment, which was recommended as the standard method for schistosomiasis parasitological diagnosis by WHO in 1980 (8); or reporting emergence or absence of acute schistosomiasis in the trials of assessing some drug's efficacy in controlling morbidity; (v) the studies were either randomized controlled trials (RCTs) or non-randomized control trials (nRCTs); (vi) reports with raw data, which could be changed into relative risk (RR) and 95% CI RR and 95% CI were reported. Exclusion criteria were: (i) study participants were not human; (ii) without control group; (iii) incomplete information; (iv) duplicate publications; (v) studies described only results without detailed background and method introduction; (vi) reviews. Figure 1 summarizes the studies selection process.

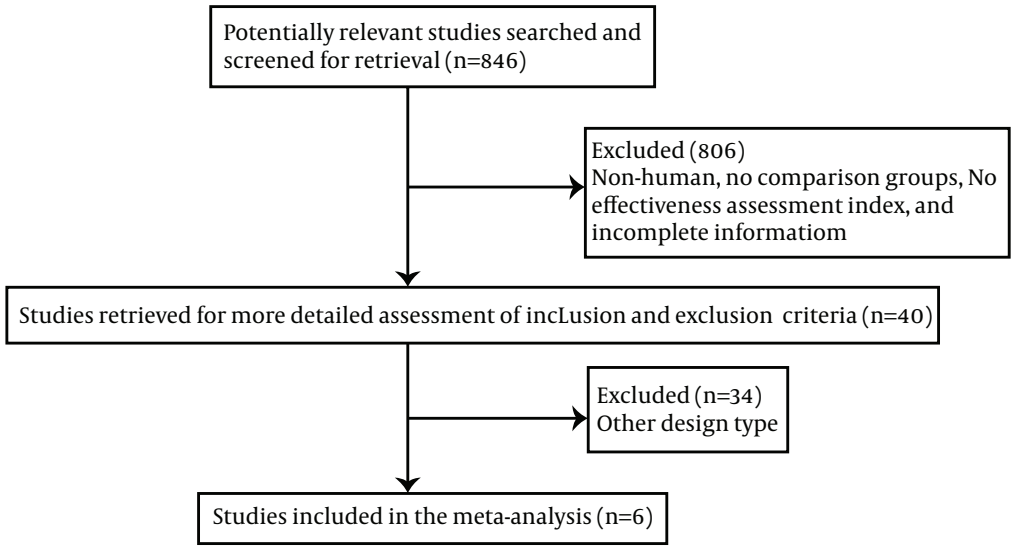

Figure 1. Flow Diagram Showing the Articles Selection Process for Present Meta-Analyses of the Efficacy Doses of Pzq for Human Schistosomiasis Treatment or Prevention

2.3. Data Extraction and Methodological/Quality Assessment

The extracted information included: first author's name and year of publication, test sites (i.e. where trials were implemented), time (i.e. when trials were implemented), participants, *Schistosoma* species, interventions, diagnostics methods, follow-up time, raw dichotomous data of efficacy assessment (NO. of positive/NO. of diagnosed), RRs and their 95% CIs, type of study design (RCT or nRCT), and intervention purposes (prevention or treatment). The quality of included RCTs was assessed by examining whether there is randomization, blinding, and information about follow-up and dropouts/withdrawals of participants according to the guidance of the methodological quality assessment of RCTs in the Cochrane Handbook for Systematic Reviews of Interventions 5.0 and the Jadad scoring criteria (10, 11). The score for quality scale ranges from 0 to 5 points, the higher the score, the higher the quality of trial; and a trial with a Jadad score ≥ 3 has been considered to be of ample quality.

Table 1. Assessment of Methodological Quality of the Included RCTs by Jadad Scoring

Trial	Randomized	Double-Blinded	A Description of Withdrawals or Dropouts	Jadad Score [a]
Santos et al. 1979 (9)	1	2	1	4
Ishizaki et al. 1979 (12)	1	2	0	3
Chen et al. 1985 (13)	1	1	0	2
Wang et al. 1999 (14)	1	0	0	1
Wu, 2001 (15)	1	0	0	1
Li, 2011(16)	2	0	0	2

[a] Range 0-5 (the higher the Jadad Score is, the higher the quality of the study is).

2.4. Diseases, Interventions and Outcomes

Six articles of *Schistosoma japonica* were included in this meta-analysis. The participants of experimental groups took different doses of PZQ for treatment. The chemotherapeutic outcome evaluation was parasitological cure, which was defined as eggs-positive or eggs-negative, or emergence or absence of acute schistosomiasis symptoms.

2.5. Data Synthesis and Statistical Analysis

Meta-analyses were conducted in categories of PZQ. RRs based on dichotomous data were set as statistical indicators. Subgroup analyses were conducted according to different design types, different dosages. All the statistical analysis work was performed using the statistical package Review Manager 5 software (Cochrane Collaboration, Oxford, UK) and Stata/SE 11 (Stata. Corporation, Texas, USA) for Egger's publication bias test by LR. The fixed-effects model was used to combine study-specific RRs, when there was no significant heterogeneity among studies. Otherwise, the random-effects model was used.

3. Results

3.1. Studies Selected

Overall, 6 articles met the inclusion criteria and were finally used for this meta-analysis. Figure 1 shows the studies' selection process: The doses of PZQ for treating *S. Japonicum* are 5 mg/kg vs. 10 mg/kg vs. 20 mg/kg (14); 25 mg/kg vs. 40 mg/kg (15); 20 mg/kg vs. 40 mg/kg vs. 60 mg/kg (12); 30 mg/kg vs. 40 mg/kg vs. 50 mg/kg vs. 60 mg/kg (13); 30 mg/kg vs. 40 mg/kg (16); 50 mg/kg vs. 60 mg/kg (9).

3.2. Study Characteristics and Methodological Quality

Studies were conducted in areas that are endemic for *Schistosoma japonicum*, including Japan, The Philippines, and China (see Table 1). PZQ dosages applied ranged from a single oral dose of 5-60 mg/kg or divided (2, 3) dosages in RCTs-designed studies. For nRCTs about PZQ's efficacy, there were several types of drug administration i.e. a single oral dose of 40 mg/kg or 60 mg/kg, multiple (2, 3) oral doses of the same concentrations, two doses of 20 mg/kg, and three doses of 20 mg/kg. The follow-up time post treatment differed from studies ranging from 2 days to more than 1 year. Table 1 summarizes the Jadad scores of the included RCTs. Among the 6 RCT-designed studies, all of them have described the randomization method; three study (17) include blinded allocation or outcome measurements, and 1 studies (18) had no description of withdrawals or dropouts. Thus, four of the included RCTs were rated as providing good methodological quality based on a Jadad score of 2-5, and only one study (17) had a Jadad score of 1. The nRCTs without quality assessment were analyzed separately from the RCTs.

3.3. Meta-Analysis

The trials were stratified into sub-groups based on different doses of PZQ. The p value of the test for negative rate on the egg was 0.05, the total pooled $\geqq$ RR, and its 95% CI were calculated by combing all sub-groups. No statically significant difference among pooled RRs of sub-groups about different species was observed (RR 0.79, 95% CI 0.46 1.35, P = 0.39).

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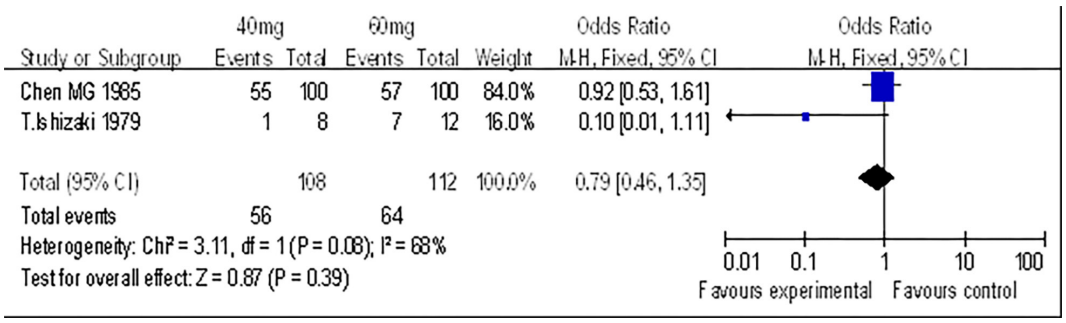

Figure 2. Forest Plots Showing the Negative Rate on the Egg Using 40 mg/kg Compared to 60 mg/kg PZQ for *Schistosomiasis japonicum* Treatment (RCTs)

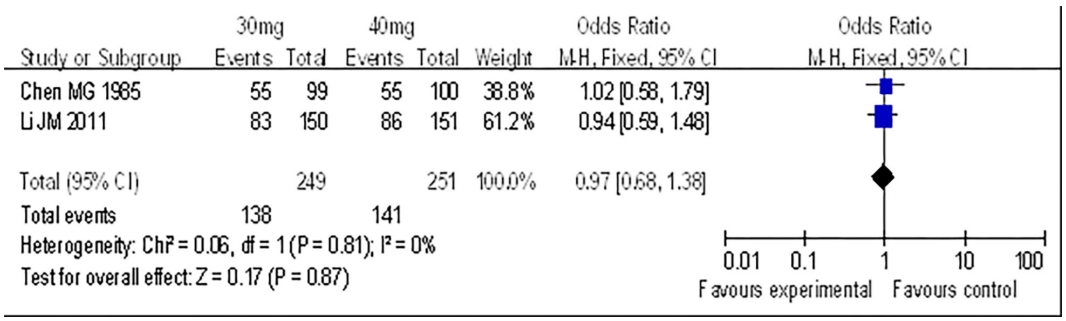

Figure 3. Forest Plots Showing the Side Effects Using 30 mg/kg Compared to 40 mg/kg PZQ for Schistosomiasis japonicum Treatment (RCTs)

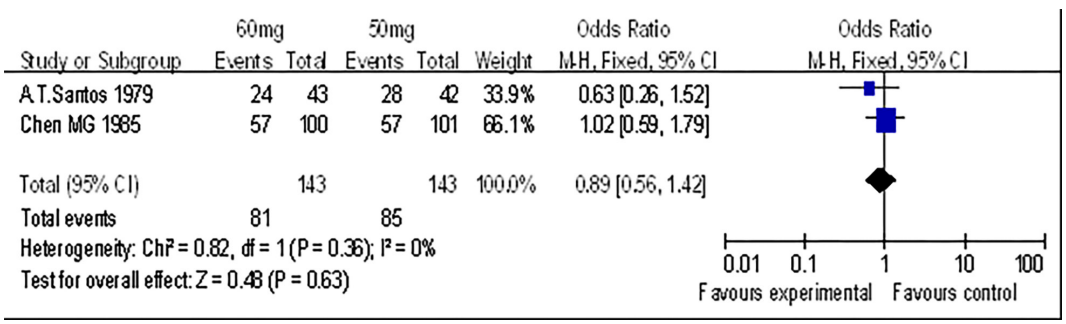

Figure 4. Forest Plots Showing the Side Effects Using 60 mg/kg Compared to 50 mg/kg PZQ for Schistosomiasis japonicum Treatment (RCTs)

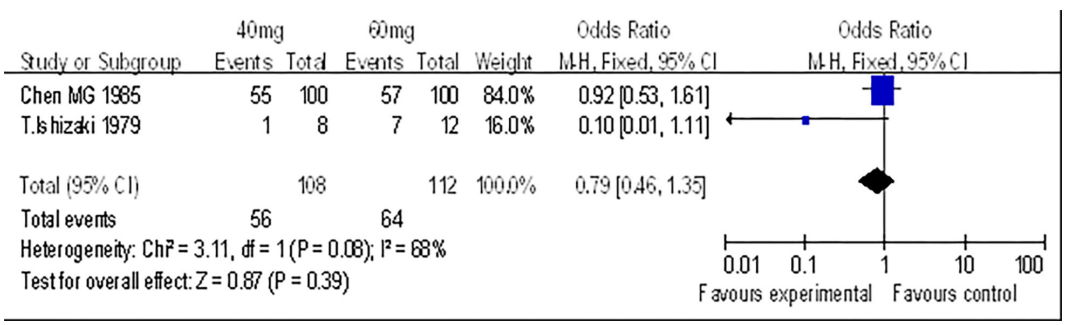

Figure 5. Forest Plots Showing the Side Effects Using 40 mg/kg Compared to 60 mg/kg PZQ for Schistosomiasis japonicum Treatment (RCTs)

4. Conclusions

Praziquantel was synthesized by Bayer and Merck in Germany in 1972 (19), and introduced for clinical use in the People's Republic of China since 1978 (19, 20). Today, PZQ is the most frequently used drug for schistosomia-

sis treatment in endemic areas, and regularly used also in large scale programs (21). PZQ exhibits stage-specific functions in killing adult worms (22-24). Our meta-analysis covering a publication period from 1979 to 2011 indicated that PZQ is still effective for *S. japonicum* with negligible variations. Our meta-analysis showed that different doses of PZQ for treating *S. japonicum*, which is no significant differences were observed among the 30 mg/kg vs. 40 mg/kg (RR 0.97, 9 5% CI 0.68 1.38, P = 0.87), 40 mg/kg vs. 60 mg/kg (RR 0.79, 95% CI 0.46 1.35, P = 0.39) or 50 mg/kg vs. 60 mg/kg (RR 0.89, 95% CI 0.56 1.42, P = 0.63). In order to reduce the side effects and the cost of money, we choose the least dose of drug for treating *S. japonicum*.

Facing the fact that PZQ is still effective for *S. japonicum*, clinical trials in the future should be specially emphasis on the following aspects: 1) ensure the group good comparability and reduce the generation of selection bias, the random allocation sequence of the report should be detailed and the random program should be hidden; 2) choose the unified international gold standard for diagnosis and severity score; 3) standardize observation time; 4) standardize expression of the data; 5) unify the standards efficacy outcomes and determine the efficacy; 6) Describe the detailed side-effect, ensure the drug is safe. It is very little quantity of the articles about using different dose of PZQ for the treatment of *S. japonicum*, so we will the articles like that more and more.

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Authors' Contributions

Damin Cai: Designing the study, evaluating the literature, analyzing the data, writing the manuscript. Si Zhang: Evaluating the literature. Julong Wu:Teaching the methods, meta-analysis. Xun Wang: Teaching the methods, meta-analysis. Xiaoling Lu: ScreenIing the literature. Huiyu Chen: ScreenIing the literature. Qian Wang: ScreenIing the literature. Xingming Ma: Designing and supervising the study, evaluating the literature, writing the manuscript.

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