Journal of the Egyptian Society of Parasitology, Vol. 54, No. 2, August 2024
J. Egypt. Soc. Parasitol. (JESP), 54(2), 2024: 259 - 266
Online: 2090-2549

EFFECTIVENESS OF SELENIUM NANOPARTICLES IN TREATMENT OF *SCHISTOSOMA MANSONI* INFECTED MICE

By

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Abstract

Selenium is an essential micronutrient plays a pivotal role in several physiological and pathological processes, mainly enzymes group called glutathione peroxidase. These enzymes play an important role in detoxification system and give protection against oxidative stress. This study evaluated Selenium nanoparticles (SeNPs) versus Praziquental (PZQ).in treating *Schistosoma mansoni*- experimentally infected mice. The study included four groups each of 10 male Swiss albino mice; G1: non-infected (control negative, G2: infected and non- treated mice (control positive), G3: Infected and PZQ treated & G4: Infected and SeNPs treated. Evaluation parameters were hepatic egg count, histopathology of liver and spleen tissues, and measurement of superoxide dismutase (SOD), glutathione (GSH) and malondialdehyde (MDA) levels.

The result showed that hepatic eggs significantly decreased (34%) in PZQ group and markedly reduced (66%) in SeNPs one. Histopathology of liver mean of number granulomas was 4, and reduced to 1.92 &1.12 in PZQ and SeNPs respectively. The reduction percent in SeNPs group increased (72%) with a highly significant granulomal number reduction and reduction in liver fibrosis. The mean diameter of granulomas in PZQ treated mice was reduced by 19.9%, and SeNPs ones by 36%. There was a significant reduction in megakaryocytes (39.45%) in SeNPs group versus (22%) in PZQ one. Schistosomiasis induced a significant reduction in GSH and SOD levels with increased MDA level compared to control negative. Treatment with PZQ and SeNPs significantly increased GSH and SOD levels, and decreased MDA level mainly in SeNPs group.

Keywords: Glutathione, Malondialdehyde, Schistosomiasis, Selenium nanoparticles, Superoxide dismutase.

Introduction

Schistosomiasis is a parasitic disease caused by blood flukes of genus *Schistosoma* and is a serious public health problem in almost 70 countries of the tropics and subtropics with poor sanitary conditions (Mitra and Mawson 2017). More than 75.3 million persons were have received treatment for schistosomiasis in 2021, out of an estimated minimum 251.4 million people who needed preventive treatment (WHO 2023). Management and eradication of schistosomiasis still a longstanding issue on the priorities of the Egyptian Ministry of Health (Elmorshedy *et al,* 2015).

Schistosoma mansoni infection mostly affects the liver by causing the formation of granuloma and hepatic fibrosis (Dkhil *et al,* 2016). Moreover, spleen is one of the important affected organs by schistosomiasis in variable degrees (Wang *et al.,* 2015).In addition, *Schistosoma mansoni* infection causes oxidative stress in the kidney, liver, and spleen (Mutapi *et al,* 2011).

In an effort to discover a viable substitute for standard medications, scientists have been studying the effects of nanoparticles and their mode of action on parasite illnesses recently (Kandeel *et al,* 2022).

Nanomedicine is a nanotechnology application for treatment, monitoring, prevention, and control of biological diseases (Abaza, 2016). In a literature review discussing effects of some nanoparticles in treatment of schistosomiasis, many substances were studied, natural and synthetic. Based on the reviewed literature, it is evident from in vitro experiments that synthetic and herbal medications loaded with nanoparticles have more substantial effects against the larval and adults of *Schistosoma* than the drug alone

(Shakib *et al,* 2023).

Selenium is an essential nutrient necessary for good health and regulates a variety of cellular processes via selenium proteins (Rahman *et al,* 2020). Selenium is essential in the prevention of a range of diseases, including infectious diseases, hypercholesterolemia, cardiovascular disease, and some malignancies (Jenkins *et al,* 2020). Selenium nanoparticles (SeNPs) have significant antibacterial activity in naked (Geoffrion *et al,* 2020) and conjugated forms, such as the selenium nanoparticles-lysozyme nanohybrid system (Vahdati and Tohidi, 2020). Also, it is important for the proper function of enzymes (glutathione peroxidase), which play an important role in detoxification system of the body and give protection against oxidative stress (Freeth *et al,* 2012).

This study aimed to assess Selenium nanoparticles (SeNPs) in treatment of *S. mansoni*- experimentally infected mice in comparison to Praziquental (PZQ).

Materials and Methods

This case-control study was done at Schistosome Biological Supply Center (SBSC), at Theodor Bilharz Research Institute (TBRI), Giza, Egypt.

Experimental animals: Forty pathogen-free mice CD1 strain (*Mus musculus domesticus*); 4-6 weeks age and weighing 20-25 g, were used. The animals were supplied by and housed throughout the study in the SBSC, at TBRI, Giza, Egypt.

All through the experimental study, mice were kept in air conditioned room at 20°C. They were fed on standard diet of hard pellets. Water was supplied in glass bottles with rubber stopper and small stainless steel cover to drop water, and bottles were placed inverted in cage wire lid. Mice were divided into equal four groups and kept in cages with 10 mice each. Each cage had a card including the strain, number, sex of mice, under daily close observations.

Study design: The study included 4 groups of 10 mice each. G1 was control negative (not infected, not treated), G2: was as control positive (infected, not treated), G3: infected and Praziquantel (PZQ) treated, & G4: infected and Selenium nanoparticles (SeNPs) treated. All mice were sacrificed on 56^{th} day post-infection (P.I.).

Parasites: *Schistosoma mansoni* cercariae were obtained from laboratory bred infected *Biomphalaria alexandrina* at TBRI, Giza.

Mice infection: All mice were infected by subcutaneous injection via their loose skin of upper back with *S. mansoni* (60±10 cercariae/mouse), suspended in 0.5ml solution (Pellegrino *et al,* 1962).

Drugs: 1- Praziquantel (PZQ); 1000mg tablets (Praziquantel-Sedico Pharmaceutical Co.6^{th} October City), was given orally in a total dose of 500mg/kg on day 46 P.I. in two consecutive days, in aqueous suspension form in 2% cremophor El (Helmy *et al,* 2009). 2- Selenium nanoparticles (SeNPs) were obtained from Nano-tech Lab. 6^{th} October City. After preparation, it was given from day 46 P.I in dose of 0.5mg/kg body weight once daily intra-peritoneal for 7 consecutive days.

Nano selenium preparation: It was manufactured by Nanotech, Cairo, Egypt (Kong *et al,* 2014): Ascorbic acid was used as a reducing agent. It is biocompatible and has good reducing properties form a spherical nanoparticle having a size range of 20 to 30nm measured using particle size analyzer.

A stock of aqueous solution of 100mM sodium selenite and 50mM ascorbic acid were prepared. Varied sodium selenite to ascorbic acid ratios (1:1, 1:2, 1:3, 1:4, 1:5, and 1:6) were reacted from the stock solution.

Preparation and coating of Se nanoparticles; Ascorbic acid was added drop wise to the sodium selenite solution under magnetic stirring at different RPM (200, 600, 1000 rpm) at room temperature for 30 min. The mixtures were allowed to react with each other in the concentrated form till the color changed from colorless to light orange and then diluted to 25ml with double distilled water. Coating of nanoparticles with 10% dextrin (obtained from maize starch) then

samples washed and dried then pelleted (Li *et al,* 2010).

Nano selenium characterization: Using High Resolution Transmission Electron Microscope (HRTEM), selenium nanoparticles has uniform shape and size with no aggregation demonstrating homogeneity and the average particle size was about 11.88 up to 51.2 nm. HRTEM was used to determine the crystal size of selenium nanoparticles at an accelerating voltage 200kV and magnification range up to 1,000,000X. The HRTEM technique was done at National Research Center laboratories, Dokki, Cairo, Egypt.

Parasitological Evaluation of therapeutic effects by liver egg count: A representative portion of the liver was taken. One gram of each liver was weighed and then plotted between two filter papers and then placed each in a test tube containing 5 ml 5% KOH solution. The tubes were incubated at 37ºC for 24 hours until the tissues were hydrolyzed. The digest was well shaken on a magnetic mixer for at least one minute. Then, 3 samples (0.1 ml each) were pipetted by the Epindorff micro-pipette, placed on a slide and examined under the low power of the microscope, one sample at a time. The number of ova in each tissue was counted in 3 slides, and the mean was calculated. The number of ova in 5 ml represents the number of ova in the weight of the liver previously digested. Histopathological studies: 1- for *Schistosoma* granuloma size and number: Formalin-fixed liver embedded in paraffin sections 5µm s stained with hematoxylin and eosin, were examin- ed by light microscopy to determine the pathological changes in liver and spleen as well as granuloma size and number in liver. Granuloma was rounded enclosing central schistosome egg or egg debris and diameters were measured by an ocular micrometer lens and calibrated with stage micrometer by a light microscope at 100x. Average diameters of 5 typic-al random granulomas /slide/5/mouse were calculated for each group (Jacobs *et al,* 1997). Average number of granulomas in the liver of random fields (10 fields/mice) was estimated by using a light microscope at 100x. 2- Spleen megakaryocytes count mean in 10 random sections in each group was estimated by a light microscope at a 400x (Freitas *et al,* 1999).

Biochemical parameters: After dissection, a piece of liver was perfused with a PBS solution, pH 7.4 contained 0.16mg/ml heparin. Liver tissue was homogenized in 5-10ml cold buffer (50mM potassium phosphate, pH 7.5.) per gram tissue, and centrifuged at 4,000rpm for 15 minutes at 4°C. The supernatant was removed for assay and storage on ice. The following biochemical levels were estimated; Glutathione (GSH) level (Ensafi *et al,* 2008), Superoxide dismutase (SOD) activity (Nishikimi *et al*, 1972), and Malondialdehyde (MDA) assay (Ohkawa *et al,* 1979).

Statistical analysis: Data were expressed as means± SD and analyzed by One Way ANOVA to compare between multiple means (SPSS 20.00 software package program). Statistically significant difference was considered at the level of $p < 0.05$.

Ethical Considerations: The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Suez Canal University, reference research 4050#.

Results

Mean of egg count in PZQ treated mice was reduced by 34.4 % than control mice (mean 5472), but with remarkable reduction in SeNPs treated mice by 65.9 % than control mice(mean 2841.8) indicated a highly significant reduction in SeNPs treated mice.

In positive control, mean number of granulomas in 10 fields was 4, while reduced to 1.92 & 1.12 in PZQ and SeNPs mice respectively. Reduction in SeNPs mice was (72%) indicating highly significant reduction in granulomas' number and liver fibrosis.

Mean diameter of granuloma in PZQ treated mice was reduced (19.9%), but in SeNPs treated mice was more than (36%).

There was a significant rise in positive control as compared to negative control mean

of megakaryocytes was 21.8 versus 8.9 respectively. In treated mice there was a significant reduction in megakaryocytes number 36.6%, with mean 17, in SeNPs treated and 19.9 % in PZQ treated with mean 13.2.

Biochemically infection caused a significant reduction in GSH & SOD levels in liver tissue as compared to control negative. Treatment with PZQ & SeNPs significantly increased (GSH) & (SOD) levels, especially with SeNPs treated by potent anti-inflammatory and antioxidant effect. Also, infection caused a significant increase in (MDA) levels as compared to negative control. PZQ and/or SeNPs treatment caused a significant decrease in MDA levels as compared to positive control, especially more significant with SeNPs treated mice by prominent anti-inflammatory and antioxidant effect.

Liver tissue was examined for granuloma numbers and diameters. *S. mansoni* in control positive showed multiple foci of granulomas consisting of severe lymphocytic and plasma cells and few eosinophilic cellular infiltrations throughout the liver parenchyma with fibrin and collagen deposition. Many granulomas have intra-lesional schistosome eggs. Liver parenchyma in between adjacent granulomas was very narrow.

The infected and PZQ treated mice showed distorted *S. mansoni* eggs of variable sizes with moderate decrease in granulomas' size and number and increase in the normal liver parenchyma in between neighboring granulomas. The inflammatory cellular infiltration was moderate with the cellular infiltrates mainly surrounded the periphery of eggs.

Infected and SeNPs treated mice showed a significant reduction in granulomas' size and number. Granulomas contained mostly dead or calcified ova surrounded by mild lymphocytosis with larger areas of normal liver parenchyma in between. Control negative showed normal histological splenic picture with stroma formed of a capsule and septa, parenchyma forming white pulp scattered irregularly in a red pulp background, and with minimal megakaryocytes number. In control positive, splenic showed megakaryocytes large number and inflammation.

In the PZQ treated mice, spleen showed reduction in the megakaryocytes number. Bur, in SeNPs treated mice, spleen showed marked reduction in the megakaryocytes number.

Details were given in tables (1 & 2) and figures (1, 2, & 3).

Table 1: Mean values and reduction percentages in assessed parasitological and histopathological parameters among groups.

Parameter/groups	Mean ± SD	Reduction%	Statistical analysis	
			F-test	*P value**
Liver egg count /g tissue				
Infected non-treated	8343.60 ± 4265.27	--		
PZQ	5472.00 ± 781.98	34.41	13.31	<0.01
SeNPs	2841.83 ± 601.20	65.94		
Liver granulomas number/ 10 fields				
Infected non-treated	4.00 ± 0.316	--		
PZQ	1.92 ± 0.228	52	279.43	<0.01
SeNPs	1.12 ± 0.228	72		
Liver granulomas' diameter (µm)				
Infected non-treated	29.94 ± 2.397	--		
PZQ	23.98 ± 0.980	19.9	442.11	<0.01
SeNPs	19.06 ± 0.937	36.34		
Splenic megakaryocytes count/ 10 fields				
Non infected non treated	8.90 ± 1.85	--		
Infected non-treated	21.80 ± 1.09	--		
PZQ	17.00 ± 1.58	22.02	65.57	<0.01
SeNPs	13.20 ± 1.44	39.45		

F-test = ANOVA test * Significant p-value <0.01

Table 2: Mean values and reduction percentages in biochemical parameters among groups:

Parameter/groups	Mean ± SD	Statistical analysis	
		F-test	*P value**
Glutathione levels (GSH) in liver tissue (mmol/g tissue)			
Non infected non treated	1.778 ± 0.094	680.35	<0.01
Infected non-treated	0.432 ± 0.037		
PZQ	0.594 ± 0.040		
SeNPs	1.484 ± 0.029		
Superoxide dismutase levels (SOD) in liver tissue (U/g tissue)			
Non infected non treated	3.644 ± 0.114	279.43	<0.01
Infected non-treated	1.676 ± 0.103		
PZQ	2.268 ± 0.209		
SeNPs	3.080 ± 0.238		
Malondialdhyde level (MDA) in liver tissue (nmol/g tissue)			
Non infected non treated	12.400 ± 0.353	54.675	<0.01
Infected non-treated	16.200 ± 0.529		
PZQ	14.540 ± 0.415		
SeNPs	12.740 ± 0.743		

Discussion

Nanoparticles vary in size from 10 to 100 nm and can be made in a variety of ways. In actuality, they are regarded as the biological mimics and nano-machines that may deliver medications and genetic components by targeting cells and extracellular components (Elmi *et al,* 2013).

Selenium is one of the essential micronutrients with antioxidant & anti-inflammatory activity (MacFarquhar *et al,* 2010) counteracts free radicals, preserve structure and function of DNA, proteins and chromosomes against oxidation injury (El-Demerdash, 2004). Its' supplementation decreases anemia and trypanosomiasis-induced organ damage (Da Silva *et al,* 2014) and have anti-leishmanial effect (Mostafavi *et al,* 2019). Also, it causes apoptosis in *Plasmodium falciparum* blood cells (Surhadji *et al,* 2011) and as an antioxidant in *Trichinella spiralis*-infected rats (Gabrashanska *et al,* 2010).

Praziquantel is cost-effective drug for schistosomiasis and didn't kill immature worms (Munisi *et al,* 2017). Also, it's well known side effects (Rodriguez-Morales, 2012).

In the current study, criteria used for assessing PZQ and SNPse therapeutic effects were; hepatic egg count, histopathological changes of liver (granuloma number and size) and spleen (megakaryocytic number) and some biochemical parameters in liver tissue including glutathione, malondialdhyde and superoxide dismutase levels.

In the present study, mice treated with SNPs showed a significant reduction by 65.94% (2841.8; mean of eggs count) with comparison to positive control (mean 8343.6 eggs) while the percentage of reduction in PZQ group was 34.4% (5472). This agreed with Dkhil *et al.* (2016), who found that intraperitoneal injection of SeNPse and oral PZQ in *S. mansoni* infected mice caused a decrease in liver egg count in treated mice, which was more evident with using PZQ than with SeNPs, but the last item disagreed with the present results. Besides, eggs density was reduced with Dkhil *et al.* (2015) when they used different concentrations gold nanoparticles as comparison to PZQ in treating *S. mansoni* infected mice. Reduction was more than 60% in mice treated with a dose of 1mg/kg AuNPs than 50% with PZQ. This more or less was in the efficacy favor of nanoparticles used in the present study. Also, in the present study, there was a significant reduction in granuloma size and number as compared to positive control (36.34% & 72% respectively) when using SeNPs and (52% & 19.9 % respectively) when using PZQ. This agreed with Dkhil *et al.* (2016), who found that granuloma size was significantly reduced (400±31µm) and (370±29µm) by SeNPs and PZQ, respectively versus positive control (750±55µm).

In the present study, splenic tissue's extra-

medullary hematopoiesis, cellular stress, and toxicity were indicated by increase in the megakaryocytic count, due to infection. This agreed with Elsheikha *et al.* (2008), who reported that lymphoid follicles with significant germinal centers and few megakaryoctyes were hyperplastic due to mice infected with various *S. mansoni* doses.

In the present study, there was a significant reduction in number of megakaryotes in spleen of mice treated with PZQ (22 %) and SeNPs (39.45%) as compared to positive control showed increase in response to tissue stress and tissue inflammation due to infection. El Sokkary *et al.* (2002) used melatonin as an anti-inflammatory against *S. mansoni* infected mice found a marked reduces in megakaryocytes' number.

In the present study, a marked decrease was in hepatic GSH & SOD was in positive control due to infection versus negative control, but with marked increase in MDA levels. Also, mice treated with SeNPs showed a marked increase in GSH & SOD levels; 1.48 mmol/g tissue & 3.08U/g tissue respectively. This was quite normal in negative control. A significant decrease was in MDA levels in SNPs treated mice (12.74nmol/g tissue). This agreed with Dkhil *et al.* (2016), who found that *S. mansoni* infection, caused a substantial decrease in the hepatic GSH level, but with marked increase in the MDA level as compared to negative control.

Conclusion

Praziquantel treated *S. mansoni* infected mice caused a significant reduction in hepatic egg count, and granuloma size & number, megakaryocytic count in spleen, enhancing liver antioxidants activity. Selenium nanoparticles treated mice gave a significant decrease in all parameters than praziquental. So, selenium nanoparticles are promising drug.

The authors declared that neither they have any conflicts of interest nor received any funds. Besides, they equally shared in this study, and approved manuscript publication.

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Explanation of figures

Fig.1: HRTEM done to use SeNPs showed average size ranged between 11.8 to 51.2 nm.
Fig 2: Stained mice liver showed granulomas and inflammatory reactions: A&B; control positive, C & D: PZQ; E & F: SeNPs.
Fig.3: Stained mice spleen (H&E) showed megakaryocytes (black arrows). A; normal spleen, B; control positive. C: PZQ; D: SeNPs.
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