



## Assessment of hepatic periportal Fibrosis in *Schistosoma mansoni* Infected Sudanese Patients after Treatment with Praziquantel

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### ABSTRACT

*Schistosoma mansoni* infection in Sudan cause serious health problems and economic consequences especially among schoolchildren, women of reproductive age and the working group of agriculture-associated people resulting into serious health and economic consequences. Praziquantel has been introduced as the drug of choice for the infected people. The reversal of the serious pathology (PPF) had been a dream in the past time but now, and according to different reports becomes a reality. The aim of this study was to cast a light on the possible factors that affect changes in the grade of PPF 12 months after treatment of the patients with praziquantel. The study enrolled 100 Sudanese nationals diagnosed as schistosomiasis patients with active *Schistosoma mansoni* infection complicated with different grades of PPF were enrolled in the study. All the participants underwent abdominal ultrasonography evaluating the grade of PPF and given praziquantel as treatment according to appropriate dose for each of them (40 mg/kg BW). They were further assessed by ultrasonography 12 months later. It was found that, 46 (46%) grades of PPF regressed to the lower grades of fibrosis, 34 (34%) remained stable and 20(20%) progressed to the higher grades of fibrosis. Age and gender were significantly associated with changes in grades of PPF. Regression of PPF among females and young age group patients was more likely than that for males and old patients. Ethical approval for the study was obtained from the ethical committee of the University of Gezira and from the State Ministry of Health, Wad Medani .Sudan and informed consent was declared to the participants prior to commencement of the study .

Keywords: PPF, Praziquantel, *Schistosoma mansoni*.

### المستخلص

البلهارسيا التي تسببها شistosoma مانسوناي من الأمراض المتوطنة في العالم و خاصة في وسط السودان حيث تعتبر هذه المنطقة أهم منطقة إقتصادية في القطر. غالبا ما يصيب هذا المرض الأطفال في عمر المدارس و

النساء في عمر الإنجاب و العاملين في الزراعة مؤديا إلى نتائج صحية و إقتصادية خطيرة. دواء البرازيكوانتيل أدخل كأفضل علاج للمرضى. التعافى من التليف حول المسار البابى للكبد كان يعتبر فى الماضى حلما و لكن الآن و وفقا لتقارير مختلفة أصبح حقيقة. الهدف من هذه الدراسة هو تسليط الضوء على العوامل المحتملة التى تؤثر فى تغير التليف حول المسار البابى للكبد 12 شهرا عقب العلاج بدواء البرازيكوانتيل. حوت هذه الدراسة 100 من السودانين الذين شخضوا كمرضى بلهارسيا شيسيتيسوما مانسوناي ومعقدة حالتهم بدرجات مختلفة من التليف حول المسار البابى للكبد. خضع كل المشاركين لكشف بالموجات فوق الصوتية للبطن لتقويم درجات التليف حول المسار البابى للكبد. عولجوا بعد ذلك بدواء البرازيكوانتيل وفقا لوزن كل منهم (40 ملجم/كجم) ثم قوم التليف 12 شهر بعد العلاج بذات الطريقة. وجد أن التليف قد تراجع فى 46 (46%) من الحالات و أن 34 (34%) لم تتغير حالة التليف لديهم و أن 20 (20%) تدهورت حالة التليف لديهم إلى مستويات أسوأ. إتضح أن العمر و الجنس مرتبطان إحصائيا بدرجات التليف. مستوى التعافى من التليف وسط النساء و ذوى الأعمار الصغيرة أفضل من الرجال و المرضى كبار السن.

## INTRODUCTION

The Schistosomes are trematodes that are typically digenetic but atypical to other trematodes in being dioecious<sup>(1)</sup>. The main Schistosoma species affecting humans are *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum*. The first two species are common in Sudan causing intestinal and urinary schistosomiasis; one of the most endemic diseases causing high morbidity and mortality<sup>(2)</sup>. The freshwater bodies being natural or manmade such as in the irrigated agricultural schemes are the main reservoirs. Schistosomiasis due to *Schistosoma mansoni* is very common in Gazera scheme; the main irrigated agricultural scheme in Sudan<sup>(3)</sup>. Heavy and chronic infections commonly lead to portal hypertension with very serious fatal consequences such as bleeding oesophageal varices<sup>(4)</sup>. The adult couple of *Schistosoma mansoni* travels from the portal vasculature in the liver against the blood stream to reside commonly in the venous plexus of the mesenteric veins in the large intestine and may live for a decade or more<sup>(5)</sup>.

After mating each female lays about 300 eggs per day<sup>(5)</sup>. Some of the laid eggs are passed in stool, the other portion retained in the intestinal wall and the remaining eggs are gushed back to the liver. This last portion of the egg load constitutes the main pathogenic stage in schistosomiasis<sup>(6)</sup>. The eggs elicit immunological reaction with the immune system of the body leading to formation of granulomas around the eggs in the small portal venules of the liver ending up into peri-portal fibrosis (PPF)<sup>(7)</sup>. The peri-portal fibrosis obstructs the flow of the portal blood through the liver to the inferior vena cava leading to portal hypertension<sup>(3)</sup>. The peri-portal fibrosis comes out due to deposition of collagen around the portal tract giving a continuum of three grades, grade I, II, and III<sup>(8)</sup>. The severity of the disease is a consequence of the severity of fibrosis<sup>(7)</sup>. It has been reported that the severity of fibrosis depends on the regulation of cytokines<sup>(10)</sup>. It has been reported that successful treatment with praziquantel leads to regression of peri-portal fibrosis refuting the notion of permanent fibrosis<sup>(9)</sup>. However, only a

small percentage of individuals infected in an area of endemicity actually develop a severe form of the disease. The T-cell-mediated host reaction to these eggs results in the formation of granulomas, which consist of T cells, B cells, macrophages, fibroblasts, and a large number of eosinophils, and though largely mediated by Th2 cells, T helper 1- (Th1)-type responses can contribute to the tissue destruction<sup>(10)</sup>. Early responses to the egg antigens are of both the Th1 type and Th2 type, with a subsequent shift to a long-lasting Th2 response. The Th2 response is associated with the production of interleukin-10 (IL-10); which down-regulates interleukin-5 (IL-5) and interferon- $\gamma$ , significantly reducing liver damage associated with the granulomas<sup>(9, 10)</sup>. IL-10 also reduces the expression of the costimulatory molecules CD80 and CD86 on the local macrophages. Presentation of egg antigens in the absence of these CD28 costimulatory molecules leads to T-cell anergy, thus reducing the intensity of the inflammatory response generated against eggs antigens. Similarly, continuous activation of TH2 cells yields considerably high amounts of interleukin-4 (IL-4) which activates B cells to elicit a high level of immunoglobulin E (IgE) antibody during human infection<sup>(9, 10)</sup>. The orally administered praziquantel (PZQ) is the drug of choice for treatment of schistosomiasis. The granulomatous reaction that develops around the dead parasites causes complete disintegration of the parasite within two weeks and later on resolves the fibrotic lesions around the egg<sup>(11)</sup>. The aim of this study is assess to the pattern of change in the periportal fibrosis in *Schistosoma*

*mansoni* infected Sudanese patients in Al Managil locality, Gezira State, Sudan.

## MATERIALS AND METHOD

This descriptive study was conducted in a village in Al Managil with about 4000 inhabitants on May 2010-Aug 2012. One hundred people were enrolled in the study after being diagnosed as having schistosomiasis with peri-portal hepatic fibrosis by stool examination and abdominal ultrasonography. Fifty-two of them were females and forty eight were males with age range of 16-50 years. Each participant underwent ultrasonographic examination to the liver and spleen by (SSD 500 echo camera and 3.5- MHz convex probe; Aloka, Amsterdam, the Netherlands) stressing on the portal area and her/his profile was recorded. The degree of peri-portal fibrosis was graded as F 0, F I, F II and F III according to the standardized Cairo classification<sup>(12)</sup>. Grade 0 (F0) corresponds to normal liver with no thickening of the PPB wall and peripheral portal branches (PPB) diameters (outer to outer) of ~2-3 mm. Grade 1 (F1) corresponds to a pattern of small stretches of fibrosis around secondary portal branches and PPB diameters of ~ 4 mm. Grade II (FII) still shows the patchy fibrosis observed in F1, but a continuous fibrosis affects most second-order branches, and PPBs appear as long segments of fibrosis. Grade III (FIII) shows a thickening of the walls of most PPBs. The liver size, peripheral portal branches (PPBs), the degree of PPF, thickness of PPB wall, spleen size and splenic vein (SV) diameter were assessed, see figure (1). Three stool specimens collected from each participant were concentrated and examined microscopically for the presence of the eggs of *Schistosoma*

*mansoni*. The egg load (eggs/g of stool) was estimated using Kato's method. The viability of the eggs was tested by the hatching test <sup>(5)</sup>.

Each participant was treated with praziquantel at a dose of 40mg/Kg BW. The peri-portal fibrosis for the participant was then assessed by periportal ultrasonography after 12 months of praziquantel treatment and their profiles were recorded and compared with initial results before treatment.

Statistic analysis was done using SPSS program Chi square test.

### RESULTS:-

Ultrasound examination of untreated schistosoma mansoni infected patient revealed that 64%,20%,and 8% patient had mild (FI),moderate (FII) and severe (FIII) PPF, respectively ; no normal

pattern (F0)was observed .after treatment there was a significant shift towards lower PPF grades and 38% cases reversed to normal (F0) state (Table 1).

As can be seen from table 2 ,48%of PPF regressed to lower grades after PZQ treatment ;34from FI to F0,four from FII to F0,six from FII to FI

And two from FIII to FII.

Twenty percent of PPF progressed towards higher PPF grades ;seven from FI to FII, twelve from FII to FIII and one from FI to FIII .thirty four percent of PPF remained without change ;22inFI ,six in each FII and FIII grades

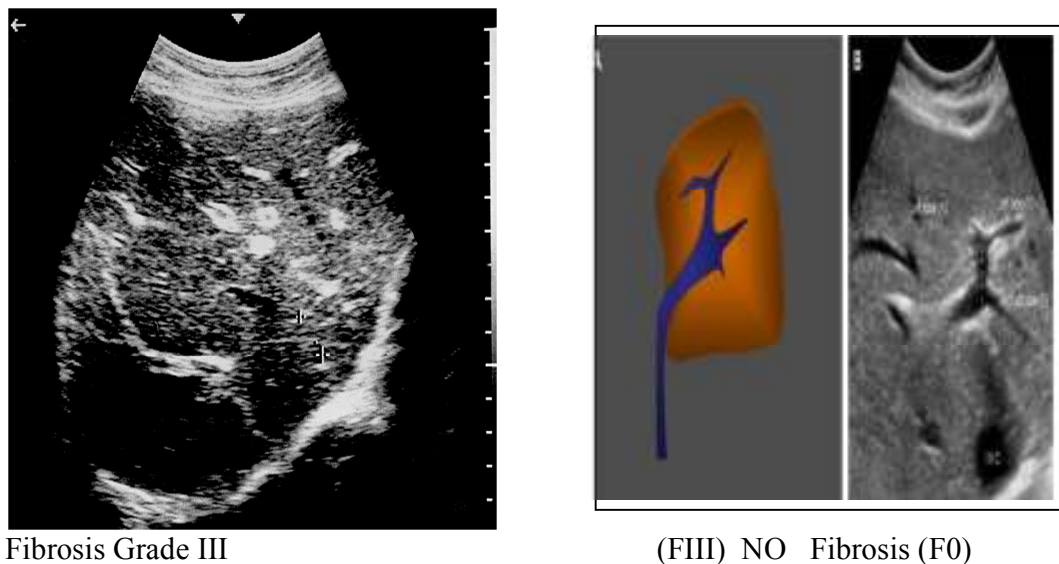
The change in PPF after PRQ treatment in relation to age and gender can be seen in table 3 regression of PPF was relatively better in females and youngest patients (16-20 years old ) compared to males and other age groups .



Fibrosis Grade I (FI)



Fibrosis Grade II(FII)



**Figure 1: Ultrasonographic grading of periportal fibrosis, FI, FII and FIII. Narrowing of hepatic veins is obvious in FIII**

*Table 1: The PPF grades in Schistosoma mansoni infected patients before and after 12 months of treatment with PZQ.*

Phases	Grades of Peri-portal fibrosis					Total	No (%)
	F0	FI	No	FII	FIII		
	No (%)		(%)	No (%)	No (%)		(%)
Before treatment	0 (0)	64 (64%)		28 (28%)	8 (8%)		(100)
After treatment	38 (38%)	28 (28%)		15 (15%)	19 (19%)		(100)

$P = 0.0001, P = 0.000$

*Table 2: Change in PPF grades 12 months after treatment with PZQ*

Type of change in PPF	Grades of PPF				Total
	FI-F0	FII-F0	FII-FI	FIII-FII	
Regression	34(34%)	4 (4%)	6 (6%)	2(2%)	46 (46%)
Progression	FI-FII	FII-FIII	FI-FIII		
	7 (7%)	12 (12%)	1 (1%)		20 (20%)
Stable	FI	FII	FIII		
	22 (22%)	6 (%)	6 (6%)		34 (34%)
					<b>100 (100%)</b>

Table 3: changes in PPF in response to treatment with PZQ months according to the age and gender after 12 month

Age group in years	Regression of PPF In female	Regression of PPF in male	Stability of PPF In female	Stability of PPF in male	Progression of PPF in female	Progression of PPF in male
16-20	7	5	7	5	0	3
21-25	5	4	2	0	1	2
26-30	3	2	4	2	1	3
31-35	4	4	4	2	1	3
36-40	3	3	2	1	1	2
41-50	2	4	4	1	1	2
Sub total	24	22	23	11	5	15
<b>Total</b>	<b>46</b>		<b>34</b>		<b>20</b>	

## DISCUSSION

Hepatic periportal fibrosis that occurs in schistosomiasis due to *Schistosomamansoni* infection leads to portal hypertension that can prove serious and even fatal with bleeding oesophageal varices (6, 8). Praziquantel was accepted internationally as the treatment of choice for patients with schistosomiasis resulting into cure of the patients (14). Reversal of PPF after PZQ treatment was investigated in mice and PPF in humans with promising results and reported to occur in humans (15-17). In this study ultrasonography gave valid evaluation of hepatic pathology caused by schistosoma mansoni infection and the change of PPF after treatment with PZQ ,complete remission was observed in 38 (38%) of PPF cases 12 months after PZQ treatment base on ultrasound evaluation . Such a finding was reported in previous studies (18, 19). Praziquantel treatment decreases the parasitic load by killing the adult Schistosomes and kills and dislodges the eggs from the portal tracts (19, 20). This step stops further PPF formation and participates in PPF resolution with the probability that dead

ova are less immunogenic. The dose of praziquantel and the post treatment assessment can constitute important factors in lessening the severity of PPF as previously reported (20). In this study, the regression of PPF differed according to the severity with better regression in low grades PPF than in high grades (table 1) which was a reported before (20). However, some of the PPF cases remained stable mainly in F1 grade and this seems to contradict the notion that the less severe PPF is amenable to regression. The severity of PPF may not coincide with its chronicity because it has been stated that the young PPF was easily resolvable by praziquantel treatment (19, 20). Moreover, the genetic factors cannot be overlooked. In the present finding some of PPF even progressed towards severity . In this respect, eradication of the parasites from the body should be assured, as failure of cure or re-infection will lead to adverse results. Time that elapsed after treatment and genetic factors may play roles in the progression of PPF another possibility is that patient might have had immature parasites at the time of PZQ treatment which later mature to induce hepatic



lesion ;PZQ is not effective against immature schistosome .

The improvement of PPF was found to be better among the females compared to the males and such a finding was reported before in Sudan <sup>(19)</sup>. However, females might have been harboring lower parasitic load than the males; a situation that could have been resolved by the egg count. The age could be a significant factor in the change of the grade in response to treatment with praziquantel . In endemic areas such as the present study area, the risk of exposure to infection and the chronicity of the disease may be directly proportional to the age of the patients.

PPF in schistosomiasis is an immunological process and the response to treatment with praziquantel affects and is affected by this immunological process and other factor . Therefore, the change in PPF post treatment with praziquantel is a multifactorial issue that needs further studies .

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