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Field-based evaluation of a reagent strip test for diagnosis of *Schistosoma mansoni* by detecting circulating cathodic antigen in urine before and after chemotherapy

Mengistu Legesse*, Berhanu Erko

Aklilu Lemma Institute of Pathobiology, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia

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Summary The sensitivity of a reagent strip test for the diagnosis of schistosomiasis by detecting circulating cathodic antigen (CCA) in urine was evaluated under field conditions using 251 stool and urine samples collected from a *Schistosoma mansoni*-endemic area of Ethiopia. The specificity of the test was evaluated in an area where schistosomiasis is not endemic. Stool samples were examined microscopically using duplicate Kato slides and formol-ether concentration methods. The effectiveness of the test in monitoring efficacy was also evaluated following chemotherapy. The results revealed that detection of CCA in urine using the one-step reagent strip test was superior to the stool examination methods ($P < 0.05$) in indicating the prevalence of the disease. Assuming the combination of parasitological test results as the gold standard, the sensitivity and specificity of the test were 82.1% and 75.9%, respectively. The results of egg counts suggested the potential use of urine CCA in indicating the intensity of infection as an alternative to parasitological methods. The sensitivity and specificity of the test were 75% and 73.7%, respectively, following chemotherapy. Diagnosis of *S. mansoni* infection in urine using reagent strips would provide information on the prevalence of the disease, although further study is needed to improve its sensitivity and specificity.

1. Introduction

In Ethiopia, intestinal schistosomiasis due to *Schistosoma mansoni* infection is a widely distributed disease in several localities of the country, with a prevalence rate as high as 90% in schoolchildren (Ayele and Tesfa-Yohannes, 1987; Erko et al., 2002; Jemaneh, 1998; Kloos et al., 1978). Epidemiological assessment of the disease is usually carried out by demonstration of the parasite egg in faeces using Kato technique or the formol-ether concentration method. Although these techniques are feasible in the situation of poor nations where the disease is endemic, repeated stool examination is

* Corresponding author. Fax: +251 1 275 5296.
E-mail address: dlegessem@yahoo.com (M. Legesse).

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needed to increase the sensitivity of the techniques, especially in the case of light infection and for efficacy evaluation (De Vlas and Gryseels, 1992; Ebrahim et al., 1997; Gryseels and De Vlas, 1996). In epidemiological studies, repeated stool examination is operationally difficult (Barreto et al., 1990) and people are usually reluctant to provide repeated stool samples.

Detection of specific antibodies against the different stages of the parasite using immunological techniques has been suggested as a solution to minimise the problem of low sensitivity of the parasitological techniques (Hamilton et al., 1998; Hancock and Tsang, 1986; Rossi et al., 1991; Van Lieshout et al., 2000). However, their lower specificity in differentiating light infection from heavy infection, or active infection from persistence of antibodies after treatment, as well as their high cost make these techniques inadequate for epidemiological studies and control programmes (Doenhoff et al., 1993; Spencer et al., 1991).

Assessment of schistosome circulating anodic antigen and circulating cathodic antigen (CCA) in serum or urine of infected individuals using ELISA has been proposed as an alternative technique to overcome those problems inherent in the detection of antibodies (Deelder et al., 1989; Van Etten et al., 1994; Van Lieshout et al., 1993, 2000). Nevertheless, the applicability of ELISA-based techniques is less visible in a Third World situation where there are financial constraints and where laboratory settings are not well developed. Moreover, ELISA-based methods cannot routinely be used in the field for community diagnosis.

In an effort to improve immunological-based techniques for the diagnosis of schistosomiasis at the field level, Van Dam et al. (2004) evaluated a newly developed one-step reagent strip test for the detection of schistosome CCA in urine and claimed that it has high sensitivity as well as specificity for the epidemiological study of schistosomiasis. However, it is of practical importance to evaluate the effectiveness of such a new technique in several schistosomiasis-endemic countries prior to its application for routine diagnosis or epidemiological study of the disease. Therefore, this study was undertaken to compare the effectiveness of the one-step reagent strip test with conventional stool examination techniques in the diagnosis of *S. mansoni* in an endemic area of Ethiopia.

2. Materials and methods

2.1. Study area and study population

In July 2005, a cross-sectional study was conducted in Dudycha village where the prevalence of *S. mansoni* was found to be 43.2% (Legesse et al., in press) to evaluate the sensitivity of rapid reagent strip test for the diagnosis of infection with *S. mansoni* by detecting CCA in urine. The village is located on the southeast of Lake Ziway shore, approximately 165 km to the south of Addis Ababa at an altitude of 1657 m above sea level. Dudycha village had approximately 740 households and most of the inhabitants were engaged in crop production and rearing of livestock.

2.2. Selection of the study population and data collection

After explaining the aim of the study and obtaining informed consent from the leader of Dudycha village, house-to-house visits were made to inform the head of the households to come themselves or to present their eligible families (>5 years) to a central place for stool and urine examinations. Then, a disposable small piece of clean plastic sheet and cup were distributed to each individual (guardian/parent in the case of children) to provide fresh stool and urine samples, respectively.

Stool specimens were processed using Kato technique, template-delivering 41.7 mg of stool in duplicate slides for each subject from the same stool sample, as previously described (Ebrahim et al., 1997). The slides were microscopically examined on the spot for the eggs of *S. mansoni* and other intestinal helminths. Egg count was performed for *S. mansoni* and the intensity of infection was expressed as egg count per gram of stool for each subject (WHO, 2002).

Approximately 1 g of the same stool sample was also transferred into plastic vials containing 10% formalin and transported to the laboratory. The samples were processed by the formol-ether concentration method and qualitatively examined for *S. mansoni* and other helminth eggs.

Urine specimens were immediately tested using Schistosomiasis One Step Test for the detection of *Schistosoma* CCA according to the manufacturer's protocol (B.V. European, Veterinary Laboratory, Woerden, The Netherlands). The positivity of the urine samples by the reagent strip was classified as strong positive (scored as 1) and weak positive (scored as 2).

The specificity of the test was evaluated using stool and urine samples collected from 58 schoolchildren from Elala-Gojo and Finland primary schools, Holeta area, approximately 40 km to the west of Addis Ababa, an area situated at an altitude approximately 2507 m above sea level and known to be non-endemic for schistosomiasis.

2.3. Treatment and stool and urine sample collection for efficacy analysis

Praziquantel (40 mg/kg body weight) was distributed to all individuals found to be positive for schistosomiasis either by Kato or reagent strip test during the initial survey. One hundred and twenty-one subjects presented during the distribution day and swallowed the tablets in the presence of the research team and were considered for the efficacy analysis. Six weeks after treatment, stool and urine samples were collected from those individuals who were treated and volunteered to provide stool and urine samples for efficacy testing (Nibbeling et al., 1998). The samples were processed both by Kato method and reagent strip test.

2.4. Data analysis

Data were analysed using SPSS version 10.0 software (SPSS Inc., New York, NY, USA). Chi-square test was used to determine the proportion of difference in positivity. Differences were considered significant at a P-value of <0.05.

The reagent strip was evaluated in terms of sensitivity and specificity. A combination of the Kato and formol-ether concentration techniques was used as the gold standard.

2.5. Ethical considerations

The aim of the study was explained to the responsible bodies at district and community levels as well as to the study population to obtain verbal consent. Those individuals who were found to be positive for *S. mansoni* and other intestinal helminths were treated with appropriate doses of praziquantel and albendazole, respectively.

3. Results

During the initial survey, a total of 251 stool and urine samples were collected from 161 males and 90 females (age range 5—75 years, mean age 20.0 years) from Dudycha village. Most of the participants (65.7%) were in the age range 5—20 years. Of the total 251 stool and urine samples collected, 151 (60.2%), 86 (34.3%) and 189 (75.3%) were found to be positive for *S. mansoni* infection by Kato, formol-ether concentration and reagent strip methods, respectively ($P < 0.001$). Fifty-six (22.3%) and 27 (10.8%) subjects were found to be positive and negative, respectively, by all three methods.

3.1. Kato and formol-ether concentration methods

Of the 151 stool samples positive by Kato, 93 (61.6%) were found to be negative by the formol-ether concentration method. Similarly, of the 86 samples positive by formol-ether concentration, 28 samples (32.6%) were found to be negative by Kato method. Of the total 251 subjects, 58 (23.1%) were positive both by Kato and formol-ether concentration methods, whereas 72 subjects (28.7%) were negative by both methods. Of the 58 positive subjects, 2 (3.4%) were found to be negative by reagent strip test. On the other hand, among the 72 negative individuals by Kato and formol-ether concentration, 42 (58.3%) were found to be positive by reagent strip test.

3.2. Kato and reagent strip methods

Among the total 251 subjects, 130 subjects (51.8%) were positive both by Kato and reagent strip test, whilst 41 individuals (16.3%) were negative by both methods (Table 1). Ten subjects (4.0%) were negative by Kato and reagent strip tests but positive by formol-ether concentration.

3.3. Formol-ether concentration and reagent strip methods

Of the 86 positive samples by formol-ether concentration, 13 samples (15.1%) were found to be negative by reagent strip test. Similarly, among 189 positive urine samples by the reagent strip test, 116 samples (61.4%) were found to be negative by the formol-ether concentration method. Of the total subjects, 73 individuals (29.1%) were positive by reagent strip test and formol-ether concentration. Of these, 17 (23.3%) were found to be negative by Kato method. Forty-nine subjects (19.5%) were negative by reagent strip test and formol-ether concentration. Of these, 20 subjects (40.8%) were found to be positive by Kato method.

3.4. Stool examination and urine

Considering the results obtained both by Kato and formol-ether concentration techniques, 179 subjects (71.3%) were found to be positive by stool examination compared with 189 (75.3%) positive subjects by urine test ($P > 0.05$). On the other hand, 147 subjects (58.6%) were positive both by stool and urine examination, whereas 30 subjects (12%) were negative by both methods (Table 2). The sensitivity of the reagent strip test was found to be 82.1%. The positive and negative predictive values were 77.8% and 48.4%, respectively.

Since predictive values could be influenced by prevalence, the positive and negative likelihood ratios were also calculated as an alternative to sensitivity and specificity. The positive likelihood ratio was found to be 3.41 whereas the negative likelihood ratio was 0.236.

3.5. Intensity of infection

Of the total 151 positive subjects by Kato, 70 (46.4%), 50 (33.1%) and 31 (20.5%) subjects were found to have light, moderate and heavy infections, respectively. Among individuals with light, moderate and heavy infections, 15 (21.4%), 4 (8.0%) and 1 (3.2%) subjects were negative by the reagent strip test, respectively.

Among the total of 189 positive urine samples tested by reagent strip test, 62 samples (32.8%) were grouped as strong positive whilst 127 (67.2%) were weak positive. Among the 62 strong positive samples, 11 samples (17.7%) were found to be negative by the Kato method. Similarly, among the 127 weak positive samples, 48 samples (37.8%) were found to be negative by the Kato method. Most of the subjects found to be strong positive by reagent strip test belonged to the moderate to heavily infected group.

Table 1 Association of Kato method with reagent strip test in the diagnosis of *Schistosoma mansoni*

Kato	Reagent strip	
	Positive	Negative
Positive	130	21
Negative	59	41

Table 2 Association of urine test with faecal examination in the diagnosis of *Schistosoma mansoni*

Urine	Stool	
	Positive	Negative
Positive	147	42
Negative	32	30

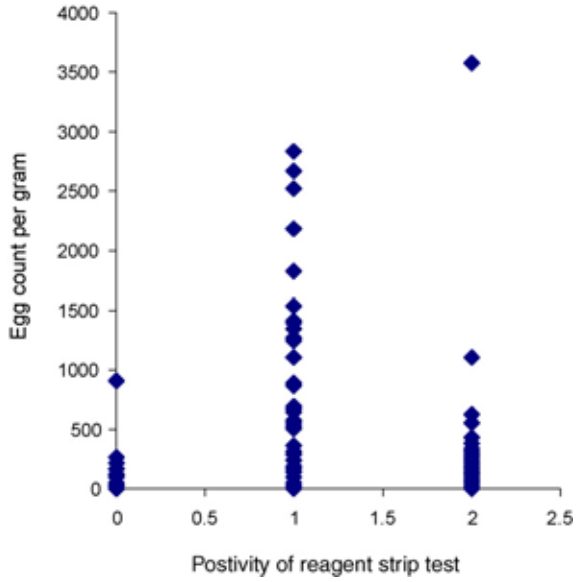

Figure 1 Association between reagent strip test score and the intensity of *Schistosoma mansoni* infection expressed as egg count per gram of stool sample.

On the other hand, the majority of subjects classified as weak positive were found to be in the light infection group (Figure 1).

3.6. Other intestinal helminths

Among the total 251 subjects, 32 (12.7%), 25 (10.0%), 4 (1.6%), 14 (5.6%) and 11 (4.4%) were positive for trichuriasis, ascariasis, hookworm infection, taeniasis and entrobiasis, respectively. Of the 42 subjects who were positive for schistosomiasis by reagent strip test but negative both by Kato and formol-ether concentration, 6 (14.3%), 2 (4.8%), 1 (2.4%) 1 (2.4%) and 4 (9.5%) subjects were positive for trichuriasis, ascariasis, hookworm infection, entrobiasis and taeniasis, respectively.

3.7. Control subjects

None was found to be positive for schistosomiasis among the 58 stool samples collected from schoolchildren in a non-endemic areas both by the Kato and formol-ether concentration methods. Nevertheless, 14 subjects (24.1%) were found to be positive for schistosomiasis by the reagent strip method. Regarding the other intestinal helminths, 26 (44.8%), 9 (15.5%) and 2 (3.4%) subjects were positive for ascariasis, trichuriasis and hookworm infection, respectively. Among the 14 positive subjects, approximately 71.4% were free of intestinal helminths as confirmed by the stool examination results, whilst only 3 (21.4%) and 1 (7.1%) subjects were positive for ascariasis and trichuriasis, respectively. The specificity of the reagent strip test was found to be 75.9% as determined using the control subjects.

Table 3 Association of urine test with faecal examination in the diagnosis of *Schistosoma mansoni* for efficacy evaluation

Urine	Stool	
	Positive	Negative
Positive	12	10
Negative	4	28

3.8. Efficacy evaluation

Among 121 individuals who swallowed the praziquantel tablets in the presence of the research team and considered for efficacy evaluation during the initial survey, 54 (44 males and 10 females) subjects provided stool and urine samples 6 weeks post treatment for the efficacy evaluation. Of these subjects, 16 (29.6%) and 22 (40.7%) individuals were found to be positive by Kato method and reagent strip test, respectively, whereas 12 subjects (22.2%) were positive by both methods (Table 3). The sensitivity of the reagent strip test was 75% and its specificity was 73.7% for the efficacy evaluation.

4. Discussion

This study was undertaken to evaluate the effectiveness of a recently developed reagent strip test (Van Dam et al., 2004) for the diagnosis of infection with *S. mansoni* by detecting CCA in urine under field conditions. The results revealed that detection of CCA in urine using one-step reagent strip test is superior both to the Kato method and formol-ether concentration for diagnosis of *S. mansoni*, as previously reported (De Clercq et al., 1997; Polman et al., 1995; Van Dam et al., 2004). Nevertheless, a significant difference was not found compared with the results obtained by the combination of

Table 4 Sensitivity, specificity, PPV and NPV of reagent strip/dipstick test observed under field-based conditions in the present study and in the studies by Van Dam et al. (2004) and Stothard et al. (2006)

Variables	Present study (%)	Previous studies (%)	
		Van Dam et al. (2004)	Stothard et al. (2006)
Sensitivity	82.1	100	83
Specificity	75.9	87	81
PPV	77.8	79.6	84
NPV	48.4	0	84

PPV: positive predictive value; NPV: negative predictive value.

Kato and formol-ether concentration methods. Assuming the parasitological results as the reference test, the sensitivity of the reagent strip test was found to be comparable with results observed elsewhere (Stothard et al., 2006), but lower than results reported by Van Dam et al. (2004). However, the specificity and positive predictive value observed in this study were slightly lower compared with those previous reports (Stothard et al., 2006; Van Dam et al., 2004), as shown in Table 4.

The disparity observed between the present and previous studies might be due to difference in the prevalence of the disease, which could influence the predictive values. The higher the prevalence, the more likely a positive test would be predictive of the disease. Thus, the positive predictive value of the reagent strip test or the dipstick test could be high in areas where the prevalence of *S. mansoni* is high (Stothard et al., 2006; Van Dam et al., 2004), whereas it is low in low prevalence areas. On the other hand, the negative predictive value is expected to be high as the prevalence of the disease decreases. In contrast, a low negative predictive value was observed in this study, although the prevalence of schistosomiasis in the study area appeared to be low.

Determination of positive and negative likelihood ratios might be more useful to describe the accuracy of a screening test than the sensitivity and specificity, irrespective of the prevalence (Dujardin et al., 1994). In this study, the positive likelihood ratio was found to be 3.41, which would indicate a high prevalence of *S. mansoni* in the study area. Specificity is also one of the basic features of a diagnostic test that accurately identifies subjects without the targeted problem (disease) (i.e. specificity is expected to provide a minimum of false positives). Thus, a test with high specificity is preferable in areas with a high prevalence of disease. A specificity rate as high as 90% was reported for a reagent strip test for the detection of CCA in a schistosomiasis non-endemic area of Tanzania (Van Dam et al., 2004). In contrast, detection of CCA in serum and urine resulted in a low specificity in Senegal and Burundi (Polman et al., 2000). Similar to this latter report, a considerable number of schoolchildren (24.1%; 14/58) were found to be positive for schistosomiasis by the reagent strip test in an area where the disease was not suspected. Although a slightly lower specificity of the urine CCA assay was suggested to be acceptable for a non-invasive screening test (Polman et al., 2000), further investigation is recommended on the specificity of the current reagent strip test.

A study by Van Lieshout et al. (1995a) suggested that detection of CCA in urine using ELISA is as sensitive as the parasitological method in demonstrating low intensity of infection. In contrast to this report, Stothard et al. (2006) observed low sensitivity of urine CCA in detecting light infection with *S. mansoni* using the dipstick method. In the present study, most of the subjects who were negative by the reagent strip test had a light infection as determined by the Kato method, which is in agreement with the latter finding. Nevertheless, the result of our study suggested the potential use of urine CCA in indicating the intensity of infection with *S. mansoni* as an alternative to the parasitological methods as reported previously (Stothard et al., 2006; Van Dam et al., 2004; Van Lieshout et al., 1995b).

One of the advantages of detecting circulating antigens in serum or urine from schistosomiasis patients is their high effectiveness in monitoring efficacy following chemotherapy with praziquantel (De Clercq et al., 1997; Nibbeling et al., 1998; Van Lieshout et al., 1991, 1994). Van Lieshout et al. (1994) observed a high level of CCA in urine from *S. mansoni* patients 6 weeks post treatment with praziquantel (40 mg/kg body weight). In contrast, Nibbeling et al. (1998) reported a complete disappearance of CCA from urine in *S. mansoni* patients 6 weeks post treatment with the same dose of praziquantel. In this study, assessment of eggs in stool and CCA in urine 6 weeks post treatment with praziquantel (40 mg/kg body weight) revealed a positivity rate of 30.2% by Kato method and 41.5% by reagent strip test, although approximately 95.5% of the positive samples were detected as a light infection in both cases.

In conclusion, the results of the present study suggest that diagnosis of *S. mansoni* by detecting CCA in urine using a newly developed reagent strip would provide information on the prevalence of the disease in highly endemic areas. Nevertheless, further study is needed to improve its specificity and sensitivity in low endemic areas.

Conflicts of interest statement

The authors have no conflicts of interests concerning the work reported in this paper.

Authors' contributions

ML and BE designed the study and participated in data collection; ML carried out data analysis and drafted the manuscript. ML and BE read and approved the final manuscript. ML and BE are guarantors of the paper.

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