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Original Article

Evaluation of Leukocyte Esterase Reagent Strips in Rapid Bedside Diagnosis of Spontaneous Bacterial Peritonitis

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ABSTRACT

Introduction: Spontaneous bacterial peritonitis is defined as an ascitic fluid infection without an evident intraabdominal surgically treatable source. Spontaneous bacterial peritonitis is one of the severe complications in patients with cirrhosis and ascites. Without early antibiotic treatment, this complication is associated with high mortality rate. Leukocyte esterase dipstick test can rapidly diagnose spontaneous bacterial peritonitis. The study was done to evaluate the diagnostic accuracy of leukocyte esterase dipstick test for the diagnosis of spontaneous bacterial peritonitis.

Materials and Methods: This was cross-sectional prospective study. Paracentesis was performed on admission. The ascitic fluid obtained at bedside was immediately tested with reagent strip. Ascitic fluid was then analyzed for neutrophil cell count. The result of reagent strip was compared with ascitic fluid cell count for determination of sensitivity, specificity, positive predictive value and negative predictive value of the test.

Results: Total 76 patients were enrolled in this study. Leukocyte esterase reagent strip correctly detected 23 (51%) positive and 45 (42.6%) negative cases of SBP. The sensitivity, specificity, positive predictive value, negative predictive value of leukocyte esterase dipstick test to diagnose spontaneous bacterial peritonitis were 88.46%, 90%, 82.14% and 93.75% respectively.

Conclusions: The leukocyte esterase dipstick test can be used as rapid test for diagnosis of spontaneous bacterial peritonitis due to its high diagnostic validity.

Keywords: Ascites; Cirrhosis; Leukocyte esterase; Spontaneous bacterial peritonitis

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INTRODUCTION

Liver cirrhosis is the final common pathway for a wide variety of chronic liver diseases. Approximately 50% of patients with compensated cirrhosis will develop ascites over a period of 10 years.[1] Spontaneous bacterial peritonitis (SBP) is defined as an infection of ascitic fluid (AF) without any evidence of an intra-abdominal surgically treatable source.[2]

The prevalence of SBP was 5% to 10% in cirrhotic patients with ascites.[3] The prevalence of SBP is much lower (3.5%) in asymptomatic outpatients and its outcome seems to be better than SBP occurring in hospitalized patients.[4] A study done in 2006 showed that the mean delay from paracentesis to a validated polymorphonuclear leukocyte (PMN) result out-of-hours was more than 4 hours even in standard laboratories.[5] Hence, rapid and accurate diagnostic tests are necessary for SBP.

The results of the ascitic fluid analysis are usually delayed and completely operator dependent. The delay in diagnosis would lead to increased morbidity and mortality. Besides in many centers, analysis of ascitic fluid is rarely done in the emergency setting. Thus, diagnostic dilemmas can occur especially if the patient is asymptomatic. Henceforth, the use of leukocyte esterase reagent strip (LERS) for the diagnosis of SBP can be critical. The objective of this study is to evaluate the diagnostic accuracy of LERS in the diagnosis of SBP by comparing the findings with standard laboratory PMN counts.

MATERIALS AND METHODS

This was a cross-sectional prospective study done for one year. The study was primarily based in the emergency department of Bir Hospital for one year. The study was approved was approved by the Institutional Review Board (IRB) of National Academy of Medical Sciences (NAMS). Written consent was taken. The sample size was calculated using the following formula: n= (Z2) (P) (1-P)/d2, where, n=required sample size, Z= Z statistic for a level of confidence (for 95% level of significance, Z = 1.96), P=estimated proportion in the population, d= precision or maximum tolerable error. A study in the Nepal done in 2003 found the prevalence to be 24.69%.[6]clinical and laboratory characteristics and the response to antibiotics. Methods: We had prospectively evaluated 81 cirrhotic patients with ascites during one-year period. All SBP patients were treated with cefotaxime, 2gm IV, every 12h for 5days. Results: Of these 81 patients, 24.67% of patients (n=20 A sample size of 73 was estimated.

Patients fulfilling the inclusion criteria (patients with chronic liver disease with diagnosis of SBP) and providing written consent were included in the study. Patients with ascites due to any cause other than liver cirrhosis, history of receiving antibiotics ten days prior to the hospital admission (which could alter the ascitic fluid analysis report), those with secondary peritonitis or with the possibility of super-added secondary peritonitis as ulcerated leaking umbilical hernia were excluded from the study. Standard of care was provided to all patients. Under all aseptic conditions, diagnostic ascitic tapping was performed in all the patients. 10 ml of ascitic fluid was drawn and send to the laboratory for diagnostic evaluation. Furthermore, the ascitic fluid obtained at bedside was immediately tested in a clean, dry test tube with reagent strip Multistix® 10 SG according to the manufacturer's guidelines for urine testing. The color of Reagent Square was compared with the color chart on the bottle, which read as either negative, trace or three-tier positive (+1, +2, +3). The result of the reagent strip was recorded in the respective questionnaire. Depending upon the results of the reagent strips, patients were administered either treatment or prophylactic doses of antibiotics. i.e., 2 gm of cefotaxime in case of positive result and 1 gm for negative results. The information in the patient's questionnaire and results of diagnostic tests including relevant blood parameters, ascitic fluid analysis and reagent strip was entered in computer and data analysis was done accordingly.

A PMN of >250 cells/ml of ascitic fluid was used as the cut off value for the diagnosis of SBP. The data in the questionnaires was used to determine various factors related to liver cirrhosis including sex predominance, cause, symptomatology, and grading of severity of the same. The grading of severity was done using Child Turcotte Pugh's (CTP) classification for chronic liver disease. The occurrence of SBP in patients with different values of albumin, bilirubin and INR was also assessed as a secondary objective of the study. Data entry was done in Microsoft excel and analysis was done using SPSS. Sensitivity, specificity, PPV and NPV of the reagent strips was calculated using relevant statistical methods. ROC curve was evaluated.

RESULTS

A total of 76 patients were collected in the study time. Among the 76 patients, 53 (69.73%) were males and the remaining 23 (30.26%) were females. Chronic alcohol consumption related liver disease was the most common cause of cirrhosis accounting for 77.9% (59) of the total cases. This was followed by chronic viral hepatitis B and C, each accounting for 9.2% (7) and 5.3% (4) of cases respectively. The remaining were 3 (3.9%) cryptogenic cirrhosis, single cases of cardiac cirrhosis, non-alcoholic Steatohepatitis (NASH) and Wilsons disease, each accounting for 1.3% of the total cases.

Among the 76 patients included, 85% (65) of them were in Child's class C indicating a worse prognosis. The remaining small fractions were in Class B and A with a distribution of 12% (9) and 2 (3%) respectively. 28 (36.84%) of the patients had SBP as per the results of the manual ascitic fluid PMN count. 48 (63.15%) of the patients had a negative PMN count, and hence no SBP. Culture was negative in all cases. While performing LERS in the given patients, 48 patients were negative, 16 were trace positive, 21 were 1+, 9 were 2+ and 6 were 3+ positive (Fig. 1).

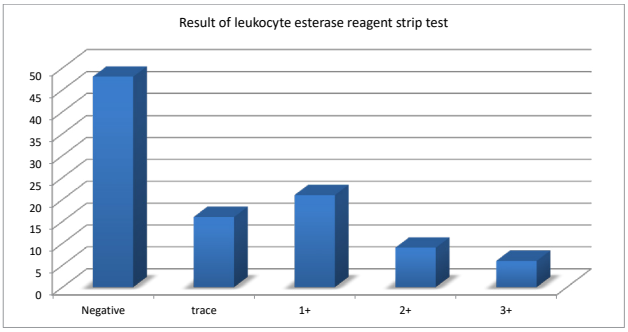

Figure 1: Results of leukocyte esterase strip test (n=76)

Table 1 shows the result of the LERS in patients who had or did not have SBP using the 1+ (positive) as cut off point. Accordingly, there were 23 true positive and 5 false positive results. Similarly, 3 results were false negative while 45 were true negative.

Table 1: Diagnostic accuracy of the LERS test (n=76)

	SBP Present	SBP Absent	Total
LERS Positive	23	5	28
LERS Negative	3	45	48
Total	**26**	**50**	**76**

The diagnostic accuracy results of the LERS were then calculated using the Medcalc statistical software. The sensitivity, specificity, PPV and NPV of the reagent strips were 88.46%, 90.00%, 82.14% and 93.75% respectively with 95% confidence interval (Table 2). Similarly, the strips had a positive likelihood ratio of 8.85% and negative likelihood ratio of 0.13%.

Table 2: Diagnostic test result interpretation (n=76)

Calculations	Results	Confidence Interval
Sensitivity	88.46%	69.82% to 97.42%
Specificity	90.00%	78.17% to 96.63%
Positive likelihood ratio	8.85	3.81 to 20.55
Negative likelihood ratio	0.13	0.04 to 0.37
PPV	82.14%	63.09% to 93.87%
NPV	93.75%	82.78% to 98.62%

The Receiver Operator Curve (ROC) for the reagent strip has an Area Under Curve (AUC) of 0.97 (Figure 2). This was calculated using a confidence interval of 95%.

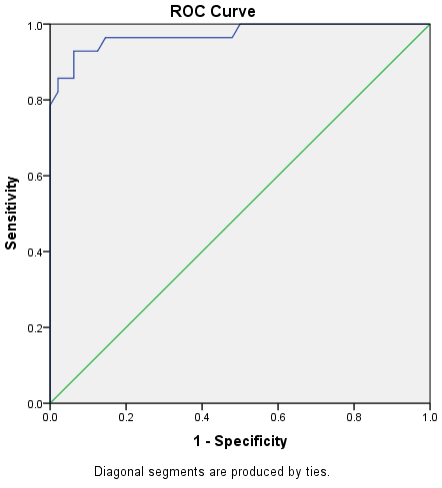

Figure 2: The Receiver Operator Curve (ROC) for the reagent strip

DISCUSSION

Liver disease is of big public health importance in any country and depends largely on the geopolitical and social factors. Chronic alcohol consumption was the most common cause of cirrhosis, which accounted for 59 (77.6%) cases in our study. A cross-sectional study done in Bir hospital in 2008 found that the alcohol consumption was the most common cause for liver cirrhosis accounting for 60.8% of the total cases. Following alcohol consumption, chronic hepatitis B and C were the other common causes of cirrhosis including 14.8% patients.[7] The common causes of chronic liver diseases in the world are alcohol abuse and infection with hepatitis B virus (HBV), and hepatitis C virus (HCV) and this was similar in this study as well. The community prevalence of both HBV and HCV infections in Nepal is low. Prevalence of HBsAg, a marker of HBV infection is 0.9%, and anti-HCV, a marker of past exposure to HCV is 0.38%. However, HBV and HCV accounted for 40% and 14% respectively of the liver cirrhosis in Nepal.[8]

A total of 28 cases among the 76 were found to have SBP in our context. In the study done by Syed VA et al in Dharan the occurrence of SBP was 24.69% of the patients with cirrhotic ascites.[6] In a study from India, Ayokunle et al, reported similar prevalence of SBP as 66.7% in hospitalized patients.[9] The prevalence of SBP depends on severity of liver dysfunction, being higher in advanced liver disease. This accounted for a prevalence of 36.18 %, which was slightly higher than observed in the above-mentioned studies.

Patients with ascites undergo surveillance paracentesis upon admission to the hospital; this procedure is also performed in patients who develop any signs or symptoms of infection. The net effect is that now approximately 13% patients with SBP have no signs or symptoms of infection.[10] When symptoms do occur, the most common are fever, abdominal pain and/or tenderness, and altered mental status. The only features of SBP in some patients are leukocytosis, encephalopathy or worsening renal function. In this study, abdominal distension was the most common clinical presentation that was found in 63 (82.9%) patients. This was followed by jaundice in 48 (63.2%), fever in 24 (31.6%), abdominal pain in 31 (40.8%), altered sensorium in 18 (23.7%), oliguria in 13 (17.1%), melaena in 10 (13.2%) and hematemesis in 4 (5.3%) of patients. On clinical examination, all the patients had ascites. This was because only cirrhotic patients with ascites were included in the sample size. This was followed by icterus in 65 (87.8%), abdominal tenderness in 47 (63.5%), fever in 20 (27%), splenomegaly in 40 (54.1%), asterixis and hepatomegaly in 15 (20.3%) each, hypotension in 13 (17.6%) and petechiae, purpura in 7 (9.5) patients.

A study evaluating the prevalence of SBP among patients with liver cirrhosis that was conducted in Dharan in 2007 observed that 85% of the patients had child's class C at presentation.[6]clinical and laboratory characteristics and the response to antibiotics. Methods: We had prospectively evaluated 81 cirrhotic patients with ascites during one-year period. All SBP patients were treated with cefotaxime, 2gm IV, every 12h for 5days. Results: Of these 81 patients, 24.67% of patients (n=20 As discussed previously, most patients present to hospitals in late stages in our context as well as one third belonged to CTP class C. A lot of factors including social, cultural, geographical and economic factors play a role in these late presentations.

Rapid diagnosis of spontaneous bacterial peritonitis is very important in patients with cirrhosis and ascites because of high rate of mortality and morbidity if treatment is delayed. One study has found the prevalence of SBP to be 26.4 % in Nepal.[6] However, more studies may be needed to confirm this result. Various studies in Pakistan found the prevalence of SBP to be widely variable ranging from 32% to 51%.[11] The high prevalence of SBP in these regions mandate a rapid diagnostic test for the condition, so that timely effective antibiotics can be initiated in time. This may also abolish the unnecessary use of antibiotics for patients who do not have SBP. The LERS have been widely evaluated and found to be good diagnostic efficacy.PMN count in ascitic fluid is the gold standard for the diagnosis of SBP. Due to poor prognosis of SBP,

antibiotics should be initiated immediately after diagnosis of the infection.[12] However, in small hospitals with limited laboratory facilities, counting of PMN leukocytes in the ascitic fluid cannot be performed on an emergency basis. In addition, in the case of inflammatory cell clumping, the laboratory analysis of ascitic fluid is not possible even in the academic hospital.

The availability of the urine strip test makes rapid bedside test with immediate initiation of antibiotic treatment possible. Various tests for the diagnosis of SBP have been developed like nitric oxide (NO), tumor necrosis factor (TNF) and interleukin-6 (IL-6), in ascitic fluid. However, routine measurement of these cytokines is not practical in a clinical setting. In this study leukocyte esterase reagent strip correctly detected 23 (51%) positive and 45 (42.6%) negative cases of SBP from total 76 ascitic fluid samples. Five cases were detected as false positive in which dipstick showed +1 or greater reading for a PMN count below 250/mm^3. False positive results can arise from detection of leukocyte esterase activity in the absence of intact cells. Esterase activity originating other than from leukocyte such as pancreas could produce false positive results.[13] There were 3 false negative results in patients with PMN cell count ≥250/mm^3. In this instance perhaps the PMN were not activated because only activated PMN cell releases the leukocyte esterase which could explain to some extent the observed negative test result.[14] The sensitivity, specificity, PPV and NPP of our study were 88.46%, 90%, 82.14% and 93.75% respectively. This study was done using 1+ as the cutoff point between positive and negative results. A similar study done by Nanik at al. in 2011 found a sensitivity, specificity, PPV and NPV of 92%, 95%, 96%, and 90% respectively.[13]

There is great potential in using leukocyte esterase reagent strips for diagnosis of SBP. The reagent strips are easy to use, do not require expertise, are rapid and low cost can be performed bedside. This test could be performed by the physician, house officer, nurse, or any other qualified technician collecting the ascites fluid. The result of the test could initiate appropriate management while standard ascitic fluid analyses are pending. Thus, the use of this diagnostic modality could save lives by prompting early therapy. High NPV of dipstick test could make it useful bedside screening tool, especially in ambulatory setting like OPD and emergency room. Patients with negative testing can be quickly discharged. Considering the mortality from SBP, this test will help to improve the management of SBP.

CONCLUSIONS

This study has shown a good sensitivity and specificity of LERS in diagnosing SBP. This will be of particular benefit in remote hospitals with less affluent health systems. A larger multicenter study should be done to give more validity to the findings of this study.

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