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SPONTANEOUS BACTERIAL PERITONITIS; EVALUATION OF ROLE OF ASCITIC FLUID LACTATE DEHYDROGENASE IN DIAGNOSIS

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ABSRACT... Objectives: To find out the diagnostic accuracy of ascitic fluid Lactate Dehydrogenase in diagnosis of Spontaneous bacterial peritonitis using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm^3 as a Gold Standard. **Study Design:** Cross sectional (validation) study. **Setting:** This study was conducted in department of Medicine, Madina Teaching Hospital Faisalabad. **Duration of Study:** 6 months starting after approval of synopsis (From:01-06-2016 to 30-11-16). **Methodology:** 10 ml of ascitic fluid was withdrawn from these patients, and sent for cytology and biochemistry. Ascitic fluid cell count, total protein, albumin and LDH wascalculated along with serum albumin and serum LDH. Serum LDH and ascitic fluid LDH was calculated by using Cobas C311 Roche Analyzer, serum/ascitic albumin gradient (SAAG) was calculated by subtracting ascitic albumin from serum albumin to prove portal hypertension as a cause of ascites. AsciticLDH/serum LDH ratio was calculated by dividing ascitic LDH by serum LDH.Absolute neutrophil count was derived from total WBC count. **Results:** In our study, mean age was calculated as 45.37+11.13 years, 53.75% (n=43) were male and 46.25% (n=37) were females. Frequency SBP on gold standard was recorded in 52.5% (n=42). Diagnostic accuracy of ascitic fluid lactate dehydrogenase in diagnosis of spontaneous bacterial peritonitis using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm^3 as a gold standard was recorded as 82.22%, 85.71%, 88.09%, 78.95%, 83.75% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate, positive likelihood ratio was calculated as 5.75 and 0.21 for negative likelihood ratio was calculated as 5.75. **Conclusion:** The diagnostic accuracy of ascitic fluid Lactate Dehydrogenase is higher in diagnosis of Spontaneous bacterial peritonitis using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm^3 as a Gold Standard.

Key words: Spontaneous Bacterial Peritonitis, Diagnostic Accuracy, Ascitic Fluid, Lactate Dehydrogenase.

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INTRODUCTION

Spontaneous bacterial peritonitis is a potentially fatal but reversible condition in patients with cirrhosis. By definition it is bacterial infection of the ascitic fluid without a localized source.[1]

SBP is having prevalence of 58% in Pakistan. It occurs in the background of severe hepatic cirrhosis.

According to an international study, the ratio of ascitic/serum lactate Dehydrogenase (LDH) ≥ 0.5[2] is having sensitivity of 80%, specificity of 88%, positive predictive value (PPV) of 66.7%, negative predictive value (NPV) of 93.7% and accuracy of 63.3% in diagnosis of SBP, while no local data is available at present in this regard.

SBP is diagnosed when an absolute polymorphic neutrophil count is greater than or equal to 250 cells/mm^3 in the ascitic fluid, with or without a positive ascitic fluid culture and without localized infection source.

At present this is the only criteria available for diagnosis of SBP and it is taken as a gold standard. These investigations are expensive and require time.

While ratio of ascitic/serum LDH is until now not included in gold standard and it can be measured in ascitic fluid and serum before gold standard and it is a less expensive investigation as compared to the gold standard.

Timely diagnosis of SBP is vital for patients, because the death rate among untreated patients is about 50%.[4] It will be a great addition in gold standard if we can prove the diagnostic validity of Ascitic fluid LDH in SBP. In this way we can diagnose SBP much earlier than other tests included in the gold standard can do this. Internationally, A lot of work is being done on it. But in Pakistan no studies are available in this regard.

MATERIAL AND METHODS

Cross sectional (validation) study was conducted in department of Medicine, Madina Teaching Hospital Faisalabad. Duration of study was 6 months starting after approval of synopsis from 01-06-2016 to 30-11-2016. By using sensitivity, specificity and sample size calculator sensitivity=80%[5]. Specificity=88%[5]. Prevalence = 58%[4]. Precision for sensitivity= 10%, precision for specificity= 10% and confidence interval=95%. Sample size = 80. Non probability consecutive sampling was done.

SAMPLE SELECTION

Inclusion Criteria

The patients of both male and female sex above 14 years of age with cirrhosis of any duration, having ascites along with clinical features like fatigue, anorexia, weight loss, and muscle wasting. Jaundice, spider angiomata, skin telangiectasias, palmar erythema, white nails (leukonachia), disappearance of lunulae, and finger clubbing are included.

Exclusion Criteria

Patients with non-cirrhotic ascites, evidence of secondary peritonitis, haemorrhagic ascites and evidence of intra-abdominal malignancy are excluded.

Data Collection Procedure

10 ml of ascitic fluid was withdrawn from these patients, and sent for cytology and biochemistry. Ascitic fluid cell count, total protein, albumin and LDH wascalculated along with serum albumin and serum LDH. Serum LDH and ascitic fluid LDH was calculated by using Cobas C311 Roche Analyzer, available at hospital laboratoryserum/ ascitic albumin gradient (SAAG) was calculated by subtracting ascitic albumin from serum albumin to prove portal hypertension as a cause of ascites. AsciticLDH/serum LDH ratio was calculated by dividing ascitic LDH by serum LDH. Absolute neutrophil count was derived from total WBC count. The data was collected by proforma having all the necessary details.

Data Analysis Procedure

The whole data was included via and assessedtrough SPSS V-20.Mean and standard deviation was calculated for all the quantitative variables like age. Frequency and percentage was calculated for all qualitative variables like gender and true positive, sensitivity, specificity, PPV, NPV and diagnostic accuracy was calculated by constructing 2 × 2 table by taking ascitic fluid absolute neutrophil count as gold standard.

RESULTS

A total of 80 cases were enrolled to determine the diagnostic accuracy of ascitic fluid LDH in diagnosis of SBP using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm^3 as a Gold Standard.

Age distribution of the patients shows that 46.25% (n=29) were between 15-40 years of age while 53.75%(n=51) were between 41-70 years of age, mean+sd was calculated as 45.37+11.13 years. (Table-I)

Age(in years)	No. of patients	%
15-40	29	46.25
41-70	51	53.75
Total	80	100
Mean+SD	45.37+11.13	

Table-I. Age distribution (n=80)

Gender distribution of the patients was done, it shows that 53.75% (n=43) were male and 46.25% (n=37) were females. (Table-II)

Gender	No. of patients	%
Male	43	53.75
Female	37	46.25
Total	80	100

Table-II. Gender distribution (n=80)

Frequency of SBP on gold standard was recorded in 52.5% (n=42) whereas 47.5% (n=38) had no findings of the morbidity. (Table-III)

Diagnostic accuracy of ascitic fluid LDHin diagnosis of SBP using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm as a gold standard was recorded as 82.22%, 85.71%, 88.09%, 78.95%, 83.75% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate, positive likelihood ratio was calculated as 5.75 and 0.21 for negative likelihood ratio was calculated as 5.75. (Table-IV)

SBP	No. of patients	%
Yes	42	52.5
No	38	47.5
Total	80	100

Table-III. Frequency of SBP on gold standard (n=80)

The data was stratified for age and gender. (Table-V&VI)

Ascitic Fluid Lactate Dehydrogenase	Ascitic Fluid Absolute Neutrophil Count Equal To Or Greater Than 250 CELLS/mm3		Total
	SBP(Positive)	SBP(Negative)	
Positive	True positive(a) 37	False positive (b) 5	a + b 42
Negative	False negative(c) 8	True negative (d) 30	c + d 38
Total	a + c 45	b + d 35	80

Table-IV. Diagnostic accuracy of ascitic fluid ldhin diagnosis of SBP using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm^3 as a gold standard (n=80)

Sensitivity = a / (a + c) x 100 =82.22%
Specificity = d / (d + b) x 100 = 85.71%
Positive predictive value = a / (a + b) x 100 =88.09%
Negative predictive value = d / (d + c) x 100 =78.95%
Accuracy rate = a + d / (a + d + b + c) x 100 = 83.75%
Positive Likelihood Ratio: Sensitivity/1–Specificity: 5.75
Negative Likelihood Ratio: Sensitivity/1 – Specificity: 0.21

Ascitic Fluid LDH	Ascitic Fluid Absolute Neutrophil Count Equal To Or Greater Than 250 CELLS/mm3		P value
	SBP (Positive)	SBP (Negative)	
Positive	True positive(a) 14	False positive (b) 1	0.0001
Negative	False negative(c) 3	True negative (d) 11	

Table-V. Stratification for to age 15-40 years

Sensitivity = a / (a + c) x 100 =82.35%
Specificity = d / (d + b) x 100 = 91.67%
Positive predictive value = a / (a + b) x 100 =93.33%
Negative predictive value = d / (d + c) x 100 =78.57%
Accuracy rate = a + d / (a + d + b + c) x 100 = 86.20%

Ascitic Fluid LDH	Ascitic Fluid Absolute Neutrophil Count Equal To or Greater Than 250 CELLS/mm3		P value
	SBP(Positive)	SBP(Negative)	
Positive	True positive(a) 23	False positive (b) 4	0.000
Negative	False negative(c) 5	True negative (d) 19	

Table-VI. 41-70 years

Sensitivity = a / (a + c) x 100 =82.14%
Specificity = d / (d + b) x 100 = 82.60%
Positive predictive value = a / (a + b) x 100 =85.18%
Negative predictive value = d / (d + c) x 100 =79.17%
Accuracy rate = a + d / (a + d + b + c) x 100 = 82.35%

DISCUSSION

Spontaneous bacterial peritonitis is the infection of the ascitic fluid without any respectable source of infection in the peritoneal cavity. Its incidence in ascitic patients lies between 7-30%.[6] LDH and tumor markers like VEGF can be used todifferentiate benign from malignant diseases.[7] Internationally, a lot of work is being done on it.

But in Pakistan no studies are available in this regard. That is why diagnostic accuracy of ascitic fluid LDH is being researched here so that it can be included in criteria for diagnosis of SBP which is taken as a gold standard worldwide.

In our study, out of 80 cases, 46.25%(n=29) were between 15-40 years of age while 53.75%(n=51) were between 41-70 years of age, mean+sd was calculated as 45.37+11.13 years, 53.75%(n=43) were male and 46.25%(n=37) were females. Frequency SBP on gold standard was recorded in 52.5% (n=42).[8] Diagnostic accuracy of ascitic fluid LDHin diagnosis of SBP using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm^3 as a gold standard was recorded as 82.22%, 85.71%, 88.09%, 78.95%, 83.75% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate, positive likelihood ratio was calculated as 5.75 and 0.21 for negative likelihood ratio was calculated as 5.75.[9]

The findings of our study are in agreement with an international study, where the ratio of ascitic/serum LDH≥ 0.5 is having sensitivity of 80%[5], specificity of 88%5, positive predictive value (PPV) of 66.7%[5], negative predictive value (NPV) of 93.7%[5] and accuracy of 63.3%[5] in diagnosis of SBP.

Previous studies showed that there is high level of LDH in ascetic fluid associated with malignancies than with benign conditions.[10] According to studies carried out by Boyer et al, patients with cirrhosis had higher level of LDH in ascitic fluid than those with malignancies (167±9 vs. 913±228 SU).[11] Light et al proposed that LDH and total protein analysis should be done for ascitic fluid too as it is done with pleural fluid. The cut-off values to differentiate between ascitis associated with liver disease and other causes are, as follows: LDH= 400 SU, fluid/serum LDH ratio of 0.6, and fluid/serum total protein ratio of 0.5. Levels higher than the cut-offs for any 2/3 parameters indicate a cause not associated with liver disease, while values below the cutoffs for all 3 parameters highly suggest cirrhosis is causing this ascites.

Ascites can be caused by many diseases and carries anpoor prognosis which is mainly dependent on the actual cause. Mostly it is caused by cirrhosis and if infection occurs, it further worsens the ascites. Ascitic fluid should be investigated by checking its gross appearance, biochemical tests likeLDH, WBCs, RBCs, culture and PCR, viscosity, 1H NMR spectroscopy, VEGF, and tumor markers. These investigations along with clinical examination and imaging will help in diagnosing the actual cause. In absence of the local data, our findings are primary and needs to be verified through someother local studies.

CONCLUSION

The diagnostic accuracy of ascitic fluid LDHis higher in diagnosis of SBP using ascitic fluid absolute neutrophil count equal to or greater than 250 cells/mm^3 as a Gold Standard. However, someother local data is required to validate our findings.

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– Unknown –

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