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Clinical Study of Ascites with Special Reference to Serum Ascites Albumin Gradient and Serum Ascites Cholesterol Gradient

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Abstract: ***Background: Ascites being a common clinical problem with a vast spectrum of etiologies, biochemical parameters are required to differentiate ascites which can correlate with pathogenesis. Aims of the study were to determine the sensitivity, specificity and diagnostic efficacy of serum ascites albumin Gradient (SAAG) and that of ascitic fluid total protein (AFTP), evaluating their diagnostic role in identifying the etiology of ascites, to determine the diagnostic efficacy of Ascitic fluid cholesterol and serum ascites cholesterol gradient (SACG) in diagnosis of malignant ascites. Methods: In this study, 50 patients of ascites were evaluated for ascitic fluid total protein, albumin, cholesterol, SAAG and SACG along with ultrasound. Results: Sensitivity, Specificity, and Diagnostic accuracy of SAAG for Portal hypertension were 95.5%, 100%, 96% respectively, whereas those of AFTP for exudative/transudative ascitis were 100%, 75%, 78% respectively. Similarly with a cut off level of 70mg% and 54 mg%, ascitic fluid cholesterol and SACG are having diagnostic accuracy of 96% and 98% respectively. Conclusions: SAAG is much more superior to AFTP in differential diagnosis of Ascitis. Ascitic fluid cholesterol and SACG are simple and cost effective methods to separate malignant ascitis from non-malignant causes even in small centres with limited diagnostic facilities.***

Keywords: Malignant ascitis, Portal hypertension, Serum ascites cholesterol gradient, Serum ascites albumin gradient

1. Introduction

Ascites is the pathological accumulation of fluid in the peritoneal cavity.[1] The patients who suffer from ascites present a diagnostic and therapeutic problem. Abdominal paracentesis with careful analysis of ascitic fluid should be a very early step in evaluating patients with ascites. It is the most rapid and most effective method in the diagnosis of ascites. The traditional classification of ascites into exudative and transudative involves estimation of ascitic fluid total protein (AFTP) which is high > 3 gm/dl in exudative and < 3 mg/dl in transudate.[2] This classification however, is unable to correctly identify the etiological factors responsible for its causation.[3, 4] In contrast the Serum – Ascites Albumin Gradient (SAAG)-(defined as serum albumin concentration minus ascitic fluid albumin concentration) has been proposed a physiologically based alternative criterion in the classification of ascites. In case of portal hypertension, oncotic pressure gradient between plasma and ascitic fluid has to be raised, to counter balance the high hydrostatic pressure driving the fluid to the intraperitoneal cavity.[5] The difference between the serum and ascitic albumin concentration was used to differentiate ascitic fluid into gradient ≥ 1.1 gm/dl in case with portal hypertension and < 1.1 gm/dl in ascites unrelated to portal hypertension(5). Various studies have shown superiority of SAAG in classifying ascites compared to transudate-exudate concept.[6-8] The present study was undertaken to evaluate the value of SAAG in the differential diagnosis of ascites. Now Ascitis due to malignancies are on rise and difficult to diagnose by routine Ascitic fluid analysis. although SAAG accurately differentiate Ascitis due to Portal Hypertension from other causes, but SAAG is not able to differentiate between malignant ascites and tuberculous ascites as both are having low SAAG (<1.1 gm%)(9). Fluid cytology has low sensitivity for malignancy as the differentiation between reactive atypical mesothelial cells and malignant cells is sometimes difficult.(10, 11).Most of the time, diagnosis in not possible without invasive and expensive investigations like CT abdomen, biopsy and FNAC of peritoneal nodes and diagnostic laparotomy/laparoscopy. So there is a need for more specific and a highly sensitive new marker in presumptive diagnosis of ascites. There are few studies regarding ascitic fluid cholesterol level and SACG (serum ascites cholesterol gradient) as a sensitive, cheap and non-invasive parameter in diagnosing malignancy related ascites(12-16) According to Rana et al, Total Ascitic protein (70%), Ascitic serum protein ratio (74%), ascitic leukocyte count (54%), and malignant cytology (82%) yielded much lower diagnostic efficiency than ascitic fluid cholesterol (94%) in the diagnosis of malignant ascites.(12).Again a study shows cholesterol has been found to clearly differentiate between tuberculous and malignant ascites(16).The elevated cholesterol levels in malignancy is due to the increased vascular permeability, increased cholesterol synthesis and release from malignant cells implanted on peritoneum.(12, 16)

2. Methods

This Prospective observational study on “ascitic fluid analysis with special reference to SAAG and SACG” has been carried out in department of Pathology, Cygnus Hospital, Kurukshetra (Haryana) during year 2019. All 50 patients with ascites were subjected to detailed history and thorough clinical examination, a base line investigation - CBP, LFT, RFT, Serum Cholesterol, Serum Albumin, ECG

and ultrasound scan of abdomen were performed. Diagnostic paracentesis was done with prior written consent using 20-22 gauge 2.5 inch disposable needles under sterile precautions using Z tract Technique. Around 50 ml fluid was aspirated and fluid was immediately sent for Biochemical Analysis for Albumin, Total Protein, Cholestrerol, Glucose, and ADA, Cytological Analysis for Cell counts and Differential count. Serum and Ascitic fluid Albumin were estimated in autoanalyser by Bromocresol green. Total Protein was estimated in autoanalyser by Biuret methods. The serum cholesterol and Ascitic fluid cholesterol were also estimated. Serum samples for Cholesterol and Albumin were also sent at same time as Ascitic fluid sample for accurate calculation of SAAG and SACG. SAAG and SACG were calculated simply subtracting the ascitic fluid value from the serum value.

Diagnosis of liver cirrhosis conformed by clinical features of Portal HTN and Hepato-cellular failure, alcoholic history, and ultra sound. Heart diseases conformed by clinical history, ECG, X ray chest. HCC and malignant deposit in liver conformed by clinical history, liver biopsy alfa-fetoprotein, ultra sound abdomen, and CT abdomen, ascitic fluid study for malignant cells. TB peritonitis conformed by clinical history, ultra sound abdomen, ascitic fluid ADA,, ascitic fluid AFB.

3. Statistical analysis

The results were statistically analyzed by independent T test . A two tailed probability value of <0.05 was taken as indicating significance.

4. Result

50 cases of Ascitis in the age range of 20year to 85 year were included in the study irrespective of etiology. The distribution of ascites among the males and the females was more or less equal with 38 males (76 %) and 12 (24%) females with majority of the cases i.e. 31 (62%) are aged above 50 years.

Table 1: Etiological distribution

Etiology	Total number (n=50)
Cirrhosis	44
Tuberculous ascites	05
Hepatocellular carcinoma	01
Decompensated heart failure	-
Pancreatitis	-
Nephrotic syndrome	-

Table 1 shows cirrhosis of the liver (88%) ranked first followed by tuberculous peritonitis (10%) and malignant ascites(02%).

Table 2: Distribution of ascites on the basis of ascetic fluid total protein

Etiology	AFTP≥ 3	AFTP<3
Cirrhosis	11	33
Tuberculous ascites	05	0
Hepatocellular carcinoma	01	0

Table 3: Comparison of AFTP and exudative/transudative

Pathophysiology	Exudate (Expected AFTP>3)	Transudate (Expected AFTP<3)
AFTP≥3	06(True positive)	11(False positive)
AFTP<3	00(False negative)	33(True negative)
Sensitivity	100%	
Specificity	75%	
Positive predictive value	35.29%	
Negative predictive value	100%	
Diagnostic accuracy	78%	

Based on Pathophysiology of Ascitis, 50 cases of ascites were expected to have portal hypertension related etiology (Cirrhosis 44+ Hepatocellular Carcinoma 01) and 05 remaining cases without portal hypertension (Tuberculous ascites 05) which was subsequently confirmed by Presence or Absence of Ultrasonographic findings suggestive of Portal Hypertension.

Table 4: Distribution of ascites on the basis of SAAG

Etiology	SAAG≥1.1	SAAG<1.1
Cirrhosis	43	01
Tuberculous ascites	0	05
Hepatocellular carcinoma	0	01

Table 5: Comparison of SAAG and portal hypertension

Pathophysiology	Portal HT (expected high SAAG)	Non Portal HT (expected low SAAG)
High SAAG(≥1.1)	43(True positive)	00(False positive)
Low SAAG(<1.1)	02(False negative)	05(True negative)
Sensitivity	95.5%	
Specificity	100%	
Positive predictive value	100%	
Negative predictive value	71.4%	
Diagnostic accuracy	96%	

Table 6: Comparison of mean SAAG with mean AFTP in cases of ascites having portal hypertension from others with normal portal pressure

	Portal hypertension (n=45)	Non Portal Hypertension (n=5)	P value
Mean AFTP(gm/dl)	2.623±1.355	5.588±1.547	0.000
Mean SAAG(gm/dl)	1.345±0.408	0.640±0.288	0.000

Statistical Test: Independent T test

Table 7: Comparison of AFTP and SAAG in differential diagnosis of ascites

Parameters	AFTP	SAAG
Sensitivity	100%	97.7%
Specificity	75%	100%
Positive predictive value	35.29%	100%
Negative predictive value	100%	83.33%
Diagnostic accuracy	78%	98%

The five variables calculated for both SAAG and AFTP are noted in Table: 7, clearly indicates with no doubt that SAAG is a significantly better parameter than AFTP in determining the etiology of ascites and correlates well with the pathogenesis, i.e., Presence of portal Hypertension or not.

Table 8: Comparison of the diagnostic accuracies of SAAG and AFTP as per etiology in present study

Etiology	SAAG	AFTP
Cirrhosis	98%	22%
Tuberculous ascites	98%	76%
Hepatocellular carcinoma	90%	68%

Table 8 shows that even for individual etiologies, diagnostic accuracies of SAAG are much better than AFTP especially in Cirrhosis and in tuberculous ascites.

Table 9: Analysis of mean ascitic fluid cholesterol and mean SACG in distinguishing malignant from non malignant ascites

	Malignant ascites(n= 1)	*Non-malignant ascites(n= 49)*	*P value*
Ascitic fluid cholesterol (gm/dl)	100±0.00	51.06±18.18	0.010
Mean SACG(gm/dl)	37±0.00	93.69±26.35	0.038

Statistical Test: Independent T Test

Table 10: Diagnostic values of SACG and ascitic fluid cholesterol in separating malignant from non malignant ascites

Parameter	Cut off value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Ascitic fluid cholesterol(mg/dl)	>70mg%	100%	95.9%	33.3%	100%	96%
SACG(mg/dl)	<54mg%	50%	100%	50%	100%	98%

As shown in Table 10, at a cut off level of 70mg%, Ascitic fluid cholesterol has sensitivity 100%, specificity 95.9%, positive predictive values 33.3%, negative predictive value 100% and diagnostic accuracy 96%. Similarly At a cut off level of 54mg%, SACG has sensitivity 50%, specificity 100%, positive predictive values 50%, negative predictive value 100% and diagnostic accuracy 98%.

5. Discussion

For many years, the ascitic total protein concentration has been used to determine whether ascitic fluid was a transudate (AFTP<3 gm%) or exudate (AFTP ≥3gm%). These exudates – transudate concept was based on the fact that exudates fluid is from the inflammed and tumor laden peritoneal surface hence it is high in protein suggestive of peritonitis or malignant ascitis. The transudate fluid is from normal peritoneal surface and is low in protein and is formed commonly due to increase in portal pressure in accordance with Starling hypothesis. Various studies have challenged accuracy of traditional exudates-transudate concept which does not truely reflect the pathophysiology.

Again the relationship between ascitic protein concentration and character as transudate or exudates does not hold true in many conditions as it does not take the value of serum albumin into account. Gupta et al reported that 24% of patients with uncomplicated cirrhosis had an ascitic total protein concentration greater than 3 gm% suggestive of exudates.[8] Present study also supports the above fact as it shows diagnostic accuracies of AFTP in Cirrhosis, tubercular ascites and Malignancy is 22%, 76% and 68% respectively which is much less than that of SAAG which is 98%, 98% and 90% respectively.

Hence SAAG defined as the serum albumin concentration minus the ascitic fluid albumin concentration, had been proposed as a physiologically based alternative in the classification of ascites first by Hoefs.[17]Thereafter, several investigators have also demonstrated superiority of SAAG in distinguishing portal hypertensive ascites (SAAG >1.1 g/L) and non-portal hypertensive ascites (SAAG <1.1 g/L).[3, 8, 9] Portal hypertension results in an abnormally high hydrostatic pressure gradient between the portal bed and the ascitic fluid. A similarly large difference must exist between the ascitic fluid and the intravascular oncotic forces. As albumin is major determinant of oncotic pressure in the serum, SAAG is directly related to oncotic pressure gradient and thus proportional to portal pressure gradient and does not vary even in patients treated with diuretics, heart failure, albumin infusion and in presence of SBP.[1, 6]Above views are supported in present study which shows Sensitivity, Specificity, Positive predictive value (PPV), Negative predictive value (NPV) and Diagnostic accuracy of SAAG and Portal hypertension were 95.5%, 100%, 100%, 71.4%, 96% respectively, whereas those of AFTP and exudative/ transudative ascitis were 100%, 75%, 35.29%, 100%, 78% respectively. All data's tabulated and analysed above validated high statistical significance.

Mechanism of raised Ascitic fluid cholesterol in Malignant Ascitis

An enhanced movement of plasma lipoproteins like LDL and HDL into peritoneal cavity due to increased permeability of malignant serosal epithelia is likely explanation of the raised cholesterol levels especially in Peritoneal Carcinomatosis as described by Jungst et al.[18] It has also been suggested that a minor fraction of cholesterol in malignant ascites might be derived from fragile cell membranes of malignant cells as cholesterol is a constituent of cell membrane (Gerbes et al).[19] Third mechanism may be due to obstruction in lymph flow causing a rupture of lymphatic channel, which leads to secretion of chyle into the peritoneal cavity.

6. Conclusion

The present study concluded that the presence of high SAAG indicates portal hypertension even in presence of high ascitic fluid protein. It is superior to previously proposed transudate-exudate classification, because of its higher diagnostic accuracy and it provides a better approach to pathogenesis of ascitic fluid collection. SAAG does not provide exact etiology of ascites especially in low SAAG conditions like tubercular and malignant ascites, in our present study with small sample size, we got only one malignant ascites with diagnostic accuracy 96% and 98% of fluid cholesterol and mean SACG with a cut off level of 70mg% and 54mg% respectively than SAAG which is only 90%.Hence fluid cholesterol and SACG are simple and cost effective biochemical markers, can be utilized to separate

malignant ascites from non-malignant causes even in small centres with limited diagnostic facilities.

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