

Effect of Endoscopic Sphincterotomy and or Sphincteroplasty during Endoscopic Retrograde Cholangiopancreatography (ERCP) on the levels of CA19-9

Aadil Ashraf, Basharat Ahmad, Mushtaq Khan, Insha Zahoor

Abstract

Objective: The relationship between CA19-9 and jaundice has been analysed and studied to find possible adjustments to increase the sensitivity, specificity and predictive value of the test in differential diagnosis of hepatobiliary diseases associated with jaundice. The aim of the study was to observe the change in the level of CA 19-9 after endoscopic sphincterotomy or sphincteroplasty and whether the levels of CA 19-9 after sphincterotomy or sphincteroplasty can differentiate between malignant and benign obstruction.

Materials and methods: In this prospective study, 200 patients undergoing ERCP were included and the change in levels of CA 19-9 before and after ERCP were documented and analysed.

Results: A total of 200 patients were recruited in the study from May 2019 to June 2021. The mean age of the patients was 48.76 ± 17.02 years {5,85}. Of the two hundred patients in our study, 130 (65%) were females and 70 (35%) were males with a female to male ratio of 1.85:1. 159 (79.5%) patients had benign disease and 41 (20.5%) patients had malignant disease. Among patients with benign disease, Choledocholithiasis (30.5%) was the most common etiology followed by Cholelithiasis with Choledocholithiasis (28%) and least common was papillary adenoma (0.5%), whereas in patients with malignant disease, Cholangiocarcinoma (9.5%) was the most common etiology. Fall in CA19-9 level within 72 hrs. of papillotomy during ERCP was seen in 125 (62.5%) of patients, rise in CA19-9 level was seen in 46 (23.0%) patients and no change occurred in 29 (14.5%) patients.

Conclusion: We found that fall in serum levels of CA19-9 in benign group following biliary drainage was more than the rise and no change; and this fall in CA19-9 level in benign group was more than that in the malignant group.

Key words: CA19-9, ERCP, CA 19-9 in benign liver disease.

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Introduction

Serum carbohydrate antigen 19-9 (CA19-9), a tumor marker for malignancies of the hepatobiliary tract and pancreas, is frequently elevated in a number of non-malignant conditions that are associated with jaundice. The CA 19-9 tends to normalize following the restoration of biliary drainage with the help of ERCP (Endoscopic Retrograde Cholangiopancreatography).[1]

CA19-9 is mainly distributed in the fetal pancreas, gallbladder, liver, intestine and other tissues, and in healthy adult pancreas, bile duct epithelium, etc. In healthy people, CA19-9 is synthesized and secreted by bile duct and pancreatic duct epithelial cells, transported to the common bile duct and pancreatic duct, and then discharged through the duodenum. CA19-9 in the bile duct cells is rarely released into the peripheral blood under normal circumstances. CA19-9 level increases in peripheral blood in some malignant tumors, including pancreatic

Author Affiliations

Aadil Ashraf, DM Consultant Medical Gastroenterology, Asian Institute Of Gastroenterology, Hyderabad, **Basharat Ahmad**, MD, Sher I Kashmir Institute Of Medical Sciences, Soura, **Mushtaq Khan**, DM, Professor Gastroenterology, Sher I Kashmir Institute Of Medical Sciences, Soura, Insha Zahoor GP DHA.

Correspondence

Dr Aadil Ashraf, MD, DM, Consultant Medical Gastroenterology, Asian Institute Of Gastroenterology, Hyderabad, Telangana, India
Email: draadilgastro@gmail.com
Mobile: +91-9596251400

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Keywords

Endoscopic Sphincterotomy, Endoscopic Cholangiopancreatography, Retrograde CA19-9

cancer, gastric cancer, gallbladder carcinoma etc as well as benign diseases such as pancreatitis, cholangitis, and choledocholithiasis.[2-4] Occasionally, bile duct stones, inflammation and other benign diseases can lead to markedly elevated levels of serum CA19-9.[5,6] Elevated levels of CA19-9 can be seen in healthy individuals also.

Benign conditions associated with elevated levels of CA19-9 include biliary tract obstruction, Cholangitis, Inflammatory bowel disease, acute or chronic pancreatitis, liver cirrhosis, cystic fibrosis, thyroid disease etc.

Malignant conditions associated with elevated levels of CA19-9 include bile duct cancers, pancreatic cancers, colorectal cancer, gastric cancers, ovarian cancers, hepatocellular cancers, Esophageal cancers etc.

Ca19-9 and pancreato-biliary cancer:

Biliary tract cancer is a heterogeneous tumor entity mostly diagnosed at an advanced stage and need palliative treatment with chemotherapy and/or biliary drainage, both of which showing benefits over no therapy or best supportive care.[7] Serum CA 19-9 levels have been used for preoperative staging, assessment of resectability and prognosis of pancreato-biliary cancer, as well as diagnosis of tumor recurrence.[8] The upper normal limit of CA19-9 is 37 U/mL.

CA19-9 is a tumor marker that increases in pancreatic and biliary malignancies and it has been used as a test for their diagnosis. In pancreatic cancer, CA19-9 has been reported to have 70%-80% sensitivity and 80%-90% specificity in tumor diagnosis, whereas in cholangiocarcinoma without history of sclerosing cholangitis, the sensitivity and specificity are 77.9% and 76.3%, respectively.[9,10]

CA19-9 is increased not only in patients with pancreatic or biliary cancers but also in benign biliary diseases which often present with jaundice and is therefore often misleading, reducing significantly the diagnostic accuracy of this marker.[11]

The relationship between CA19-9 and jaundice has been analyzed and studied to find possible adjustments to increase the sensitivity, specificity and predictive value of the test in differential diagnosis of hepatobiliary diseases associated with jaundice. Therefore, some authors have suggested adjusting CA19-9 value by dividing it by the serum bilirubin value.[12,13]The overall low specificity and sensitivity of this assay precludes its use as a screening tool for pancreatic cancer.

An elevated tumor marker level needs to be interpreted within the context of the patient's history, physical examination, diagnostic imaging and laboratory workup findings.

Ca19-9 and obstructive jaundice:

Obstructive jaundice is the most common condition that is associated with significant elevation in serum carbohydrate antigen (CA 19-9). Elevation of serum CA 19-9 in patients with obstructive jaundice may

depend on multiple factors: CA 19-9 production by irritated bile duct cells exposed to the increased biliary pressure [14]; inflammatory proliferation of epithelial cells which produce CA 19-9 accumulation of CA 19-9 in the lumen due to biliary obstruction and increased permeability between bile and blood with subsequent reflux into the circulation; decreased clearance of biliary mucins due to cholestasis. and inability to degrade the antigen in the liver due to hepatic dysfunction. Because of these dysfunctions, a strong correlation between serum CA 19-9 concentration and the standard parameters of cholestasis namely alkaline phosphatase, gamma-glutamyl transferase (GGT) and bilirubin has been demonstrated. Therefore, further measurement of CA 19-9 after the jaundice subsides can be helpful in discriminating those patients with persistent elevation of CA 19-9 due to malignancies.[15]

The aim of the study was to observe: The change in the level of CA 19-9 after endoscopic sphincterotomy or sphincteroplasty. Whether the change in the levels of CA 19-9 after sphincterotomy or sphincteroplasty can differentiate between malignant and benign obstruction.

Material and methods

This study was a prospective study conducted in the Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar from June 2019 to May 2021.

Subjects

A total of 200 patients who were admitted in the Department of Gastroenterology during the study period for Endoscopic Retrograde Cholangiopancreatography (ERCP) were recruited in this study.

Inclusion criteria

All the patients who underwent either sphincterotomy and or sphincteroplasty during Endoscopic Retrograde Cholangiopancreatography (ERCP) were included in the study.

Exclusion criteria

Patients who had already undergone sphincterotomy and or sphincteroplasty were excluded from the study.

Clinical assessment

All the patients whosoever gave consent were subjected to detailed history and examination after taking proper consent according to predefined protocol as depicted in the proforma. Blood samples were collected from each patient before ERCP and within 72 hours following ERCP. CBC, LFT were done before ERCP and CA 19-9 levels were estimated from the blood samples obtained before and within 72hrs of ERCP, after performing the procedure. ECG, chest x-ray, ultrasound abdomen, CECT abdomen and MRCP were performed before ERCP.

Method of CA19-9 estimation

Sera was separated from each sample and levels of CA19-9 were determined in each sample. CA19-9 level estimation was done in the Department of Immunology and Molecular Medicine using

“Chemiluminescence two site immunoenzymatic (sandwich) assay”.

The CA19-9 antigen assay is a two-site immunoenzymatic (sandwich) assay. Sample is added to a reaction vessel along with paramagnetic particles coated with polyclonal goat anti-biotin antibody, mouse monoclonal-biotin conjugate, and a buffered protein solution. After incubation in a reaction vessel, separation in a magnetic field and washing remove materials not bound to the solid phase. A monoclonal alkaline phosphatase conjugate is then added. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-phos 530 is added to the vessel and the light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of CA19-9 antigen in the sample.

Statistical Analysis

Statistical package for social sciences (SPSS) ver. 22 was used for data analysis. The results were expressed as percentages or mean±SD, as specified. Categorical data was analyzed by using Pearson’s Chi-square test and quantitative data by using two sample independent t-test. P-value less than 0.05 was considered as statistically significant.

Results

A total of 200 patients were recruited in the study from May 2019 to June 2021. The mean age of the patients was 48.76±17.02 years {5,85}. Of the two hundred patients in our study, 130(65%) were females and 70(35%) were males with a female to male ratio of 1.85:1.

Patients recruited in our study had varied etiology of underlying biliary obstruction. 159 (79.5%) patients had benign disease and 41(20.5%) patients had malignant disease. Mean age of the patients with benign disease was 46.72±17.620 years and that of the patients with malignant disease was 56.71 ± 11.587 years {Fig 1}. Benign diseases were more common in females (70.4%) and malignant diseases were more common in males (56.1%) and the difference was statistically significant (p<0.001) {Fig 2}.

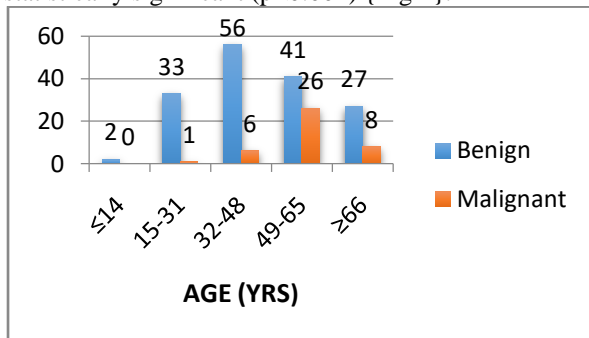
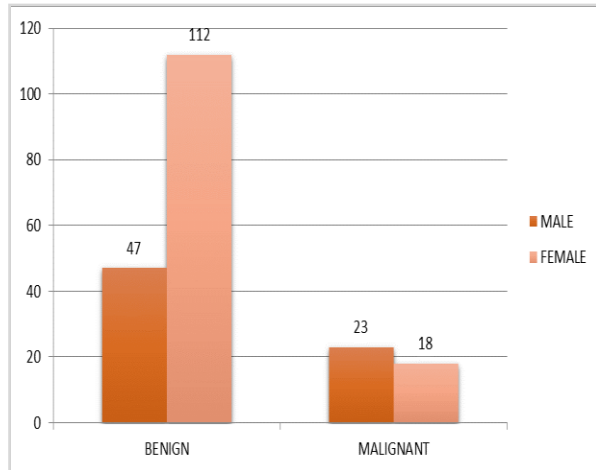


Fig 1: Age distribution of patients in benign and malignant disease.

Fig 2: Sex distribution of the two groups.

Various causes of biliary obstruction included: Choledocholithiasis (30.5%), Cholelithiasis with

choledocholithiasis (28.0%), Cholangiocarcinoma with extrahepatic biliary obstruction (9.5%), Chronic calcific pancreatitis (7.5%), acute pancreatitis with choledocholithiasis (5.0%), Pancreatic carcinoma with extrahepatic biliary obstruction (4.0%), Periampullary carcinoma with extrahepatic biliary obstruction



(3.0%), Carcinoma GB with extrahepatic biliary obstruction (3.0%), Choledochal cyst (2.5%), CBD stricture (2.0%), Biliary ascariasis with choledocholithiasis (2.0%), Biliary ascariasis (1.5%), Acute pancreatitis with biliary ascariasis (1.0%) and Papillary adenoma(0.5%). Among patients with benign disease, Choledocholithiasis (30.5%) was the most common etiology followed by Cholelithiasis with Choledocholithiasis (28%) and least common was papillary adenoma (0.5%), whereas in patients with malignant disease, Cholangiocarcinoma (9.5%) was the most common etiology {Fig 3}.

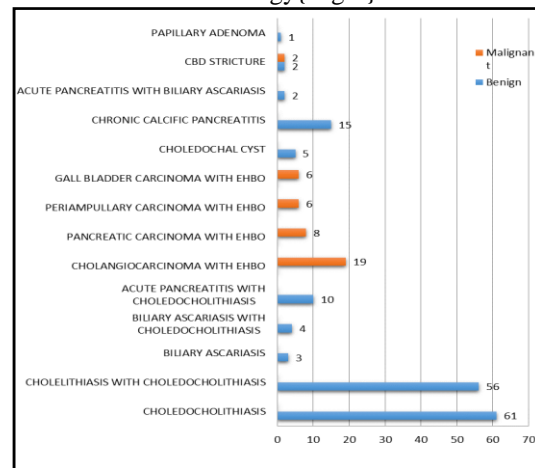


Fig 3: Etiology of biliary obstruction.

Clinical Presentation

The most common clinical presentation was pain abdomen in patients with benign disease and pain abdomen with vomiting and jaundice in patients with malignant disease {Fig 4}. Pain abdomen was present in around 92% of patients, jaundice in 40% of patients, vomiting in 37% of patients and fever in 15% of patients.

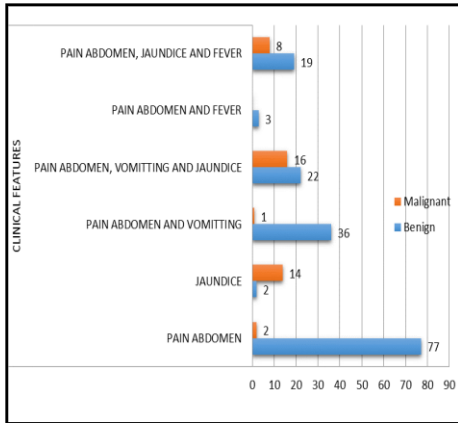


Fig 4: clinical profile of studied population.

Out of 200 patients, 24(12%) had cholangitis, including 17(8.5%) patients with benign disease and 7(3.5%) patients with malignant disease and the difference between malignant and benign groups was found to be statistically insignificant(p=0.262). {Fig 5 }

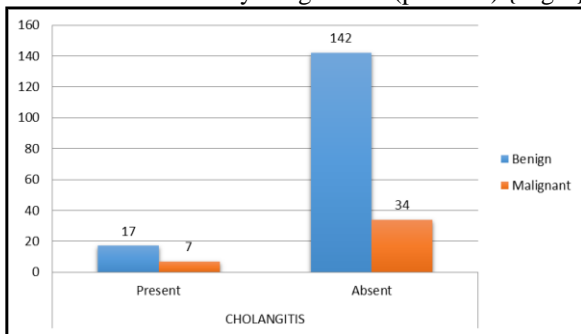


Fig 5: Clinical profile of studied population.

Effect of Sphincterotomy and or Sphincteroplasty on CA 19-9 Levels

Fall in CA19-9 level within 72 hrs. of papillotomy during ERCP was seen in 125(62.5%) of patients, rise in CA19-9 level was seen in 46(23.0%) patients and no change occurred in 29 (14.5%) patients. In patients with benign disease (n=159), fall in CA19-9 level, within 72 hrs. of papillotomy during ERCP, was seen in 103(64.8%) patients, rise in CA19-9 level was seen in 36(22.6%) patients and no change occurred in 20(12.6%) patients, whereas in patients with malignant diagnosis, fall in CA19-9 level was seen in 22(53.7%) patients, rise in CA19-9 level was seen in 10(24.4%) patients and no change occurred in 9(22.0%) patients {Table 1& Fig.6}.

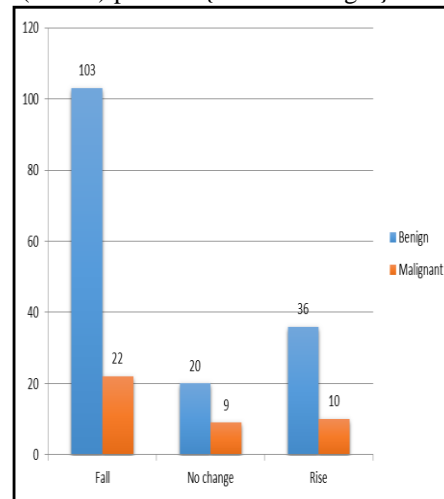


Fig 6: Change in CA 19-9 post sphincterotomy

	BENIGN OR MALIGNANT DIAGNOSIS		MEAN	STD. DEVIATION	P-VALUE
CA19-9 LEVEL BEFORE PAPILOTOMY(U/ml)	Benign	15	91.3	279.268	≤0.0001
	Malignant	9	2	731.114	
	t	41	1210.00		
CA19-9 LEVEL WITHIN 72 HRS OF PAPILOTOMY(U/ml)	Benign	15	89.1	279.172	≤0.0001
	Malignant	9	89	757.402	
	t	41	1191.54		

Table 1: Change in CA 19-9 levels post sphincterotomy.

Discussion

Increased levels of CA19-9 are not only seen in malignant biliary tract diseases but in benign diseases also. It becomes very difficult to differentiate between malignant and benign biliary disorders purely on the basis of CA19-9 levels and is possible only if there are associated clinical or other features suggestive of malignancy.

This study was undertaken to see the effect of sphincterotomy/sphincteroplasty during Endoscopic Retrograde Cholangiopancreatography (ERCP) to relieve the biliary obstruction, on the serum levels of CA19-9 and determine any relationship between the change in the levels of CA19-9 with the cause of

obstruction, whether benign or malignant, following drainage procedure. We observed either change or no change in the serum levels of CA19-9 within 72 hrs of biliary drainage procedure during ERCP. The change included both decrease or increase in the serum levels of CA19-9.

Fall (64.8% in benign group & 53.7% in malignant group) and rise (22.6% in benign group & 24.4% in malignant group) in the serum levels of CA19-9 within 72 hours of endoscopic papillotomy/sphincteroplasty were not statistically significant to differentiate the two groups. However, no change in the levels of CA 19-9 within 72 hours of endoscopic papillotomy/sphincteroplasty were

observed more in malignant obstruction than benign disorders which was statistically significant.

CA19-9 levels before ERCP were higher in malignant group than benign group. Similar observations were made by Budzynska et al [16] and Lin et al.[17] Syed MM et al[18] also reported in their studies that serum CA19-9 levels were significantly higher in malignancies.

In the current study, before release of obstruction, CA19-9 levels were higher in malignant group (1210.00±731.11 U/mL) than benign group (91.32±279.26 U/mL) with a significant difference; and after release of obstruction, the CA19-9 levels were again much higher in malignant group (1191.54±757.40 U/mL) than benign group (89.189±279.17 U/mL) with a highly significant difference. Similar findings were reported by Syed MM et al. [18] In their study they have shown that before ERCP, CA19-9 levels were higher in malignant group(1155.06±879.79 U/mL) than in benign group (402.41±261.99) with a statistically significant difference, but after ERCP, CA19-9 levels were much higher in malignant group (936.36±866.82) than in benign group (11.97±9.20) with a highly significant difference and there was statistically significant decrease in CA19-9 level in the benign group, which is in contrast to our findings as there was no significant decrease in CA19-9 level in benign group with papillotomy during ERCP in our study. The reason could be that we have done serum CA 19-9 level estimation before and within 72 hrs of ERCP and that they have done it before and after 7-10 days of the release of the obstruction.

Marelli D et al[20] studied 128 patients with obstructive jaundice including 87 patients with pancreatico-biliary malignancies and 42 patients with benign diseases. In 38 patients from group A (Malignant group-Pancreatobiliary tumors) and 22 from group B (Benign group), ERCP was performed with the purpose of relieving jaundice. Decrease in serum bilirubin levels confirmed the resolution of cholestasis in all cases. A different trend of CA19-9 decrease was observed between the two groups. In patients with benign diseases, jaundice relief was associated with a decrease of serum CA19-9 in all cases except one. In the malignant group, CA19-9 level following biliary drainage was found to be elevated in 16 patients (42%), remained steady in 3, and decreased in 19 (50%). After biliary drainage, decrease of serum CA19-9 was observed in 19 of 38 malignant cases and in almost all benign cases. In our study we also found that fall in CA19-9 levels was seen more in patients with benign disease (64.8%) as compared to patients with malignant disease (53.7%). Marelli D et al [20] have reported fall in the CA19-9 levels following biliary drainage in almost all benign cases, whereas in our study fall in CA19-9 levels following biliary drainage was seen in 64.8% of benign cases. This difference in fall of CA19-9 levels could be due to the fact that we have done CA19-9

level estimation within 72 hrs of biliary drainage and that they have done it atleast one week after biliary drainage. They have also reported that there was an increase in CA19-9 levels in 16 patients (42%) in malignant group, whereas in our study we found that CA19-9 level increased in 26.5% of patients and remained unchanged in 22.0% of patients with malignant disease. This difference could be because CA19-9 estimation post biliary drainage in our study was done within 72 hrs.

In a similar study by Bhuyian et al¹, which included 63 cases of obstructive jaundice with elevated baseline CA 19-9 level (>37U/mL), patients with malignant disease had high CA19-9 levels both before (732.0±58.0 U/mL) and after ERCP (713.6±75.9 U/mL) as compared to patients with benign disease (before ERCP: 309.6±65.6U/ml; after ERCP:101.2±26.3U/mL) and after biliary drainage, serum CA 19-9 levels measured after two weeks, reduced significantly in benign conditions whereas there was no significant change in malignant cases (p=0.721).

In a subgroup of jaundiced patients (16 benign and 15 malignant cases), follow-up CA19-9 levels were determined 2 weeks after biliary drainage by Mann DV et al.[21] The median CA19-9 level was lower in benign cases (102 U/ml) than those with pancreatobiliarytumors (910 U/ml; P<0.01), although the overlap was substantial. In benign jaundiced cases, a positive correlation was observed between bilirubin and CA19-9 elevation (R=0.41, p<0.01). Relief of jaundice was associated with a fall in CA19-9 level in all benign cases and in nine of the 15 with malignancy.

CA19-9 decrease in benign conditions has been documented in several other studies performed on a lower number of patients.[6,22] Other authors observed that post drainage levels, even if slightly decreased, may remain elevated also in benign diseases.[3] Extremely elevated CA19-9 values may require longer than a week to return to values within the normal range.[2]

Thus in our study we found that fall in serum levels of CA19-9 in benign group (64.8%) following biliary drainage was more than the rise and no change; and this fall in CA19-9 level in benign group was more than that in the malignant group (53.7%), which is consistent with the results of various other similar studies. The serum level of CA19-9 in many patients with pancreaticobiliary cancer did not change or decrease much, which is partly attributable to the uncontrolled growth of aberrant epithelial cells, their continuous secretion of this antigen and inflammation. In contrast, most cases of benign disease showed fall in CA19-9, though there was an increase in CA19-9 levels in around 22.6% and no change in 12.6%. Thus, elevated CA19-9 level should be interpreted cautiously in patients with obstructive jaundice, unless these high levels persist after the obstruction has been removed. A repeat assay for CA19-9, performed 2 or 3 weeks after resolution of jaundice, may help in differentiating

between malignant and benign diseases causing biliary obstruction and further studies are needed.

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