



Original Article

Importance of Serum CA 19-9 Level in Hepatolithiasis Patients Undergoing Liver Resection

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Abstract

Background: Hepatolithiasis is a known risk factor for intrahepatic cholangiocarcinoma (ICC). There is no non-invasive tool for understanding the malignant changes in biliary epithelium prior to surgery.

Patients and Method: Thirty-six patients (male; 12, female; 24) with hepatolithiasis who underwent liver resection from July 2018 to June 2019 were included in the study. Operations were done left hepatectomy (58.3%), right hepatectomy 2(5.6%) and left hepatectomy with extrahepatic duct excision, clearance of right hepatic duct system followed by Roux-en-Y hepaticojejunostomy (36.1%). Serum CA 19-9 level was measured in each patient before and 7 days after surgery. Resected specimens were examined and labeled as hyperplasia, biliary intraepithelial neoplasia (BillIN) and ICC. Association between preoperative serum CA 19-9 levels and biliary epithelial changes were analyzed. Postoperative serum CA 19-9 levels were compared with preoperative levels to understand the accuracy of biliary tissue removal by surgery.

Results: The patients who had preoperative serum CA19-9 levels less than 100 U/ml; none had ICC. In contrast the patients who had preoperative serum CA19-9 levels more than 100U/ml; 4 (57.1%) had ICC. Further analysis showed that 80% (4/5) patients had ICC whose preoperative serum CA19-9 level was more than 1000 U/ml. The serum CA19-9 levels after liver resection were significantly reduced compared to preoperative levels in patients with BillIN and CCA supports the effective removal of abnormal biliary tract.

Conclusions: Preoperative serum CA19-9 level may predict ICC association with hepatolithiasis and postoperative CA19-9 level may help in accuracy of biliary tissue removal by surgery.

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Introduction

Hepatolithiasis is a risk factor for intrahepatic cholangiocarcinoma (ICC).¹ It has been reported that repeated cholangitis due to stone in biliary system causes hyperplasia, dysplasia to carcinoma sequence in stone containing bile duct²⁻⁴. In 2005, Zen et al.⁵ published an article on histopathological changes of biliary epithelium of large intrahepatic ducts containing stones. They described the changes of biliary epithelium as hyperplasia, regenerative changes, biliary intraepithelial neoplasia (BilIN)-1, (BilIN)-2, (BilIN)-3 which are early stages of ICC. Unfortunately, there is no tool for understanding the malignant changes in hepatolithiasis patients prior to surgery. As a result it is not clear which patients already have cholangiocarcinoma or will eventually develop carcinoma. Moreover many surgeons are not willing to perform hepatic resection considering the hepatolithiasis as a benign disease. Therefore, novel stratification strategies including easily accessible parameters are needed to determine the possible factors that ultimately lead to ICC. Serum CA 19-9 is the most frequently used biomarker for diagnostic and treatment predictive purposes in ICC patients.⁶ Its efficacy in screening test has been widely analyzed although its usefulness as a diagnostic tool has not yet been established.⁷

This study is undertaken to understand whether there is any relationship between serum CA 19-9 levels and the biliary epithelial changes in hepatolithiasis. As there is no non-invasive tool for understanding the associated malignant changes in hepatolithiasis before surgery, this study may help in understanding the malignant transformation by assessing pre-operative serum CA 19-9 levels. Moreover, post-operative measurement of serum CA 19-9 level can help affirm that the pre-operative increase in the biomarker was due to the biliary epithelial changes caused by hepatolithiasis and the removal of the source led to its reduction.

Patients and methods

Thirty-six patients who admitted with the diagnosis of hepatolithiasis undergoing liver resection in the department of Hepatobiliary Pancreatic and Liver Transplant Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from July

2018 to June 2019 were included in the study. There were 12 males and 24 females with age; mean 38 years (range: 22 to 77 years). Patients were presented with abdominal pain only; 18 (50%), with cholangitis; 14 (38.9%) and with persistent jaundice, sepsis or ICC; 4 (11.1%). The duration of symptoms before treatment was less than 5 years in 20 (55.5%) patients, 5 to 10 years in 10 (27.8%) patients, and more than 10 years in 6 (16.7%) patients. Stones were present in left lobe; 21 (58.3%), in right lobe; 2 (5.6%), and in both lobe; 13 (36.1%) of liver (Fig.1). All patients were treated with appropriate antibiotics for controlling cholangitis and sepsis before surgery. Operations were done left hepatectomy in 21 (58.3%) patients, right hepatectomy in 2 (5.6%) and left hepatectomy, extrahepatic duct excision, clearance of right hepatic duct system with the help of peroperative choledochoscope followed by Roux-en-Y hepaticojejunostomy in 13 (36.1%) patients.

Serum CA 19-9 level was measured in each patient before operation after controlling cholangitis and sepsis and 7 days after resection of liver. Resected specimens were sent to the Department of pathology, Bangabandhu Sheikh Mujib Medical University for histopathological examination using Haematoxylin and Eosin (H-E) staining. Epithelial changes were labeled as hyperplasia, biliary intraepithelial neoplasia and ICC (Fig. 2). Patients were divided into three groups on basis of preoperative serum CA19-9 levels; patients with CA 19-9 below 37 U/ml, patient with CA19-9 within 37 to 99 U/ml, and patients with CA19-9 more than 100 U/ml for purpose of analysis. Association between preoperative serum CA 19-9 levels and biliary epithelial changes were analyzed. Postoperative serum CA 19-9 levels were compared with preoperative levels to know the effectiveness liver resection. Chi square test, Student t-test, One-way ANOVA test were used for statistical analysis; p-value <0.05 was considered as significant.

Results

The mean preoperative serum CA19-9 level was in 250.0 ± 598.1 U/ml (range: 0.8 to 2540.0 U/ml) in 36 patients. It was less than 37 U/ml in 23 (63.9%) patients, within 37-99 U/ml in 6 (16.6%) patients

and more than 100 U/ml in 7 (19.5%) patients. Biliary epithelial changes were labeled as hyperplasia in 21 (58.3%) patients, BillN in 11 (30.6%) patients and ICC in 4 (11.1%) patients. The patients who had preoperative serum CA19-9 levels less than 37 U/ml; none had CCA, 15 patients had hyperplasia and 8 patients had BillN changes. The patients who had preoperative serum CA19-9 levels within 37-99 U/ml; also none had CCA, 5 patients had hyperplasia and 1 patient had BillN changes. In contrast the patients who had preoperative serum CA19-9 levels more than 100U/ml; 4 (57.1%) had ICC, 1 had hyperplasia and 2 patients had BillN changes (Table-1). The result showed that association ICC was more in patients whose preoperative serum CA 19-9 level more than 100 U/ml than whose level less than that and the difference was significant ($p < 0.005$). Further analysis of 7 patients [Table-2] with serum CA19-9 level more than 100 U/ml showed that 80% (4/5) patients had ICC whose preoperative serum CA19-9 levels were more than 1000 U/ml (rang: 1100-2540 U/ml). The mean postoperative serum CA19-9 level at 7th postoperative day was 69.0 ± 204.2 U/ml. The serum CA19-9 levels after liver resection were significantly reduced ($p < 0.005$) when compared to preoperative levels in patients with BillN and ICC (Table -3).

Discussion

The incidence of ICC associated with hepatolithiasis is 5-13 %.⁸ Uenishi et al.⁹ from Japan in 2009 reported the incidence of ICC with hepatolithiasis is 11.6%. Cheon et al.¹⁰ from South Korea in 2009 reported the incidence of ICC with hepatolithiasis is 9.0%. Tabrizian et al.¹¹ from Italy in 2012 reported the incidence of ICC with hepatolithiasis is 23.3%. Lin et al.¹² from Taiwan in 2013 reported that the incidence of ICC with hepatolithiasis is 4-7%. Zhu et al.¹³ from China in 2014 reported the incidence of ICC with hepatolithiasis is 5-2%. The present study reveals that 11.15% patients of hepatolithiasis are associated with ICC and 30.6% patients are associated with BillN which is a premalignant condition. Our data is almost similar with other published data from different part of the world specially the South East Asian country. All these data including ours support that a quite considerable number of patients with

hepatolithiasis are associated with either premalignant or malignant condition. Till now, these associated biliary epithelial changes can be understood after surgical removal and histopathological examination of resected specimen. Therefore it is important to know before surgery whether the patient with hepatolithiasis is associated with any malignant changes. It is required to design the treatment plan and counsel the patient properly before surgery regarding subsequent treatment plan and prognosis of the condition.

Clinically it is difficult to detect early ICC that occurs as complication of hepatolithiasis as the symptoms tend to be vague and insidious. Accurate diagnosis of hepatolithiasis associated ICC is very difficult in preoperative imaging studies and even during operation, since the affected liver segment is often fibrotic and scarred. Moreover, unlike the mass forming type, intraductal type of ICC is especially to predict through conventional diagnostic tools whether an accompanying malignancy exists in patients with hepatolithiasis. But earlier diagnosis is crucial as it is reported that ICC with hepatolithiasis is associated with significantly poorer survival than ICC alone.¹⁴

CA19-9 is a universally applicable biomarker for detecting cholangiocarcinoma, hepatocellular carcinoma, colorectal, gastric and esophageal carcinoma. It is also increases in other benign conditions such as cholangitis,¹⁵ hepatitis,¹⁶ liver cyst,¹⁷ heart failure,¹⁸ thyroiditis,¹⁹ rheumatoid arthritis²⁰ etc. Therefore its sensitivity and specificity varies from study to study. In 2004, Qin et al.⁶ demonstrated that CA19-9 level > 37 U/ml is associated with 77.14% sensitivity in diagnosing ICC. Van Beers et al.²¹ reported in 2008 that the sensitivity of CA19-9 level above 100U/ml in diagnosing ICC is 53- 67% with specificity of 76-87%. Deng et al.²² showed that the sensitivity and specificity of diagnosing ICC are 69.3% and 66% respectively. All these reports support the role of CA19-9 levels in predicting ICC. The interesting findings of the present study are that hepatolithiasis with CA19-9 levels lower than 100 U/ml does not show any malignant changes in the biliary epithelium although few premalignant changes and mostly hyperplastic changes are seen. In contrast,

hepatolithiasis with CA19-9 levels more than 1000 U/ml, 80% shows malignant changes in the biliary epithelium. Another interesting findings of this study is that after resection of the diseased part of liver, serum CA19-9 level decreased significantly in compare to preoperative levels suggesting that biliary changes in the epithelium is related to serum CA19-9 level. In a prospective study of 58 patients pathologically diagnosed hepatolithiasis with ICC and 189 patients diagnosed a hepatolithiasis alone, Yang et al.²³ demonstrated that serum CA19-9 >100 U/ml as an independent risk factor for ICC associated with hepatolithiasis which supports our present data.

In conclusion, preoperative serum CA19-9 level may predict ICC association with hepatolithiasis and postoperative CA19-9 level may help in accuracy of biliary tissue removal by surgery.

However, more patients, long duration and more advanced histopathological study for determining biliary epithelial changes will be needed for final conclusion.

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