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A PROSPECTIVE STUDY OF THE ASSOCIATION BETWEEN HELICOBACTER PYLORI AND GALLSTONE DISEASES

General Surgery

Dr. K. Ujwal PG Resident, Department of General Surgery, IMS and Sum Hospital, SOA deemed to be University, Bhubaneswar, Odisha, India.

Dr. Suman Saurav Rout Assistant Professor, Department of General Surgery, IMS and Sum Hospital, SOA deemed to be University, Bhubaneswar, Odisha, India.

Prakash Kumar Sahoo* Professor, Department of General Surgery, IMS and Sum Hospital, SOA deemed to be University, Bhubaneswar, Odisha, India.*Corresponding Author

ABSTRACT

Diseases of the gall bladder are one of the most common surgical ailments that the general surgeons encounter. *H. Pylori* infection is most commonly associated with gastric diseases like chronic gastritis, peptic ulcer and gastric carcinoma, however growing evidence have drawn attention to its role in extragastric diseases. So our aim of this study is to assess the incidence of Helicobacter pylori in patients who are being treated for Gall bladder diseases. The study enrolled fifty patients with cholelithiasis, 24 patients showed positivity for *Helicobacter pylori*. We have also analysed the type of calculi in post cholecystectomy specimen and compared it with the positivity of H pylori. Out of the 24 patients with cholesterol type of stones, 14 showed positivity for Helicobacter. Only four out of the twelve patients with multiple pigmented stones were positive for this bacterium on UGIE with RUT whereas the other 8 showed negativity to *Helicobacter pylori*. A total of 14 patients were noted to have multiple mixed stones among which only six patients were positive for this microorganism. Half of population showed positive for Helicobacter pylori on Rapid urease test. It was also observed that among the patients who had a positive RUT for *H.pylori* , a majority had Cholesterol calculi in their post cholecystectomy specimens.

KEYWORDS

Helicobacter pylori, cholecystectomy, cholelithiasis, calculi, gallstone

INTRODUCTION

Diseases of the gall bladder are one of the most common surgical ailments that the general surgeons encounter (1). Females under the age of 50 years are more frequently affected whereas after the age of 50 years gallstone diseases affect both genders equally (1). Gallstones have the potency to lead to a wide variety of clinical conditions such as acute cholecystitis, chronic cholecystitis, obstructive jaundice and acute pancreatitis that may lead to chronic pancreatitis (2). Symptoms of gallstone-related clinical conditions vary from nausea, vomiting and fatty dyspepsia to severe right hypochondrial and epigastric pain, jaundice, fever and shock. The variety of tools available to diagnose gallstone diseases and the complications associated with it can be diagnosed by using USG, CECT, ERCP, Liver function tests and Pancreatic enzymes (2) (3). Helicobacter pylori has been established as a cause for chronic gastritis, peptic ulcers, gastric carcinoma and malignant lymphoma of gastric mucosa associated lymphoid tissue (MALToma) (4) (5). The simultaneous presence of *H. Pylori* infection in the stomach and gallbladder is being studied to analyze the differences in severity of symptoms and responses to treatment (6) (7). Few studies concluded with the suggestive evidence of *H. Pylori* DNA components in bile, gallbladder tissue and/or cholesterol gallstones (8). Monstein et al reported that the detection of *H.pylori* DNA in cholesterol gallstones may indicate that *H. Pylori* is a normal flora in the gallstone or, that the formation of cholesterol gallstones maybe predisposed by the colonization of *H. Pylori* in the biliary tract (9) (10). More studies on cases and data of large number of patients having different hepatobiliary diseases should be performed in many research centers all over the world in order to verify the correlation of Helicobacter species with cholelithiasis. Earlier reports attempting to identify the DNA of Helicobacter in the gallbladder tissue of patients with various biliary diseases have shown discordant findings. Some results did not rule out the chance of Helicobacter infection being a contributing agent or cofactor in the development of biliary diseases (11). One study demonstrated the significant relation between the detection of *H. Pylori* in the gallbladders and symptomatic gallstones in these patients. Another research showed a significant correlation of *H. Pylori* infection within mucosa of both the gallbladder and stomach (12).

Infection caused by *H. Pylori* in the gallbladder may lead to cholelithiasis and subsequent cholecystitis (13) (14). This observation highlights the need for appropriate measures for prevention and eradication against the overgrowth of *H. Pylori* in the gallbladder. Unfortunately, the available literature in this area is hampered by the lack of gold standard methods in diagnosing *H. Pylori* species. Recently tested various pertinent methodological strategies include microbiological cultivation, histopathologic PCR, automated DNA sequencing, bacterial profiling by temporal temperature gradient gel electrophoresis, and southern blot analysis using a *H. Pylori* species specific primer (15) (16) (17). Over the last decade, an escalating number of studies have reported the association of *H. Pylori* infection with extra-digestive conditions. Majority of these studies have identified infection caused by *H. Pylori* based on immunological assays and urease breath test (UBT) (18).

This prospective analytical study pertains to a patient population opting for treatment at a tertiary healthcare centre, IMS & SUM Hospital, Bhubaneswar. Upper GI Endoscopy along with Rapid Urease test for Helicobacter pylori were done in patients diagnosed with Gallstone disease and admitted for Laparoscopic Cholecystectomy and in patients consenting for the study. The results were analyzed and presented with the aim of studying the etiological association between Helicobacter pylori and Gallstone diseases

MATERIAL AND METHODS

This is a prospective analytical study with gallstone diseases admitted to the Dept. of General Surgery, IMS & SUM Hospital, Bhubaneswar, to undergo Laparoscopic Cholecystectomy for a period of 2 year. The sample size was 50 minimum number of patients.

INCLUSION CRITERIA

All patients admitted with cholelithiasis and undergoing elective laparoscopic cholecystectomy and those who have agreed to be a part of the study.

EXCLUSION CRITERIA

Subjects not willing to take part in the study and patients who had received anti *H pylori* treatment in the past 6 months.

Data collection procedure: After implementing informed consent process, a detailed patient history was taken regarding the primary symptoms and any other associated complaints. Other relevant history was collected according to the study proforma. The same was documented. All the patients that were included in the study underwent routine pre-operative investigations including an ultrasound abdomen and pelvis, liver function tests including prothrombin time, INR and a pre-operative upper GI Endoscopy with Rapid Urease test for Helicobacter pylori. The types of calculi and nature of GB mucosa was documented as identified in the Post Laparoscopic Cholecystectomy Gallbladder specimens. The above details were compared and analyzed using Microsoft Excel 2019.

RESULTS

The current study is a prospective study to determine the association of Helicobacter pylori in gastric mucosa with gall bladder diseases, done at the department of General Surgery in a tertiary healthcare institute, IMS and SUM Hospital, Bhubaneswar, Odisha for a period of two years from 1st August, 2018 to 31st July, 2020. The data pertaining to these patients has been analyzed and presented in this study.

The most common age group of patients diagnosed with gall stone disease is between 51-60 years (28%, n=14). 11 patients were between the ages of 31-40 years and the same incidence of 11 was noticed in the age group of 41-50 years. As seen in the above data, the patients admitted with cholelithiasis were mostly female (78%, n=39). Only 11 (22%) of the 50 patients evaluated were male. The highest incidence of gallstone disease is seen in patients having a BMI between 25 kg/m2 and 29 kg/m2 (48%,n=24).

35 out of the 50 patients presented with dyspepsia which accounted for 70%. Pain abdomen was the second most common complaint seen in 30 patients (60%). Vomiting, Fever and Jaundice were noted in 11(22%), 7 (14%) and 2 (4%) patients respectively (Table 1).

SYMPTOM	Number of patients(percentage)
Dyspepsia	35 (70%)
Pain abdomen	30 (60%)
Vomiting	11 (22%)
Fever	7 (14%)
Jaundice	2 (4%)

Table 1: Analysis of symptoms prior to surgery

In the patients analyzed in this study, 8 (16%) of them had Type II Diabetes mellitus and 6 (12%) were known cases of Hypertension. One patient had hypothyroidism (Fig 1).

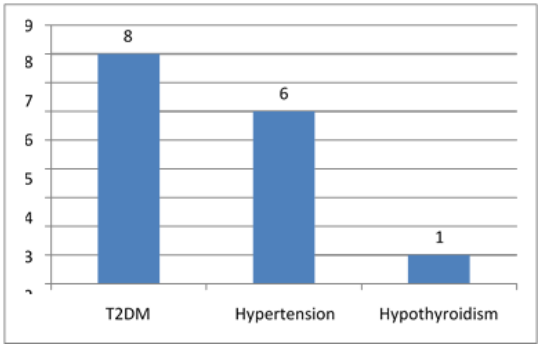

Fig 1: Graph showing co -morbidities in patients

Majority (48%, n=24) of the patients had a normal per abdomen examination at the time of admission. RHC tenderness was noted in 28% (n=14). Epigastric tenderness seen in 12% (n=6). Both RHC and Epigastric tenderness were seen in 12% (n=6) of the patients enrolled in the study (Fig 2).

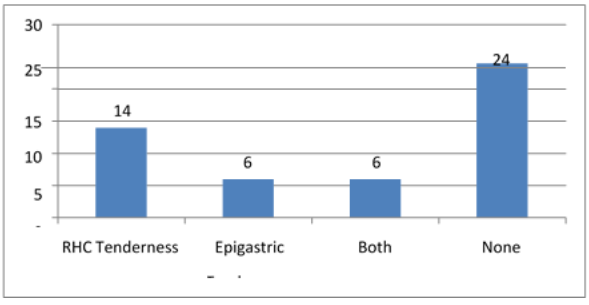

Fig 2: Graph showing distribution according to site of tenderness

Table2: Table showing number of calculi visible on pre- operative USG

Calculi on USG abdomen	Number of patients(percentage)
Multiple calculi	26(52%)
Single calculus	18 (36%)
2-3 calculi	6 (12%)

Of the 50 patients admitted with Gallstone diseases, 26 (52%) had multiple calculi whereas 18 (36%) of them had a single calculus. 2-3 calculi were noted in 6 (12%) patients (Table 2). 36% of the patients had antral erosions whereas fundic erosions were noted in 12%. Eighteen of the 50 patients had no significant abnormality detected in stomach mucosa on upper GI endoscopy (Table 3).

Table 3: Table depicting the frequency of gastritis/erosions based on site of the stomach

UPPER GI ENDOSCOPY FEATURES	NUMBER OF PATIENTS (PERCENTAGE)
Antral gastritis/erosions	18 (36%)
Fundic gastritis/erosions	8 (16%)
Both	6 (12%)
No abnormality detected	18(36%)

Of the 50 patients who were admitted with Gallstone disease, Rapid urease test after an Upper GI Endoscopy was positive for 24 patients (48%) and negative for 26 patients (52%). In the post cholecystectomy specimens evaluated for the number and type of calculi, a single cholesterol stone was the most common finding seen in 36% (n=18) of the patients. Multiple mixed stones and multiple pigmented stones were seen in 28% (n=14) and 24% (n=12) respectively (Table 4).

Table 4: Table showing the types of calculi identified in post cholecystectomy gallbladder specimens

FEATURES OF GALLBLADDER SPECIMEN	NUMBER OF PATIENTS (PERCENTAGE)
Multiple mixed type stones	14 (28%)
Multiple pigmented type stones	12 (24%)
Single cholesterol stone	18 (36%)
2-3 stones , cholesterol type	6 (12%)

In the 24 patients who were identified to have Helicobacter pylori in the stomach, 14 of them had cholesterol calculi, 6 of them were noted to have multiple mixed stones and 4 of the 24 were identified to have multiple pigmented stones. 10 patients of the 26 who were negative for Helicobacter pylori had cholesterol calculi, 8 were noted to have multiple pigmented stones. Of the 14 patients who had multiple mixed stones in the GB specimen 8 were negative for Helicobacter pylori (Table 5).

Table 5: Comparing rapid crease test results and types of calculi

RUT FOR *H.PYLORI*	CHOLESTEROL STONES	MULTIPLE PIGMENTED STONES	MULTIPLE MIXED STONES
POSITIVE	14	4	6
NEGATIVE	10	8	8

DISCUSSION

In developing nations, approximately 80% of adult population harbours *H. Pylori* infection. Kawaguchi et al were the group that first confirmed this bacterium in GB mucosa [17]. A number of studies have since tried to establish a correlation between infection by this bacterium and development of cholelithiasis and other GB disease. In our nation, *H. Pylori* presence has been reported in most duodeno-gastric conditions (18).The ways *H. Pylori* can enter bile is not fully clear but migration and colonization in the biliary tree either by moving from duodenum through the Oddi sphincter or/and by blood to bile via the liver [19] [20].

Infection by Helicobacter pylori changes the process of calculi formation in gall bladder along with complications such as cholecystitis, GB cancer and pancreatitis. The way this happens is by releasing pro-inflammatory components like IL-1, IL-6 and TNF-alpha [21] [22]. Also *H. Pylori*"s potency to cause reactions by free radicals and oxidative stress in the GB wall and bile can cause calculi to be formed.

Another research aimed at studying the pathophysiology of the way that Helicobacter spp. causes chronic cholecystitis suggested that the apoptotic process induced by the bacteria may be the cause [23]. In this study, 48% of the patients with cholelithiasis were found to have Helicobacter pylori in their gastric mucosa. This result was similar to that of a 2014 study by Helaly et al who found that this bacterium was present in about 41% of samples with chronic calculous cholecystitis [22]. An association between *H. Pylori* presence in stomach and gall bladder was also found to be significant in this study. Helaly et al also suggested that it can act as a loci for formation of stones [22].

A Greek study that was comparing serological and histopathological methods of detecting *H. Pylori* indicates a positivity of 51% and 19% respectively [24]. A research from Germany advocated that people with gall bladder calculi are approximately three and a half times more at risk of having an infection with Helicobacter [25]. The microaerophilic nature of this bacterium makes it a very difficult organism to be cultured [29]. *H. Pylori* detection in bile is difficult because the bacteria stays mostly in a coccoid form that cannot be cultured and also bile has a chemorepellant effect on the bacteria [27]. Helicobacter DNA was detected in 5 out of 8 gallbladders in 8 patients from Chile with chronic cholecystitis using PCR method (28). be due to differences in the epidemiology of Helicobacter, used PCR methods and inappropriate control groups.

Many studies evaluated the presence of *H. Pylori* in both gastric and GB tissues. Attallah et al in a 2013 study proved that around 43 percent of the study population had showed presence of Helicobacter in stomach and gallbladder concurrently [26]. But in contrast to these findings, a study done by Javaherzedeh et al in 2016, studied for Helicobacter pylori positivity in stomach and GB, found that only 14% of overall patients were positive for the bacterium, most in acute stage of their GB disease. This group also concluded that the appearance of Helicobacter pylori in the gallbladder can play a crucial role in the development of acute cholecystitis [112].

Andre de Moriciz in 2010 found out that pre malignant changes such as intestinal metaplasia, dysplasia, hyperplasia and eosinophilic inflammation of the mucosa of gall bladder were more prevalent in patients restricted to *H. Pylori* infection [22]. Another study researching the association of malignant or pre-malignant conditions of the GB with *H. Pylori* concluded that there was a definite increase in the incidence of pre neoplastic lesions such as adenomyomatosis and metaplasia in gall bladders. In 2019, study done in the northern part of India studying the correlation between infection by Helicobacter pylori infection in stomach and gallbladder mucosa. These discrepancies between the results of investigations about the association of gallstone cholecystitis and Helicobacter species in different countries or areas may concluded that there is a significant correlation. They have also hypothesized that the chronic inflammation induced by the organism can cause damage to DNA, enzymatic changes and death of the cell. These are found to be the most important factors for the progression of many cancers in our body [30].

CONCLUSION

Although *H. Pylori* infection is most commonly associated with gastric manifestations, growing evidence have drawn attention to its role in extragastric diseases. The knowledge on how this bacterium influences non-gastroduodenal disorders may shed light on new therapeutic targets in the management of these conditions. According to the results in this study, approximately half of the study population was positive for Helicobacter pylori on Rapid urease test. It was also observed that among the patients who had a positive RUT for H.pylori , a majority had Cholesterol calculi in their post cholecystectomy specimens. A study with a larger sample size preferably including both non-neoplastic and neoplastic gall bladders and with relevant serological and molecular studies will help to arrive at a definite conclusion regarding the relationship between presence of *H. Pylori* and various disorders of gall bladder.

Conflict of interest:
No potential conflict of interest relevant to this article was reported

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