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Effect of Post-Cholecystectomy on Small Intestinal Bacterial Overgrowth and Orocecal Transit Time in Gallstone Patients

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Abstract

Background: Effect of duration of cholecystectomy on orocecal transit time and small intestinal bacterial overgrowth in gallstone patients is poorly understood.

Method: 128 gallstone patients of either sex, aged between 25-68 years were enrolled. 79/128 followed after 4-6 months of cholecystectomy. 49 patients had undergone cholecystectomy 2 - 15years before study and reported gastrointestinal symptoms, classified as late post-cholecystectomy. Orocecal transit time (OCTT) and small intestinal bacterial overgrowth (SIBO) were measured by non-invasive lactulose and glucose breath tests respectively.

Results: OCTT increased significantly ($p < 0.01$) from 125.9 ± 28.6 to 145.8 ± 30.5 minutes after 4-6 months of cholecystectomy. Among late post-cholecystectomy patients, OCTT was observed to be 159.2 ± 37.8 minutes, which was significantly higher when compared with OCTT in pre-cholecystectomy patients. SIBO was present in 10/79 (12.7%) gallstone patients pre-cholecystectomy and 11/79 (13.9%) in gallstone patients post-cholecystectomy. Presence of SIBO after 4-6 months of cholecystectomy was not significantly different compared to pre-cholecystectomy in gallstone patients. However, SIBO was present in 13 / 49 (26.5%) late post-cholecystectomy patients with duration of 2-15years, which was significantly ($p < 0.05$) higher compared to pre-cholecystectomy and 4-6months post-cholecystectomy patients.

Conclusion: The study signifies that longer duration of post-cholecystectomy can lead to delayed OCTT and cause SIBO in gallstone patients. This can be mitigated by giving pro-kinetics to post-cholecystectomy patients.

Keywords: Gallstone disease; Glucose breath test; Lactulose breath test; Orocecal transit time; Post-cholecystectomy; Small intestinal bacterial overgrowth

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Introduction

Gallstone disease (GSD) is one of the most common biliary tract disorders worldwide. The prevalence varies from 5.9% - 21.9% in Western society to 3.1% - 10.7% in Asia [1]. Most gallstones are silent [2]. Approximately half of symptomatic gallstone carriers experience another episode of biliary pain within a year. These gallstone carriers are at enhanced risk of developing acute cholecystitis, and biliary pancreatitis [3]. Although most gallstone patients (GS) are asymptomatic, a progressively increased rate of cholecystectomies has been reported [4]. Thus, confirming that gallstone disease is one of the major gastrointestinal problems throughout the world.

Cholecystectomy is a widely performed surgery throughout the world. A large proportion of patients report gastrointestinal symptoms even after surgery is performed. Studies suggest that there is an increased risk of IBS in subjects who have been diagnosed as having a biliary event [5]. Post cholecystectomy syndrome is characterized by chronic or recurrent abdomen pain, diarrhea, flatulence etc.

Post cholecystectomy symptoms occur within a few weeks of surgery in some patients and months to years later in the remainder of patients. These symptoms are usually nonspecific and vary with underlying etiology. Patients after cholecystectomy

can be enrolled to assess whether bile acids have a role in regulation of small bowel transit [6]. The etiology of SIBO is diverse and frequently multi-factorial. It is considered to be a result of structural changes in the gastrointestinal tract, altered peristalsis of the small intestine, or due to disturbed normal mucosal defenses of small intestine [7]. Earlier, it was suggested that prolonged orocecal transit time enhances serum bile acids through small intestinal bacterial overgrowth [8]. SIBO is usually defined as the presence of 105 colony forming units/mL of bacteria in aspirated small intestinal fluid. Earlier, the gold standard test for SIBO was aspiration and culture of the small bowel luminal contents, but it is time-consuming, costly, invasive, and chances of contamination are there. Therefore, these days, preferred method of testing for SIBO is the measurement of hydrogen (H2) in end-expiratory breath samples of individuals after giving them glucose, and it is a safe, simple, and non-invasive technique.

Post cholecystectomy symptoms are present in number of patients [9]. But the etiology underlying symptoms present in patients after getting their gallbladder removed is not well studied. Increased SIBO may be responsible for various gastrointestinal (GI) symptoms such as diarrhea, flatulence, etc. There is a paucity of studies on assessment of orocecal transit time and SIBO in GS patients after cholecystectomy at different time intervals. Therefore, to understand the etiology behind GI symptoms after cholecystectomy, the study has been designed to assess and compare change in orocecal transit time and presence of SIBO in patients after cholecystectomy at varied time intervals.

Method

Patient selection

During 3 year study period, 79 patients of gallbladder stones, either sex and of more than 25 years of age were enrolled. They were diagnosed to have GS by ultrasonography. In this study they were followed up to 4-6 months after post cholecystectomy. 49 patients who reported cholecystectomy done at least 2-15 years before test and had dyspeptic symptoms were also enrolled in the study. These were the patients who attended Gastroenterology and Surgical services, PGIMER, Chandigarh for their GI symptoms attributed to cholecystectomy. The study was approved by Institute's Ethical Committee and written informed consent was taken from all subjects. Demographic characteristics were recorded. These patients had normal biochemistry reports. Bilirubin and alkaline phosphatase levels were also normal in the patients enrolled

Exclusion criteria

The following exclusion criteria were applied: (1) patients with prior gastric surgery / vagotomy / appendectomy; (2) patients with diabetes, obesity, liver cirrhosis, hypothyroidism, intestinal pseudo-obstruction, blind-loop syndrome, duodenojejunal diverticulosis; (3) patients who had received broad-spectrum antibiotics during the month preceding the test (which may influence the results of the hydrogen breath test, making it false-negative); (4) use of motility modifying medicines; (5) colonoscopy within 1 week before hydrogen breath test. (6). Patients having obstructive jaundice, sphinctor Oddi dysfunction or other medical conditions which may influence bowel transit time and bacterial overgrowth.

Procedures

Subjects were asked to eat low fiber diet 3 days prior to test [10, 11]. End-expiratory breath was taken after 12 hrs fasting. On the day of test, subjects were asked not to smoke and to restrict physical activities.

Lactulose hydrogen breath test for OCTT

OCTT was measured by using 15 mL of lactulose syrup containing 10 g of lactulose. 11 Patients were asked to give an end expiratory breath after 12-hours fast. They were also advised not to consume a high fiber diet 3 days before the test because these foods may cause prolonged excretion of hydrogen gas and a high fasting value. Cigarette smoking and exercise were not allowed for at least 2 hours before and during the test. End expiratory breath samples were taken after every 15 minutes up to 5 hours. Samples were analysed by gas chromatography using SC Microlyzer (QuinTron Instrument Co., Milwaukee, WI). Time taken for rise ≥ 12 ppm over the baseline value was taken as OCTT [11].

Glucose hydrogen breath test for SIBO

Subjects were given 80 g of glucose in 450 mL of water to drink after taking a basal end expiratory breath [12]. Breath samples were collected at 15-min intervals for 2 hours. Breath hydrogen (H_2) and methane (CH_4) concentrations were measured by gas chromatography using SC Microlyzer. An increase in breath H_2 and/or CH_4 concentration ≥ 12 ppm over baseline value in two consecutive readings was defined as SIBO [12].

Tests were interpreted by an experienced faculty member who was blinded to subject's condition and symptoms.

Statistical analysis

Results were expressed as mean ± SD and percentage. χ^2 test was used to analyze the presence of SIBO in both the groups. Student's paired 't' test was applied to compare the difference among patients before and after cholecystectomy and unpaired 't' test was applied to compare the OCTT between late post-cholecystectomy patients vs. pre and post-cholecystectomy patients. All statistical analyses were performed by using SPSS version 14.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Demographic characteristics

The study population consisted of 128 gallstone patients. Sex and age distribution of patients is given in **(Tables 1 and 2)** respectively. Percentage of females was more in both post (71%) as well as late cholecystectomy (67.3%) patients as compared to males **(Table 1).** Age of males and females in different groups of patients was comparable **(Table 2).** Out of 128 gallstone patients, there were 89 (69.5%) females and 39 males (30.5%). Mean ± SD of age in

Table 1 Gender distribution of gallstone patients.

Sex	Gallstone patients after 4-6 months of cholecystectomy (n = 79)	Late post cholecystectomy patients (after 2-15 years) (n = 49)
Males n (%)	23 (29%)	16 (32.7%)
Females n (%)	56 (71%)	33 (67.3%)

females was 40.6 ± 20.5 years and that of males 45.7 ± 19.6 years. Percentage of age of females and males in late cholecystectomy patients was not different than patients with cholecystectomy after 4-6 months **(Table 2).**

OCTT and SIBO

Mean ± SD and range of orocecal transit time in patients (pre-cholecystectomy, after 4-6 months of cholecystectomy and after 2-15 years of cholecystectomy) is shown in **(Table 3).** OCTT increased significantly ($p < 0.01$) among GS patients after 4-6 months of cholecystectomy as compared to pre-cholecystectomy OCTT. Line diagram showing the change in orocecal transit time among individual patients' pre and after 4-6 months cholecystectomy is shown in **(Figure 1)**. It was also observed that OCTT was further increased in gallstone patients after 2-15 years of cholecystectomy when compared with OCTT at pre-cholecystectomy and after 4-6 months of cholecystectomy. These patients showed maximum rise in OCTT up to 270 minutes **(Table 3).**

Presence of SIBO, diagnosed by non-invasive glucose hydrogen breath test, is shown in **(Table 4)**. It was observed that SIBO was not significantly different in gallstone patients before and after 4-6 months of cholecystectomy but it was significantly ($p < 0.05$) increased in late post-cholecystectomy gallstone patients. In late post-cholecystectomy patients, 26.5% of patients were positive for SIBO **(Table 4).**

OCTT of the SIBO positive patients after 2-15 years of cholecystectomy increased gradually with increase in duration of cholecystectomy **(Table 5).** Similarly, number of SIBO positive patients also increased with increase in duration of cholecystectomy **(Table 5).** But the difference for OCTT and SIBO between 5-10 years and 10-15 years post cholecystectomy was not statistically significant which may be due to less number of patients in each group. However, it is significantly higher in patients with 5-10 years and 10-15 years post cholecystectomy and patients with 2-5 years post cholecystectomy.

Symptoms of constipation were present in significantly ($p < 0.05$) higher number of gallstone patients after cholecystectomy 48/79 (60.7%) as compared to pre cholecystectomy 56/128 (43.7%) patients. Flatulence was also significantly ($p < 0.05$) higher in 70/79 (88.6%) of post cholecystectomy patients as compared to 97/128 (75.7%) pre cholecystectomy patients.

However, on assessing diarrheal symptoms in 4 months of post cholecystectomy, it was observed that 21/79 (26.5%) of patients had > 3 stools per day, and 33/128 (25.7%) pre cholecystectomy patients reported to pass > 3 stools per day. There was no significant difference in diarrheal symptoms among both the groups. But loss of appetite within 4 months of post cholecystectomy was observed in 44/79 (56.9%) patients which was significantly higher ($p < 0.05$) as compared to pre cholecystectomy 10/128 (7.8%) patients.

Table 2 Age (Mean ± SD) in years of patients.

Groups	Gallstone patients after 4-6 months of cholecystectomy (n = 79)	Late post cholecystectomy patients (after 2-15 years) (n = 49)
Males (Mean ± S.D.) Range	45.6 ± 15.7 (30-60 yrs)	43.9 ± 17.3 (27-68 yrs)
Females (Mean ± S.D.) Range	42.6 ± 16.8 (27-60 yrs)	41.3 ± 16.7 (25-67 yrs)

Table 3 Orocecal transit time (minutes) of gallstone patients.

Time	Mean ± S.D.	Range
Before cholecystectomy (n = 128)	125.9 ± 28.6	60—225
After 4-6 months of cholecystectomy (n = 79)	145.8 ± 33.5*	90—240
After 2-15 years of cholecystectomy (n = 49)	159.2 ± 37.8*	105—270

* $p < 0.01$ between pre vs. post and late post-cholecystectomy patients

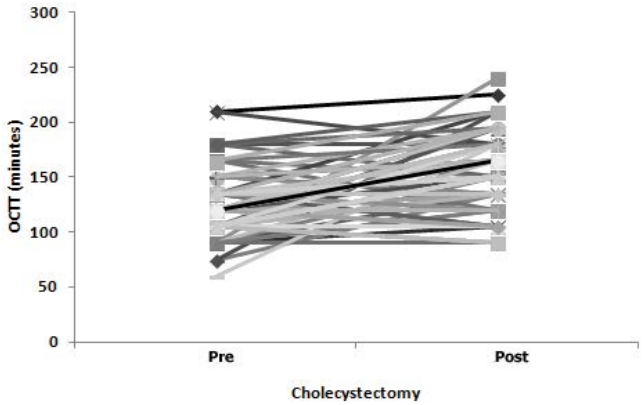

Figure 1 Line diagram showing pre and post-cholecystectomy OCTT (minutes) in gallstone patients (n = 79).

Discussion

It is commonly accepted that removal of the gallbladder is the best treatment for symptomatic gallstone disease. However, the post cholecystectomy symptoms also need to be focused upon. Present study showed that cholecystectomy induces change in orocecal transit time and these changes may translate into a noticeable modification in bowel habits of gallstone patients. Earlier, we have reported that orocecal transit time, small intestinal bacterial overgrowth and serum bile acids were significantly higher in gallstone patients as compared to controls. Thus, delayed gut motility is one of the contributing factors to GSD [8]. In current study, it was observed that OCTT was increased in gallstone patients after 4-6 months of cholecystectomy as compared to pre cholecystectomy, but no significant change was observed in presence of SIBO. On the other hand, late post cholecystectomy patients (i.e., 2 - 15 years after cholecystectomy) who had gastrointestinal symptoms, had increased percentage of SIBO when compared with pre-cholecystectomy patients. SIBO in gallstone patients after late cholecystectomy may be due to delayed OCTT and more duration of cholecystectomy.

Thus it can be assumed that although, there is an increase in OCTT after 4-6 months of cholecystectomy but SIBO was not significantly higher in these patients. These patients may develop SIBO with longer time after cholecystectomy. Therefore, the follow-up for identifying presence of SIBO in these patients should be done after every 6 months or for a longer time period. Fort et al. 1996 also reported that one month postoperatively,

Table 4 SIBO (number and percentage) in patients.

Groups	Pre cholecystectomy (n = 128)	4-6 months of cholecystectomy (n = 79)	Late post cholecystectomy (n = 49)
SIBO	10 (12.7%)	11 (13.9%)	13 (26.5%) *

* $p < 0.05$ between late post cholecystectomy vs. pre and post cholecystectomy

Table 5 OCTT and SIBO positive in late post cholecystectomy patients (n = 13).

Time	SIBO (n = 13)	Mean ± S.D. of OCTT (minutes)
2-5 years	2 (15.4%)	149.7 ± 31.6
5-10 years	5 (38.4%)	152.3 ± 28.4
10-15 years	6 (46.1%)	160.5 ± 30.9

cholecystectomy had considerably accelerated colonic transit and slightly delayed orocecal transit time [13]. They reported that on their fourth year post cholecystectomy (when transit changes had consolidated) in one third of patients, stools had increased in frequency or decreased in consistency or both as compared to before operation [13]. Increased oro-ileal transit time (OITT) has also been shown to be affected in gallstone patients in earlier study by Colecchia et al. [14]. They evaluated OITT using tauroursodeoxycholic acid load test and reported that OITT was longer in gallstone patients than in controls. Further, they showed that ursodeoxycholic acid treatment significantly reduced OITT in GS patients. Studies suggest that post cholecystectomy subjects showed a lack of marked early postprandial increase in duodenal bile acid concentration [15]. Delayed small bowel transit may be secondary to slower absorption and consequently early arrival to the ileum of partially digested fat, which is recognized as a potent inhibitory stimulus of upper intestinal motility and transit [16]. The meal rapidly travels to the distal small bowel [17], and the amount of nutrients in it may trigger a possible physiologic regulatory mechanism of small bowel transit and gastric emptying [18].

Earlier studies also suggest that functional gastrointestinal disorder [19] and sphincter of oddi dysfunction [20, 21] were leading causes of post-cholecystectomy symptoms. Another reason for longer OCTT (120 minutes) no matter in pre, postcholecytectomy or late cholecystectomy patients may be due to action of DCA mechanism on intestinal motility. In one of the study it was observed that DCA directly delays OCTT by inducing defect in contractility of intestinal smooth muscle cells by inhibiting the pace-maker currents of interstitial cells of Cajal by activating ATP sensitive K+ channels through the production of prostaglandin E2 [22].

Various GI symptoms, such as constipation, flatulance and loss of appetite have been observed in significantly higher number of post-cholecystectomy patients. Delayed intestinal transit is also an integral part of constipation. Increased microbial flora due to bacterial overgrowth present in patients plays an important role in the manifestation of symptoms present in gallstone patients. SIBO is frequently implicated as cause of diarrhea, malabsorption and to some extent intestinal mucosal inflammation in GI disorders.

Present study adds to current knowledge of etiology underlying post cholecystectomy symptoms, suggesting that delayed orocecal transit time can be one of the causes of post cholecystectomy symptoms present in number of patients.

The strength of the current study is the large number of patients, who were followed up for significant duration. Also, the tests used for assessment of bacterial overgrowth and OCTT are non-invasive.

In summary, the present study showed that cholecystectomy prolongs orocecal transit time when compared to pre-cholecystectomy in gallstone patients. This delay in OCTT would have led to small intestinal bacterial overgrowth in these patients. Although, there is increase in OCTT after 4-6 months of cholecystectomy but SIBO was not significantly higher in 4-6 months of cholecystectomy patients than pre- cholecystectomy patients. On the other hand, patients after 2-15 years of cholecystectomy had increased SIBO when compared with pre and 4-6 months post cholecystectomy patients. Thus post-cholecystectomy patients are at increased risk to develop SIBO with time after cholecystectomy. Therefore, the follow-up for SIBO of these patients should be done at regular intervals for a longer time period. Furthermore, patients of gallstones after cholecystectomy may be advised prokinetics to stabilize gastrointestinal motility and prevent SIBO.

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