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Gastroparesis in carcinoma gallbladder: a scintigraphic study

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ABSTRACT

Background: Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical gastric outlet obstruction. There is strong association of gastroparesis with carcinoma gallbladder. The aim of the study was to find out the incidence of delayed gastric emptying in carcinoma gallbladder and its correlation with symptoms of stasis and stage of the disease.

Methods: Patients diagnosed with carcinoma gallbladder and their matched controls were included in this study. Patients with mechanical gastric outlet obstruction were excluded. All patients underwent contrast enhanced computer tomography scan and radio labeled (Technitium 99) solid meal Scintigraphy study. Normal gastric emptying time was calculated from control group as Mean +2SD.

Results: 30 patients were matched with 20 controls after obtaining informed consent. Upper limit of gastric emptying time is 55.09 minutes. Adenocarcinoma was the commonest histological subtype (50%), abdominal pain was the commonest symptom (86.7%) and hepatomegaly was the commonest sign (46.7%), GETt1/2 for patients was 66.72 ± 26.52 minutes while it was 40.53 ± 7.28 minutes in controls (p <0.05). Gastroparesis increased with advancing stage of carcinoma gallbladder (p <0.05). Symptoms of gastric stasis were seen only in 15.6% of patients.

Conclusions: Patients with carcinoma gallbladder can have gastroparesis without obvious symptoms of delayed gastric emptying. This delay in gastric emptying can be documented reliably using solid meal scintigraphic study even in patients without symptoms of gastroparesis. The pathophysiology of gastroparesis needs further study. It may be prudent to remember that while performing palliative bypass surgery for gastric outflow obstruction, that in patients with carcinoma gallbladder, the gastrojejunostomy may not function as expected due to delayed gastric emptying.

Keywords: Carcinoma gallbladder, Gastroparesis, Scintigraphy

INTRODUCTION

Gastrointestinal motility disorders have long been recognized as paraneoplastic accompaniments of both gastrointestinal and extra-intestinal tumors. These are distant effects of the underlying malignancy and are not related to local effects of primary tumor or metastasis. Gastroparesis is a clinical syndrome characterized by delayed gastric emptying in the absence of mechanical gastric outlet obstruction. Symptoms may include

nausea, vomiting, early satiety, abdominal pain and bloating. Carcinoma of stomach, esophagus, pancreas, gallbladder and extra intestinal malignancies like squamous cell carcinoma of lung and brainstem glioma have been shown to cause gastroparesis with patent gastroduodenal axis. Pathophysiology of these tumors associated gastroparesis is not known. Possible mechanisms postulated include autovagotomy secondary to micro metastasis, retroperitoneal nerve invasion and production of unidentified gastroparetic factors.^{3,4}

Carcinoma of the gallbladder occurs with varying frequency in different parts of the world. It accounts for only 0.5% of all gastrointestinal cancers in the western countries, whereas in certain parts of the world like Chile, Mexico and North India, it is one of the common gastrointestinal cancers.⁵⁻⁷ It is the third commonest cause of cancer deaths in women of North India and the incidence is as high as 13.5 per 100,000 population.8 The most common presenting symptom of carcinoma gallbladder is the right upper quadrant pain, which is present in more than 80% of patients. Jaundice is another common symptom and is an indicator of poor prognosis. It is associated with unresectable disease in about 44% of patients.9 About a third of the patients of carcinoma gallbladder present with symptoms and signs suggestive of gastric stasis. The causes of gastric stasis in these patients include mechanical gastric outflow obstruction and malignant gastroparesis.

Various methods have been developed to measure gastric emptying and motility. Upper gastrointestinal barium contrast studies and oesophagogastroduodenoscopy have been used to diagnose gastric out-flow obstruction. Scintigraphy is regarded as the gold standard to measure the gastric emptying time because of its safety, economy and use of physiological meal. Solid phase is preferable to liquids, since normal gastric emptying of liquids is often preserved until there is severe motor dysfunction of the stomach. Moreover it is a noninvasive procedure which can measure gastric emptying accurately and is reproducible despite high intra- and inter-subject variability. It

There are limited studies with scintigraphy highlighting the incidence of delayed gastric emptying due to gastroparesis in carcinoma gallbladder.

This study was conducted with the objectives to find the incidence of delayed gastric emptying (gastroparesis) in patients with carcinoma gallbladder and to find the association of gastric stasis with symptoms and stage of the disease.

METHODS

This prospective case control study was conducted at the Department of General Surgery, PGIMER, Chandigarh between January 2005 and April 2006. Patients with incidental carcinoma gallbladder or proven by preoperative histopathology and retaining gastroduodenal patency demonstrated by computerized tomography or as intra-operative finding were included in the study after obtaining informed consent. Patients with mechanical gastric outlet obstruction, those with metabolic or hormonal derangements or on drugs causing motility disturbances are excluded. Twenty healthy volunteers without any gastrointestinal symptoms were enrolled as controls to define the normal range of gastric emptying time after obtaining informed consent. Institutional Ethical committee approved the study as Scintigraphic

gastric emptying is a routinely performed procedure and is proven not to have any significant radiation or additional risk to the patients.

Gastric emptying was studied using radio labeled solid phase food marker after overnight fasting. The standard meal was steamed rice cake (Idli) prepared with ready to mix powder of prefixed quantity and mixed with 1 mci of technitium^{99m} sulphur colloid. The standard meal was eaten within 10 minutes followed by drinking of 100 mL of water. This was followed by imaging the subject immediately with dual headed gamma camera in anterior and posterior directions for one minute. Imaging was repeated every 15 minutes for 90 minutes. Data was analyzed and gastric half emptying time (GETt_{1/2}) in minutes was calculated. GETt_{1/2} was compared between patients and normal control group. Statistical analysis was performed with SPSS software (version 10, Chicago, USA). Chi square test was used to analyze continuous variables while Pearson and Spearman correlation methods were used for categorical variables. Satterh Waite's method by Epi Info software program was used to compare control group with study population. p value of <0.05 was considered statistically significant.

RESULTS

During the study period, thirty-four patients (n = 34) suspected to have carcinoma gallbladder on the basis of clinical and radiological parameters, without mechanical gastric outlet obstruction were enrolled for this study. All patients were evaluated at the Department of General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Four patients were excluded from final analysis as their histopathological diagnosis was different. Two patients were diagnosed to have xanthogranulomatous cholecystitis, one had hyperplastic adenomyomatous gallbladder and another had tuberculosis of gallbladder.

Thus, the final study subjects included thirty patients (n = 30) of which 70% were females (n = 21). Age of the patients ranged from 26 to 76 years with a mean age of 30.6 years. Among the twenty healthy volunteers, 50% were females (n = 10) and their age ranged from 26 to 72 years with a mean age of 39.9 years.

The commonest presenting symptom was abdominal pain (86.7%) (n = 26), followed by anorexia (40%) (n = 12) and jaundice (23.3%) (n = 7). Symptoms suggestive of gastric stasis like nausea, vomiting, postprandial fullness and early satiety were present only in 5 patients (15.6%). Mean duration of symptoms was 7.2 months with a range from 1 week to 72 months. Eight patients (26.7%) (n = 8/30) had incidental carcinoma gallbladder. On clinical examination, 50% of patients (n = 15) had hepatomegaly while 46.7% had palpable gallbladder mass (n = 14).

Most of the patients were able to perform day to day activities 56.7% (n = 17), while 6.7% (n = 2) were

bedridden for most of the time. 50% of the patients (n = 15) had adenocarcinoma while other patients had different histological subtype.

The GET $t_{1/2}$ ranged from 28 minutes to 50 minutes in the control group with a mean of 40.53 ± 7.28 minutes while in the study group GET $t_{1/2}$ ranged from 23 minutes to 127 minutes with a mean of 66.72 ± 26.52 minutes (Figure 1, Table 1).

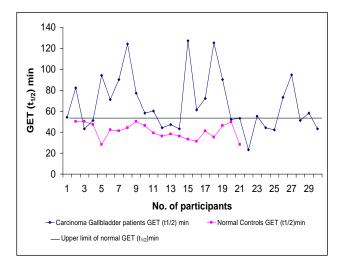


Figure 1: Difference in gastric emptying time by scintigraphy study.

This difference in GET $t_{1/2}$ was statistically significant (p = 0.029). When 55.09 minutes (Mean + 2SD) was taken as the cut off value for normal gastric emptying, 53.33% of the patients (n = 16) had delayed gastric emptying.

Table 1. Difference in gastric half emptying time in cases and controls.

Parameters	Mean t1/2	Variance
Study group	66.72±26.52	703.3
Control group	40.53±7.28	53.04

In the present study, it was found that the incidence of delayed gastric emptying increased with the advance in stage of carcinoma gallbladder. Gastroparesis was seen in 57% (n = 8/14) patients with stage IV disease and this difference was statistically significant (p = 0.029) (Table 2).

There was no statistical difference in variables (age, sex, duration of symptoms, histological type or hyperblirubinemia) between patients who had their GET $t_{1/2}$ below mean and the patients who had their GET $t_{1/2}$ above mean (p > 0.05). 43.33% of patients (n = 13) had surgery as a modality of management. Seven of 13 operated patients had lymph node metastasis (53.8%). In patients with lymph node metastasis, 42.9% (n = 3/7), showed delayed gastric emptying (GET $t_{1/2}$ above mean) while all the patients without lymph node metastasis (n =

4) (100%) had delayed gastric emptying (GET $t_{1/2}$ above mean).

Table 2: Distribution of patients with gastroparesis according to stage of disease.

Stage of Ca Gallbladder	No. of patients	No. of patients with gastroparesis
I	1	1
II	5	2
III	10	5
IV	14	8

In the present study, all patients underwent contrast enhanced computerized tomography scan of abdomen to assess the disease status. One patient had malignant ascites (3.33%) (n = 1), three patients had multiple liver metastasis (10%) (n = 3), four patients had major vascular involvement (13.3%) (n = 4) and two patients had multiple organ involvement (6.66%) (n = 2). All these patients (n = 10) were given non-operative palliative therapy. Remaining 20 patients (66.67%) underwent laparotomy and nine patients were found to have unresectable disease (30%) (n = 9) of which two patients underwent prophylactic antecolic posterior gastrojejunostomy for invasion of distal stomach. Among the nine patients, vascular encasement was found in 20% (n = 6), multiple organ involvement in two patients (6.66%) and peritoneal metastasis in one patient (n = 1).

DISCUSSION

The factors governing gastric emptying are both complex and poorly understood; however, the advent of a rapid, reproducible, relatively simple and inexpensive solidphase gastric emptying study has opened up horizons in evaluating gastric stasis syndromes. Abnormalities are being more frequently recognized in a wide variety of clinical settings including atrophic gastritis, marked metabolic derangements, advanced diabetes mellitus, scleroderma and other connective tissue disorders, diffuse neuromuscular disorders, esophageal reflux, gastrectomy and vagotomy, anorexia nervosa and bulimia, and post-viral infection. In addition, treatment with a number of pharmacologic agents including anticholinergics, tricyclic antidepressants, levodopa, opiates, aluminium antacids and ethanol can result in delayed gastric emptying of solids.

In the prospective study by Shivshanker et al. among ten patients with non-obstructing upper gastro intestinal tumor and who had symptoms of postprandial fullness, early satiety, nausea and vomiting, delayed gastric emptying was seen in 70%. Parkin et al demonstrated that 60% of their study population with pancreatic carcinoma had delayed solid-phase gastric emptying. This abnormality of emptying did not correlate with the location of the tumor or the presence of hyperbilirubinemia. Nausea and vomiting was present in 33% of patients with delayed gastric emptying and in

none of those with normal gastric emptying. Pain was more frequently seen in patients with abnormal gastric emptying. Although there were other causes of the nausea, vomiting, bloating and early satiety which so often contribute to a deteriorating nutritional situation in patients with pancreatic carcinoma, it is exciting to postulate that this may be due in part to delayed gastric emptying. ¹³

Majority of patients with carcinoma of the gallbladder present with advanced disease where resection is not possible. Halp Many of these patients with signs and symptoms suggestive of gastric outlet obstruction often needs palliation. Thirty percent of patients with carcinoma gallbladder have been reported to have symptoms suggestive of gastric stasis (nausea, vomiting, early satiety and postprandial fullness. Halp Many of these patients with carcinoma gallbladder have been reported to have symptoms suggestive of gastric stasis (nausea, vomiting, early satiety and postprandial fullness. Halp Many of these patients with signs and symptoms suggestive of gastric stasis (nausea, vomiting, early satiety and postprandial fullness. Halp Many of these patients with signs and symptoms suggestive of gastric outlet obstruction often needs patients.

The most common presenting symptom of carcinoma gallbladder is the right upper quadrant pain, which is present in more than 80% of patients. Jaundice is also not uncommon and is an indicator of poor prognosis. It was associated with unresectable disease in about 44% of patients. This was similar to the results obtained in our study as the commonest presenting symptom was abdominal pain (86.7%) and 23.3% of the patient had jaundice at initial presentation. 85.7% (n = 6) of the patients who had jaundice at initial presentation had unresectable primary tumor.

In the absence of a mechanical cause, the symptoms of outlet obstruction and/or gastric stasis could be explained on the basis of gastroparesis associated with advanced stage of disease. The incidence of malignant gastroparesis in carcinoma gallbladder has not been defined so far and the pathophysiology of delayed gastric emptying has not been well understood. The incidence has been reported to be around 60% (32% to 84%) in patients with carcinoma pancreas.^{3,4,13}

The relationship between symptomatic gastric stasis and delayed gastric emptying is multifactorial. Delayed gastric emptying can also be subclinical and patient may not have clinical symptoms of gastric stasis. Solid meal labeled gastric emptying study is a simple, noninvasive, sensitive and reproducible technique to objectively study gastric emptying patterns in human beings.¹⁶

In the present study, clinical symptoms of gastric stasis was seen only in 15.6% of patients (n = 5) while delayed gastric emptying was seen in 53.3% of the study subjects (n = 16). This was in contrast to the study by Singh et al who found clinical symptoms of gastric stasis in 32% of their patients and delayed gastric emptying by scintigraphy study in $40\%.^{17}$ Among the patients who had delayed gastric emptying (n=16), 2 (12.5%) patients had symptoms of gastric stasis. In patients with normal gastric emptying (n=14), only 3 patients (21.4%) had symptoms and the difference was statistically not significant. Scintigraphic gastric emptying study

therefore did not correlate with symptoms of gastric stasis. Hence the role of prokinetic drugs such as metoclopamide, cisapride, erythromycin and other motilin agonists is not very clear in patients with symptomatic gastric stasis or malignant gastroparesis.

Present study was not limited to those patients with symptoms of gastric stasis and indeed, we have demonstrated that tumor-associated gastroparesis may exist subclinically. Many possible factors could account for this delayed gastric emptying. All our patients had patent gastrointestinal lumens without evidence of tumor invasion, normal electrolytes, no history of smoking and were kept fasting for at least 12 hours, prior to testing. In addition, all studies were done prior to the stress of surgery.

Most of the patients were recently diagnosed and consequently had good performance status and well-preserved nutritional indices. Although delayed gastric emptying can be found in patients with diabetes mellitus, most frequently it is seen in association with peripheral neuropathy. Two of our patients were diabetics (6.67%), of whom one was on oral hypoglycemic agents and the other was on diet control with good glycemic control. Neither of them had evidence of peripheral neuropathy. It was therefore very unlikely for diabetes mellitus to be the sole cause of their gastroparesis.

Advanced stage of disease showed more incidence of gastroparesis which was similar to the results obtained by Sikora et al and Singh et al who have found significant correlation between the advanced stages and delayed gastric emptying.^{3,17} However this conclusion should be taken in the light of the small number of patients with early stage disease.

In the present study, lymph node metastasis was present in 7 out of 11 cases but only 2 patients with proven metastasis had delayed gastric emptying. This was not statistically significant. Therefore, the proposed hypothesis of autovagotomy secondary to micro metastasis is questionable.

CONCLUSION

Therefore, we can conclude from the present study that a percentage of patients with carcinoma gallbladder have delayed gastric emptying (gastroparesis) without obvious symptoms.

This delay in gastric emptying can be documented reliably using solid meal scintigraphy study but does not correlate well with the presenting symptoms. The pathophysiology of gastroparesis needs further study. It may be prudent to remember that while performing palliative bypass surgery for gastric outflow obstruction, that in patients with carcinoma gallbladder, the gastrojejunostomy may not function in the expected manner because of delayed gastric emptying.

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