

The relationship between gastrointestinal complaints and the use of pancreatin-derived medications after cholecystectomy

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ABSTRACT

Objective: The aim of this study was to investigate the relationship between pancreatin-derived medications and the treatability of gastrointestinal complaints after cholecystectomy.

Patients and Methods: The relationship between postoperative symptomatic status and the use of proton pump inhibitors (PPIs) and pancreatin-derived medications in patients admitted to our hepatobiliary surgery service who underwent cholecystectomy was retrospectively analyzed. IBM SPSS Statistics 23 (IBM SPSS, Turkey) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate the study data. Pearson Chi-Square Test and Fisher's Exact test were used to compare qualitative data. Significance was evaluated at the $p < 0.05$ level.

Results: Proton pump inhibitors and pancreatin-derivatives were prescribed to all patients in the postoperative period. Although, the rate of postoperative asymptomatic course was higher in all patients, the rate of postoperative symptoms was found to be higher in patients who received PPI and pancreatin therapy ($p = 0.001$, $p = 0.022$; $p < 0.01$).

Conclusions: Although, the high rate of asymptomatic postoperative course in all patients indicates that cholecystectomy alone is curative, some symptoms may persist in the postoperative period and it was found to be more frequent in patients who used PPI and pancreatin-derived medications in the postoperative period.

Keywords: Cholecystectomy, Pancreatin-derivatives, Proton Pump Inhibitors, Dyspepsia

1. INTRODUCTION

Dyspepsia is a combination of symptoms including subjective complaints such as upper abdominal or retrosternal pain, bloating that does not resolve with defecation, early satiety, feeling of fullness and nausea, with a wide range of differential diagnoses and can be explained by multiple pathophysiological mechanisms [1,2]. It has been reported that some patients presenting with dyspeptic complaints are diagnosed with gastritis or peptic ulcer, while many do not know the exact diagnosis [3]. In addition, it has also been reported that helicobacter pylori eradication treatment causes a significant decrease in dyspepsia complaints [4]. The main factors causing dyspepsia are gastritis, gastroesophageal reflux disease and peptic ulcer, as well as drugs and gastric malignancies [5]. Pancreatobiliary pathologies ranging from asymptomatic gallstones to malignancies are known to be among the causes of dyspepsia. Gallstones are usually clinically asymptomatic and incidentally detected. Cholecystectomy is the primary treatment

method for symptomatic or complicated gallstones, and is used prophylactically in the presence of porcelain sacs, gallbladder polyps larger than 1 cm in diameter, sickle cell anemia and hereditary spherocytosis, even if asymptomatic [6,7]. However, major biliary pathologies may produce a clinical picture with pancreatic enzyme deficiency and many may be associated with gastrointestinal symptoms. Treatment of patients with pancreatic enzyme deficiency is a difficult clinical picture, especially in patients with chronic alcoholic pancreatitis or cystic fibrosis and after pancreatectomy [8].

Pancreatic enzyme deficiency is considered in patients with symptoms such as steatorrhea, diarrhea and weight loss, and this condition is shown by various diagnostic methods. In addition, findings such as pancreatic ductal dilatation or stones by various imaging or endoscopic methods and the presence of other symptoms support pancreatic enzyme deficiency and pancreatic enzyme replacement constitutes the basic treatment strategy

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in such cases [9]. Digestion of fats is the determining factor in pancreatic enzyme deficiency, and some systemic diseases such as denaturation of lipase by gastric acid, inappropriate timing of enzymes, concomitant small intestinal mucosal diseases, rapid intestinal transit, and some systemic diseases such as diabetes and some genetic diseases such as cystic fibrosis also affect the activity of pancreatic enzymes [10]. Furthermore, it has been shown that pancreatic exocrine insufficiency may occur after gastrectomy in some patient subgroups [11].

Pancreatic enzyme replacement therapy has been found safe and effective in many complicated causes of pancreatic exocrine insufficiency, including chronic pancreatitis, cystic fibrosis and pancreatic cancer [12]. However, uncomplicated gallstones may also be accompanied by dyspeptic complaints and pancreatic enzyme replacement has been tried for treatment. In this study, we aimed to investigate the relationship between pancreatin-derived medications and the treatability of gastrointestinal complaints after cholecystectomy.

2. PATIENTS and METHODS

The data of patients admitted to the Istanbul University Cerrahpasa Medical Faculty, Hepatobiliary Surgery Service who underwent laparoscopic cholecystectomy were reviewed retrospectively. Preoperative examinations and evaluations as well as data recorded in patient files and hospital databases were analyzed, and age, gender, pre-cholecystectomy abdominal imaging results and clinics, preoperative complicated cholelithiasis status, preoperative pain and dyspepsia symptoms were recorded for each patient. The presence of complicated cholelithiasis was determined according to the preoperative history of cholangitis, choledocholithiasis, biliary pancreatitis, endoscopic retrograde cholangiopancreatography, and the presence of cholecystitis, cholecystostomy, and peroral conversion to open surgery. These findings were obtained by reviewing patient anamnesis and clinical course notes, radiological imaging and operative notes, and postoperative pathology reports in hospital databases. All patients were given perioperative antibiotic prophylaxis, and in the postoperative period, proton pump inhibitor (PPI) was prescribed once daily in the morning before meals and pancreatin derivatives were prescribed three times daily between meals. Pancreatin, a crude mixture, is derived from pig or ox pancreas and contains at least 2 United States Pharmacopeia (USP) units of lipase and 25 USP units of amylase and protease activity per milligram. The pancreatin product prescribed to the patients was 170 mg (5500 Amylase, 6500 Lipase, 400 Protease F.I.P units) (porcine origin). The symptomatic status of the patients after discharge and the use of the prescribed medications were learned by telephone. Preoperative symptoms and complaints, early postoperative symptoms at 1st month, and late postoperative symptoms at 3rd month were questioned separately. Gastritis history was recorded according to the presence of complaints and gastroscopy results. Patients without dyspeptic complaints and without gastroscopy were considered to have no history of gastritis.

Patients undergoing laparoscopic cholecystectomy who had no evidence of other organic, systemic, metabolic diseases to explain dyspeptic symptoms were included into the study; some systemic, gastrointestinal, and genetic diseases such as cystic fibrosis accompanied by pancreatic enzyme deficiency, patients who underwent major pancreatobiliary surgery, open cholecystectomies, patients who developed complications such as bilioma, biliary tract injury, etc. requiring rehospitalization after cholecystectomy, patients with pregnancy or breastfeeding status, and patients whose data could not be reached or who refused to participate were excluded. In addition, inability to provide standardization in detailing the cost for patients not using PPI and pancreatin derivatives, disregarding the treatment, considering medical treatment unnecessary/surgical sufficient, ideological and religious reasons, etc. were not examined and were excluded from the discussion for objectivity.

The study was reviewed by the Clinical Research Ethics Committee of Istanbul University Cerrahpasa Medical Faculty on 07.09.2021, and was approved with the number E-83045809-604.01.02-178270.

Statistical Analysis

IBM SPSS Statistics 23 (IBM SPSS, Turkey) program was used for statistical analysis while evaluating the findings obtained in the study. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate the study data. Pearson Chi-Square Test and Fisher's Exact test were used to compare qualitative data. Significance was evaluated at the $p < 0.05$ level.

3. RESULTS

In this study, a total of 290 patients, 61.4% (n=178) female and 38.6% (n=112) male, who underwent cholecystectomy were retrospectively analyzed. The ages of the patients ranged between 22-88 years with a mean age of 54.45 ± 13.79 years. Preoperatively, 25.2% (n=73) had complicated cholelithiasis, 31.4% (n=91) had gastritis, 74.5% (n=216) had pain and 48.3% (n=140) had dyspeptic complaints. The mean length of hospitalization was 1.44 days. All patients received perioperative antibiotic prophylaxis and PPI and pancreatin derivatives were prescribed to all patients after discharge. In the postoperative period, 33.8% (n=98) of the patients used PPIs, 48.6% (n=141) used pancreatin derivatives, and 21.4% (n=62) used both PPIs and pancreatin. In the early postoperative period, 90.7% (n=263) of the patients were asymptomatic, 5.5% (n=16) had pain and 3.8% (n=11) had dyspeptic complaints. In the advanced postoperative period, 89.3% (n=259) of the patients were asymptomatic, 4.5% (n=13) had pain and 6.2% (n=18) had dyspeptic complaints (Table I).

There was no significant difference in the distribution of symptoms in the early postoperative period and in the advanced postoperative period according to age, gender, and the presence of complicated cholelithiasis in the preoperative period ($p > 0.05$). There was also no significant difference in the distribution of symptoms according to the patients' history of gastritis ($p > 0.05$). However, in the advanced postoperative period, the

rate of dyspeptic complaints was higher than pain complaints in patients with a history of gastritis ($p=0.015$; $p<0.05$) (Table II).

In the evaluation of postoperative symptoms, the rate of postoperative asymptomatic progression was higher in all groups compared to PPI use alone, however, both pain and dyspepsia rates were higher in PPI use alone ($p=0.002$, $p=0.001$; $p<0.01$) (Table III).

Table I. Distribution of descriptive characteristics

		n	%
Age (year)	Min-Max	(Median); 22-88 (55)	54.45±13.79
	Mean±Sd		
	< 40 years	42	14.5
	≥ 40 years	248	85.5
Gender	Female	178	61.4
	Male	112	38.6
Having Preoperative Complicated Cholelithiasis	None	217	74.8
	Yes	73	25.2
Preoperative gastritis history	None	199	68.6
	Yes	91	31.4
Postoperative PPI use only	None	192	66.2
	Yes	98	33.8
Postoperative use of Pancreatin	None	149	51.4
	Yes	141	48.6
Postoperative use of PPI+Pancreatin	None	228	78.6
	Yes	62	21.4
Preoperative period symptoms	Pain	216	74.5
	Dyspepsia	140	48.3
Early postoperative period symptoms	Asymptomatic	263	90.7
	Pain	16	5.5
	Dyspepsia	11	3.8
Advanced postoperative period symptoms	Asymptomatic	259	89.3
	Pain	13	4.5
	Dyspepsia	18	6.2

(More than one symptom may occur together in each case.)
(PPI: Proton Pump Inhibitor)

Table II. Evaluation of symptoms in early postoperative and postoperative advanced periods according to the presence of preoperative gastritis history

		Preoperative Gastritis History		P
		None (n=199)	Yes (n=91)	
		n (%)	n (%)	
Early postoperative period symptoms	Asymptomatic	183 (92.0)	80 (87.9)	0.496
	Pain	10 (5.0)	6 (6.6)	
	Dyspepsia	6 (3.0)	5 (5.5)	
Advanced postoperative period symptoms	Asymptomatic	184 (92.5)	75 (82.4)	0.015*
	Pain	8 (4.0)	5 (5.5)	
	Dyspepsia	7 (3.5)	11 (12.1)	

Pearson Chi-Square Test $*p<0.05$

In the evaluation of postoperative symptoms, the rate of asymptomatic course was higher in all groups compared to postoperative pancreatin derivatives use alone; there was no significant difference in the distribution and rate of symptoms in the early postoperative period symptoms ($p>0.05$). However, in the advanced postoperative period, the rate of symptoms was higher in pancreatin users; among the symptoms, the incidence of dyspepsia was found to be higher ($p=0.001$; $p<0.01$) (Table IV).

Table III. Evaluation of symptoms in the early postoperative and postoperative advanced periods based on PPI use only

		PPI Use Only		P
		None (n=192)	Yes (n=98)	
		n (%)	n (%)	
Early postoperative period symptoms	Asymptomatic	182 (94.8)	81 (82.7)	0.002**
	Pain	7 (3.6)	9 (9.2)	
	Dyspepsia	3 (1.6)	8 (8.2)	
Advanced postoperative period symptoms	Asymptomatic	183 (95.3)	76 (77.6)	0.001**
	Pain	5 (2.6)	8 (8.2)	
	Dyspepsia	4 (2.1)	14 (14.3)	

Pearson Chi-Square Test $**p<0.01$

Table IV. Evaluation of symptoms in early postoperative and postoperative advanced periods according to postoperative pancreatin derivative use

		Use of Pancreatin Derivative Only		P
		None (n=149)	Yes (n=141)	
		n (%)	n (%)	
Early postoperative period symptoms	Asymptomatic	140 (94.0)	123 (87.2)	0.125
	Pain	6 (4.0)	10 (7.1)	
	Dyspepsia	3 (2.0)	8 (5.7)	
Advanced postoperative period symptoms	Asymptomatic	141 (94.6)	118 (83.7)	0.001**
	Pain	7 (4.7)	6 (4.3)	
	Dyspepsia	1 (0.7)	17 (12.1)	

Pearson Chi-Square Test $**p<0.01$

Table V. Evaluation of symptoms in early postoperative and postoperative advanced periods according to postoperative PPI + pancreatin derivative concomitant use

		Use of PPI + Pancreatin derivative		p
		None (n=228)	Yes (n=62)	
		n (%)	n (%)	
Early postoperative period symptoms	Asymptomatic	211 (92.5)	52 (83.9)	0.022*
	Pain	12 (5.3)	4 (6.5)	
	Dyspepsia	5 (2.2)	6 (9.7)	
Advanced postoperative period symptoms	Asymptomatic	213 (93.4)	46 (74.2)	0.001**
	Pain	10 (4.4)	3 (4.8)	
	Dyspepsia	5 (2.2)	13 (21.0)	

Fisher Freeman Halton Exact Test $*p<0.05$ $**p<0.01$

The rate of asymptomatic course was found to be higher; when the symptoms were analyzed, it was observed that the rate of being symptomatic increased in postoperative PPI and pancreatin combination use, and the rate of dyspepsia increased more than pain ($p=0.022$, $p=0.001$; $p<0.05$) (Table V). The distribution of symptoms in the postoperative period was similar according to age and gender, and according to the presence of a history of gastritis in postoperative PPI and pancreatin combination use ($p>0.05$).

When the distribution of postoperative symptoms in the combined use of PPI and pancreatin derivatives, it was observed that the rate of being asymptomatic was higher in all groups. However, the rate of symptomatic patients was higher in patients who used PPI+pancreatin combination; in patients who did not

have preoperative complicated cholelithiasis, the pain seen in the early postoperative period decreased in the postoperative advanced period, and the rate of dyspepsia increased. In patients with preoperative complicated cholelithiasis, there was no change in the rate of pain in the postoperative period, while the rate of dyspepsia increased in the postoperative advanced period ($p>0.05$). In patients who did not use PPI + pancreatin combination postoperatively, both pain and dyspepsia rates decreased in the postoperative advanced period in patients without complicated cholelithiasis. However, in patients with complicated cholelithiasis, the postoperative advanced period pain rate did not change, whereas the dyspepsia rate increased ($p=0.014$; $p<0.05$) (Table VI).

Table VI. Evaluation of symptoms in the early postoperative and postoperative advanced periods according to the presence of preoperative complicated cholelithiasis in the combination of postoperative PPI + pancreatin derivative

Use of PPI + Pancreatin derivative	Period	Symptoms	Preoperative Complicated Cholelithiasis		p
			None (n=217) n (%)	Yes (n=73) n (%)	
Yes	Early post- operative period symptoms	Asymptomatic	38 (82.6)	14 (87.5)	1.000
		Pain	3 (6.5)	1 (6.3)	
		Dyspepsia	5 (10.9)	1 (6.3)	
	Advanced post- operative period symptoms	Asymptomatic	35 (76.1)	11 (68.8)	0.771
		Pain	2 (4.3)	1 (6.3)	
		Dyspepsia	9 (19.6)	4 (25.0)	
None	Early post- operative period symptoms	Asymptomatic	160 (93.6)	51 (89.5)	0.172
		Pain	9 (5.3)	3 (5.3)	
		Dyspepsia	2 (1.2)	3 (5.3)	
	Advanced post- operative period symptoms	Asymptomatic	163 (95.3)	50 (87.7)	0.014*
		Pain	7 (4.1)	3 (5.3)	
		Dyspepsia	1 (0.6)	4 (7.0)	

Fisher Freeman Halton Exact Test

* $p<0.05$

4. DISCUSSION

Gallstones are one of the most common gastrointestinal problems in the general population. In our study where 290 patients underwent cholecystectomy, 25.2% (n=73) had a history of complicated cholelithiasis and 31.4% (n=91) had a history of gastritis in the preoperative period; when the symptoms were examined, 74.5% (n = 216) had pain and 48.3% (n = 140) had dyspeptic complaints. Cholecystectomy is the main treatment for symptomatic or complicated gallstones. Studies have shown that although dyspeptic complaints are significantly reduced after cholecystectomy, dyspepsia and abdominal pain persist in some patients. There are also studies indicating that pathologies such as gastritis, duodenitis and ulcers may accompany patients with atypical gastrointestinal complaints and that persistent symptoms may be related to them [7]. In our study, the rate of asymptomatic course in the postoperative period was significantly higher in all patients, and this result is consist with

the fact that cholecystectomy alone is curative in cholelithiasis. In our study, postoperative symptoms such as dyspepsia and abdominal pain were not related to age, gender, and complexity of cholelithiasis; however, it was shown that postoperative dyspeptic symptoms were higher in patients with a history of gastritis.

Although, the evaluation of upper abdominal pain after cholecystectomy is subjective, its frequency has been reported in the literature between 10-33% and higher in women. Although, the causes have not been fully elucidated, periampullary pathologies and oddi sphincter dysfunction have been found to be the most common etiologies [13]. In our study, the frequency of pain after cholecystectomy was between 4.5-5.5%, and no difference was found according to age and gender.

The main causes of dyspepsia include peptic ulcer disease, gastroesophageal reflux disease, biliary pathologies, some drugs and gastric malignancies [14]. Studies have shown that

the most common findings in patients with dyspepsia are erosive esophagitis and peptic ulcer disease, and treatment has been reported to cause a significant reduction in dyspepsia complaints [14,15]. It is known that proton pump inhibitors alone or in combination have a place in the treatment of diseases such as gastritis and ulcers, and pancreatic enzymes are used in the treatment of digestive disorders in which fat digestion is the determinant [10]. In our study, only PPIs were used in 33.8% (n=98), only pancreatin derivatives in 48.6% (n=141) and both PPIs and pancreatin derivatives in 21.4% (n=62) of the patients in the postoperative period.

In our study, an increase was observed in postoperative symptoms with the use of PPI alone or pancreatin derivative alone. Similarly, the combination of PPI and pancreatin derivative caused an increase in postoperative symptoms and the rate of dyspepsia was higher. When the reasons for this are examined, it should be kept in mind that pancreatic enzyme replacement may not always provide the desired beneficial effect due to enzyme inactivation by gastric acid [16]. As a matter of fact, in our study, the distribution of symptoms was found to be similar in PPI and pancreatin use when evaluated according to the presence of history of gastritis; even in the presence of preoperative complicated cholelithiasis, which has been shown to be associated with postoperative symptomatic status, PPI and pancreatin derived use did not decrease or even increased the symptoms.

Pancreatic enzyme replacement therapy (PERT) is a difficult clinical problem due to acid instability. To solve this problem, various preparations of porcine pancreatin or some fungal enzymes have been introduced to the market as enteric-coated tablets or microspheres, and sometimes combined therapies with H2 receptor antagonists are required [10]. Exocrine insufficiency occurs in more than 90% dysfunction of the pancreas and PERT is given to reduce malnutrition and morbidity to patients with insufficiency [17]. There are publications showing the benefits of routine PERT use after pancreatic resections [18]. In cases of pancreatic insufficiency after gastric surgery, PERT has been shown to improve malnutrition and improve quality of life [19]. Based on the data obtained in the study, postoperative PPIs and pancreatin derived medications had no positive effect on ongoing postoperative symptoms and even had a negative effect. Therefore, in the light of the available data, it can be concluded that such medications should be limited to major pancreatobiliary pathologies for which the indication is indisputable today. Prospective, randomized and large-scale studies are needed for more precise and effective results.

Compliance with Ethical Standards

Ethical Approval: The study was reviewed by the Clinical Research Ethics Committee of Istanbul University Cerrahpasa Medical Faculty on 07.09.2021, and was approved with the number E-83045809-604.01.02-178270.

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