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Retrospective analysis of clinical approaches in cases of perforation after endoscopic retrograde cholangiopancreatography

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Abstract

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a procedure in which endoscopy and fluoroscopy are used together to diagnose and treat problems in the pancreatic and biliary ductal systems. According to published studies, the frequency of perforation associated with ERCP is reported to be less than 1%. In our study, we aimed to retrospectively analyze the data of patients we followed after ERCP perforation to examine treatment approaches. In this study, data from 33 patients who underwent ERCP at a tertiary stage education and research hospital between November 2016 and April 2021 and were identified to have developed perforation during or after the procedure were retrospectively evaluated. The indications and outcomes of ERCP for patients, as well as laboratory and imaging findings, were analyzed in detail. The age distribution of the 33 patients included in the study ranged from 20 to 83 years, with a mean age of 57.1±17.6 years. Perforation developed during the initial ERCP procedure in 66.7% of the patients, and on seven of the ten patients in whom perforation was detected during the procedure, interventions were performed during the procedure. Although the mortality rate in patients with Stapfer type 1 or type 2 perforations (33.3%) was higher compared to the patients with type 3 or type 4 perforations (11.1%), the observed difference was not found to be statistically significant. In conclusion, the management of patients with ERCP perforation should be approached in a multidisciplinary manner, and non-operative approaches should always be considered in the appropriate patient population. Closely and dynamically monitoring of patients and algorithmic approaches should standardized.

Keywords: Endoscopic retrograde cholangiopancreatography, perforation, complication, Stapfer classification, Clavien-Dindo classification

Introduction

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a procedure in which endoscopy and fluoroscopy are used together to diagnose and treat problems in the pancreatic and biliary ductal systems. It first entered the literature in 1968 when a surgeon named William McKune and a gastroenterologist named Paul Shorb published four cases in which they placed a catheter into the Vater's ampulla using endoscopic imaging [1]. In the 1970s, after German and Japanese teams described endoscopic sphincterotomy, ERCP gained therapeutic significance in addition to diagnosis, including applications such as lithotripsy and stent placement [2].

With the increasing use of ERCP for therapeutic purposes, the frequency of complications has also increased. The complication with highest mortality and morbidity associated with therapeutic ERCP procedures is perforation. According to published studies, the frequency of perforation associated with ERCP is reported to be less than 1%. It is more commonly observed in procedures involving individuals with altered anatomy, such as those who have undergone Billroth II and Roux-en-Y surgeries, as well as cases where the gallbladder is significantly adhered and also procedure-related perforations are also more frequently seen in

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pre-cut incisions made with a needle-tip sphincterotome [3,4].

Early diagnosis of perforation and the initiation of appropriate treatment are of vital importance. The approach to be adopted after a perforation diagnosis is made depends on the timing of the diagnosis and the clinical condition of the patient. The treatment of ERCP-related perforation varies depending on the type of perforation, its severity, and the clinical symptoms. In the past, surgical treatment was more prominent, but with the development of interventional methods, there has been an increase in the frequency of non-operative approaches. In cases of ERCP-related perforations, it is important for the responsible surgeon to manage the patient and for the hospital to provide conditions conducive to a multidisciplinary approach [5]. In our study, we aimed to retrospectively analyze the data of patients we followed after ERCP perforation to examine treatment approaches.

Material and Methods

In this study, data from 33 patients who underwent ERCP at a tertiary stage education and research hospital by Gastroenterology Dept. between November 2016 and April 2021 and were identified to have developed perforation during or after the procedure and transferred to General Surgery Dept. were retrospectively evaluated. Patient data were obtained by scanning the hospital information system and medical records. Patient information, including age, gender, ERCP indication, and the number of ERCP procedures performed, was compiled by scanning the hospital information system. From the patient files, data were collected regarding anatomical variation status, when and by which method the perforation diagnosis was made (whether through Computer Aided Tomography imaging or observed during ERCP), whether an interventional procedure was performed if perforation was detected during ERCP, and data related to total/direct bilirubin, albumin, CRP values before and after the procedure, as well as antibiotic usage. The categorization of perforation cases was done according to the Stapfer classification. The postoperative follow-up and complication data of patients for whom surgery was decided were evaluated according to the Clavien-Dindo classification system.

The ethical approval for this study was granted by the University of Health Sciences Gülhane Training and Research Hospital Scientific Research Ethics Committee, during its meeting dated November 30, 2020 with decision number 2020/476.

Statistical analyses of the data were performed using the SPSS version 15.0 software package (Chicago, USA). The conformity of the variables to the normal distribution was examined using visual (histograms and probability plots) and analytical (Kolmogorov-Smirnov, Shapiro-Wilk tests) methods. Numerical data with a normal distribution were expressed as mean±standard deviation, while non-normally distributed data were presented as median, and nominal data were expressed as counts and percentages. For the comparison of two groups in numerical data, t-tests and Mann-Whitney U tests were used, taking into consideration the distribution characteristics. Nominal data were compared using the Chi-square test. In statistical analyses, p-values below 0.05 were considered statistically significant.

Results

The age distribution of the 33 patients included in the study ranged from 20 to 83 years, with a mean age of 57.1±17.6 years. 57.6% of the patients (n=19) were female, and 42.4% (n=14) were male.

Between the years of the study, a total of 3825 patients underwent ERCP; Procedure-related perforation occurred in 33 (0.86%) patients. The reasons for performing ERCP on the patients admitted in the study group are given in Table 1. Accordingly, the most common indication for ERCP is choledocholithiasis (18 patients, 54.5%). The number of patients who underwent ERCP due to periampullary carcinoma and related complications is nine (27.3%).

The diagnosis of perforation was made during the procedure in 10 out of 33 patients (30.3%). The time to diagnosis of perforation ranged from 0 to 120 hours, with a median diagnosis time of 4 hours. In 22 patients (66.7%), perforation occurred during the first ERCP procedure, in 6 patients (18.2%) during the second procedure, and in 3 patients (9.1%) during a subsequent ERCP procedure after the second one. The classification of observed perforations according to the Stapfer classification is provided in Table 2.

To the seven out of the ten patients in whom perforation was detected during the procedure, intervention was performed during the procedure. Among these seven patients, two were treated with a nasobiliary drainage catheter, two with a pigtail stent, two with a stent, and one with an endoscopic clip.

Among the patients in the research group, 42.4% (n=14) have a history of antibiotic treatment initiated before the procedure. The most commonly used antibiotics of choice for perforation were third-generation cephalosporins (60.6%). Other antibiotic groups used in order of preference include piperacillin/tazobactam (18.2%), carbapenem (12.1%), and quinolone group (9.1%). In patients who did not receive antibiotics before the procedure, the median time to initiate antibiotics after perforation was 7 (0-140) hours. Percutaneous drainage catheters were placed in 63.6% of the patients (n=21).

The median intensive care unit follow-up time was 7 (2-23) days, and clinical follow-up time was 13 (3-30) days. While 72.7% of the patients (n=24) were discharged, mortality was observed in 27.3% (n=9) of them.

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Five out of the patients with perforation (15.2%) was operated on. The characteristics of the operated patients are provided in Table 3. According to the Clavien-Dindo classification, one of the operated patients was classified as Grade I, while four were classified as Grade V. In two patients, more than one operation was performed, where in one of them, the first operation included pyloric exclusion, gastroenterostomy, and Brown anastomosis, while the second operation involved cholecystectomy, right hemicolectomy, tube choledochostomy, pancreatic tube drainage, tube duodenostomy, and ileostomy; in the other patient, the first operation consisted of primary duodenal repair and cholecystectomy, while the second operation included right hemicolectomy, end ileostomy, and repair of the cystic leak. Among the patients who underwent a single operation, one had cholecystectomy, hepaticojejunostomy, and gastroenterostomy, another had pyloric exclusion, hepaticojejunostomy, and gastroenterostomy, and another had primary duodenal repair. The time elapsed until the operation was 1 hour in one patient, 4 hours in another, 84 hours another, 12 days in another, and 27 days in another. The median intensive care unit follow-up time for the operated patients was 16 (3-18) days, and mortality was observed in 80% of the patients after the operation.

For the biochemical markers of the patients, it is observed that albumin was 3.2±0.7 g/dL, total bilirubin 2.7 (0.4-32) mg/dL, direct bilirubin 1.4 (0.1-15) mg/dL; and CRP values were 19 (1-319) mg/dL before perforation and 123 (11-400) mg/dL on the first day after perforation

The comparison of patients with and without mortality due to perforation during ERCP in terms of demographic, clinical, and laboratory results is provided in Table 4. When compared to patients without mortality, for the patients with mortality the mean age (53.5±18.2 vs. 66.7±11.8 years, p=0.023), CRP values (14.5 (1-319) and 111 (4-312) mg/dL, p=0.030) were higher, the intensive care unit follow-up durations (3.5 (2-10) and 16 (4-23) days, p=0.001) were longer, and albumin levels (3.4±0.5 and 2.8±0.8 mg/dL, p=0.033) were lower.

When investigating whether the classification of perforation according to the Stapfer classification had an impact on mortality, the research data showed that the mortality rate was higher in patients with type 1 or type 2 perforation (33.3%) compared to those with type 3 or type 4 perforation (11.1%); however, the observed difference was not found statistically significant. Similarly, in patients with a rapid diagnosis, the mortality rate was lower (20%) compared to patients with a delayed diagnosis (30.4%), but the observed difference was not found statistically significant.

The mortality rate is higher in patients who underwent surgery due to perforation compared to those who did not undergo surgery (80% and 17.9%, respectively, p=0.013). When considering the ICU follow-up time and clinical follow-up time between operated and non-operated patients, no significant difference was observed (Table 5).

Table 1. Endoscopic retrograde cholangiopancreatography indications defined in patients included in the study group

Indication	Number	Percentage
Choledocholithiasis	18 (54.5)	54.5
Cholestasis	8 (24.2)	24.2
Cholangitis	2 (6.1)	6.1
Pancreatitis	2 (6.1)	6.1
Ampullary carcinoma	1 (3.0)	3
Pancreatic carcinoma	1 (3.0)	3
Pancreatic pseudocyst	1 (3.0)	3
Total	33	100

Table 2. Distribution of the perforation types observed in the study group based on Stapfer classification

Perforation Type	Number	Percentage
Type 1	4	12.1
Type 2	20	60.6
Type 3	3	9.1
Type 4	6	18.2

Table 3. The characteristics of patients who underwent surgery due to post-ERCP perforation

Age/gender	Diagnosis time[1]	Indication	Type[2]	ICU time of stay[3]	Clinical time of stay[3]
51/F	26	Choledocholithiasis	1	18	None
78/M	3	Ampullary Ca	1	3	24[4]
74/M	70	Choledocholithiasis	2	4	3
62/F	0	Cholestasis	1	16	0
83/M	3	Biliary Pancreatitis	1	17	3

1: hour, 2: Stapfer classification, 3: day, 4: discharged

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Table 4. Comparison of demographic, clinical, and laboratory results between patients with and without observed mortality

Variable	Mortality (+) N=9	Mortality (-) N=24	p
Age (Mean±SD - year)	66.7 ± 11.8	53.5 ± 18.2	0.023*
Gender			0.442**
Male (N)	5	9	
Female (N)	4	15	
Existence of periampullary carcinoma (N)	4	5	0.212**
Perforation diagnosis time (median (min-max) - hours)	26 (0-100)	3 (0-120)	0.175***
Existence of procedure regarding perforation during ERCP (N)	1	6	0.642**
Post-perforation early diagnosis (N)	2	8	0.686**
ICU follow-up time (median (min-max) - days)	16 (4-23)	3.5 (2-10)	0.001***
Clinical follow-up time (median (min-max) - days)	3 (3-30)	14.5 (3-24)	0.395***
Catheter (+) (N)	5	16	0.690**
Pre-perforation AB regimen	5	9	0.442**
Perforation-AB beginning time (median (min-max) - days)	5 (0-50)	7 (0-140)	0.372***
Anatomic variation (+) (N)	2	5	0.635**
Albumin (Mean±SD - mgm/dL)	2.8 ± 0.8	3.4 ± 0.5	0.033*
Total bilirubin (median (min-max) - mgm/dL)	7.8 (0.6-15.8)	2.3 (0.4-32)	0.176**
Direct bilirubin (median (min-max) - mgm/dL)	4.6 (0.2-9.5)	0.9 (0.1-15)	0.182**
CRP- pre-perforation (median (min-max) - mgm/dL)	111 (4-312)	14.5 (1-319)	0.030**
CRP - post-perforation 1st day (median (min-max) - mgm/dL)	175 (11-342)	70 (18-400)	0.115**

* t test, **Chi-Square test (Fisher's exact test corrected), ***Mann Whitney U test

Table 5. Analysis of operated patients

	Operated (n=5)	Not operated (N=28)	p value
ICU follow-up time (Median (min-max) - days)	16 (3-18)	6.5 (2-23)	0.382**
Clinical follow-up time (Median (min-max) - days)	3 (3-24)	14.5 (3-30)	0.314**
Mortality ratio (%)	80	17.9	0.013*

*Chi-Square test (Fisher's exact test corrected), **Mann Whitney U test

Discussion

With the advancement of technology and an increase in the number of experienced physicians performing ERCP, its use has increased for complex pathologies such as biliary strictures and the diagnosis and treatment of malignancies, leading to a parallel increase in the frequency of complications.

Short-term complications associated with ERCP include pancreatitis, cholangitis, bleeding, and perforation, with a frequency of occurrence of around 10%. While it is believed that the frequency of pancreatitis and cholangitis increases in patients who undergo ERCP in the long term, there is a lack of an adequate number of studies on long-term complications related to the procedure [6]. The reported rate of perforation associated with ERCP in the literature ranges from 0.5% to 1% [7-9]. The risk factors identified for perforation may include sphincterotomy, prolonged procedure duration, advanced age, Oddi sphincter dysfunction, and pre-cut sphincterotomy [9,10]. The mortality rate associated with perforation reaches up to 25% [11].

In a study by Langerth et al., the frequency of perforation associated with ERCP was found to be 0.72%, with 20% mortality among patients who developed perforation and the ratio of these deaths to the total number of ERCP procedures was 0.1%; according to the data obtained from the study group, being over 80 years old and having malignancy were identified as independent risk factors for mortality [12]. In a study conducted by Patil et al., the rate of perforation associated with ERCP was found to be 1.5%, and the mortality rate among patients followed

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by surgical intervention after perforation was reported as 32% [13].

The classification commonly used for ERCP perforations is the Stapfer classification. According to the Stapfer classification, the generally accepted approach for Type 1 perforations is surgical treatment [9,12,14]. With the introduction of endoscopic treatment methods, the frequency of non-operative approaches has also increased. Some of the non-operative approaches include endoscopic clipping, endoscopic closure with fibrin glue, endoscopic stent placement, and non-operative follow-up with a vacuum-assisted drainage system [10,15-18].

Advanced age hinders patients from mounting an adequate response in severe complications like perforation. On the other hand, sepsis due to perforation can cause aggravation of existing chronic illnesses in patients. Therefore, the correlation between advanced age and a fatal course of perforation is an expected phenomenon. In a study by Ercan et al., the average age of patients who developed perforation was 61, while it was 70.4 in patients with a fatal course [19]. The results reported in the study by Langerth et al. are also similar. The average age of patients who developed perforation was 69, while it was determined to be 77 for patients with a fatal course; the development of perforation in advanced age and on a background of malignancy was considered a significant risk factor for mortality [12]. The findings obtained from our research group are similar to those in the literature. It is observed that the average age of patients who developed perforation was 57.1, while the average age of patients with perforation-related mortality was 66.7. The average age of patients with mortality after perforation is significantly higher ($p=0.023$).

In our study, the most common indication for ERCP in patients who developed perforation was choledocholithiasis (54.5%). Choledocholithiasis is also the most frequently mentioned indication for ERCP in the literature [19].

The most commonly encountered type of perforation in the study group is Type 2 perforation (60.6%). The most common cause of Type 2 perforation is sphincterotomy. As sphincterotomy is the most risky procedure in terms of perforation it is reasonable that Type 2 perforation is the most commonly expected outcome. In the study by Langerth et al., the frequency of Type 2 perforation was reported as 34%, while in the systematic review by Cirocchi et al., it was reported as 58% [12,20].

In our study, it was determined that four patients with Stapfer Type 1 perforation underwent surgery, and three of these patients died. In the study conducted by Tavusbay et al., it was reported that Stapfer Type 1 perforation was observed in five out of 29 patients with perforation, and four of these patients received surgical treatment, but three of them died [5]. In the systematic review conducted by Cirocchi et al., which included 12 studies, a total of 305 patients with perforation were analyzed. According to the analysis, the rate of patients with Stapfer Type 1 perforation is 17.7%. Out of the 54 patients with Type 1 perforation, 47 underwent surgery while seven were managed non-operatively. When the results of 42 of the operated patients whose data were available were evaluated, the mortality rate was found out to be 6.3% in patients who underwent intervention within 24 hours and 20% in those who had a delayed intervention. Of the seven patients who were followed non-operatively, three were eventually taken to surgery due to treatment failure, and two of these died [20].

In our study, similar to the literature, it is observed that patients with Stapfer Type 1 perforation were operated on at a high rate. Additionally, in our study, the mortality rate for Type 1 perforation was observed to be 33.3%, which is higher than reported in the literature. This situation could be caused due to the number of patients accepted in the study. In our study, early and late operation data could not be statistically compared due to the limited number of patients. Early operation is not the sole determining factor for a patient's mortality and may be insufficient as a standalone treatment. Therefore, it is considered more appropriate to perform surgery in some patients after clinical improvement has been achieved. Other factors that can influence the delay of surgery include the presence of comorbidities, the patient's age, the presence of cancer, the success of catheterization, and clinical improvement in the patient [19].

The early diagnosis of ERCP perforation is crucial for initiating treatment promptly and preventing sepsis and septic shock. Perforation should be noticed with the utmost care during endoscopy, and if possible, the initial intervention should be performed during the endoscopy procedure itself. After ERCP, patients should be monitored for possible complaints, and if there is suspicion of perforation, it should be evaluated with a Computer Aided Tomography (CT) scan. Patients suspected of perforation should be monitored in the intensive care unit, and early antibiotic therapy and the decision for percutaneous catheter or surgical drainage of the infectious focus should be made with the right timing. Delayed diagnosis can increase mortality and morbidity [19]. Perforation diagnosis of ten patients in our study was made during ERCP. Among the patients diagnosed during procedure, six were identified as Type 2, two as Type 3, one as Type 1 and one as Type 4. Two of these patients diagnosed during ERCP (one Type 1, other Type 2 perforation) had a fatal course. Although a higher mortality rate has been observed in patients where a rapid diagnosis couldn't be established compared to those with a rapid diagnosis, this difference is likely not statistically significant due to the small number of patients.

Patients who were lost after perforation were found to have low preoperative albumin levels and high total bilirubin and CRP values. When compared to other patients, the differences observed in albumin and CRP values were statistically significant. The low albumin level may serve as an indicator of nutritional deficiency or active inflammation in patients and provide insights into the outcomes of perforation management. Albumin

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deficiency is a negative marker of inflammation, whereas CRP is a positive marker of inflammation. After perforation, the main concern is the control of the infectious focus and the fight against sepsis. Albumin and CRP values are significant in terms of being indicators of sepsis [21]. The high level of total bilirubin is another subject of research. Some studies claim that high bilirubin levels impair wound healing and increase infectious complications, while recent studies suggest that there is no difference in postoperative complications in operated patients [22,23]. Monitoring bilirubin levels is important in patients with high bilirubin levels because it indicates the degree of cholestasis and the severity of cholestasis-related sepsis. Inflammation markers such as low albumin, high bilirubin, high CRP, and the presence of carcinoma in the periampullary region can be considered as indicators of complications in patients.

Perforation cases are often patients who have undergone sphincterotomy. In these patients, as the ampullary barrier is breached, duodenal contents can infect sterile areas. Since these patients are potential candidates for gram-negative sepsis, initiating antibiotic therapy early in the course of treatment is crucial [24]. We have initiated antibiotic therapy in some of the patients we are following due to ERCP perforation, which occurred as a result of cholangitis prior to the perforation. Of the 33 patients who developed perforation after ERCP, 14 were started on antibiotics before the procedure due to cholangitis, while 19 received antibiotics after perforation occurred. The most commonly used antibiotic regimens for perforation were, in order, 3rd generation cephalosporin + metronidazole, piperacillin/tazobactam, carbapenem, and quinolone group antibiotics. Due to regimen modifications in antibiotic therapy used upon necessity during the clinical follow up of the patients, the effectiveness of the antibiotic therapy could not be reviewed.

Conclusion

In conclusion, the management of patients with ERCP perforation should be approached in a multidisciplinary manner, and while it is possible to require surgical approaches, non-operative approaches should always be considered in the appropriate patient population. Closely and dynamically monitoring of patients and algorithmic approaches should standardized. The low frequency of ERCP perforation can lead to limitations in studies due to a low patient volume. Therefore, multicentered, high-volume, prospective, randomized controlled trials are needed to establish more clearly defined standards for the approach to this rare but highly morbid and mortal complication.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The ethical approval for this study was granted by the University of Health Sciences Gülhane Training and Research Hospital Scientific Research Ethics Committee, during its meeting dated November 30, 2020 with decision number 2020/476.

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