Early or delayed laparoscopic cholecystectomy after endoscopic cholangiopancreatography and papillotomy - does it make a difference?

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Abstract

Background Endoscopic retrograde cholangiopancreatography with endoscopic papillotomy (ERCP/EPT) followed by a cholecystectomy is a standard treatment of common biliary duct stones. It is unclear, however, what is the optimal time interval between ERCP/EPT and cholecystectomy. The primary aim of our study was to evaluate our current practice where patients are mostly operated one to three months after ERCP/EPT. The secondary aim was to determine the optimal timing for the cholecystectomy after ERCP/EPT.

Methods A retrospective analysis of 117 patients who underwent a preoperative ERCP/EPT followed by a cholecystectomy was performed. Associations between demographic characteristics, type and duration of operation, conversion rate, postoperative complications and interval time were tested using multiple linear regression. The optimal interval was studied by drawing receiver operating curve (ROC) and studying the area under curve (AUC).

Results The time interval between cholecystectomy and ERCP/EPT was not associated with the number of conversions to open surgery, duration of the operation or postoperative complications. There was no statistically significant association between any independent variable and time interval. No threshold interval could be found that would discriminate whether a patient had either operation conversion or complications or not.

Conclusion No statistically significant associations between the timing of cholecystectomy after ERCP/EPT and the rate of conversions, complications or operation duration are seen in the group. Our current practice is safe, as the time interval in our study does not affect the rate of conversions, postoperative complications or operation duration. Based on the results of our study, no recommendations regarding the optimal time for the surgery can be given. Larger prospective randomized trials are needed.
Background

Up to 33% patients with gallstones have gallstones present in common bile duct (CBDS) as well. (1,2) There are no clear evidence-based recommendations for the management of patients with choledocholithiasis. (3) CBDS management includes clearance of both bile duct and gallbladder stones. Cholecystectomy as well as one of the methods of bile duct clearance have to be performed. The latter is done through endoscopic retrograde cholangiopancreatography (ERCP) or surgical common bile duct exploration. (2–9)

In our institution a current standard of care for treatment of patients with CBDS is ERCP with endoscopic papillotomy (ERCP/EPT) and extraction of stones followed by laparoscopic cholecystectomy. Operation date is scheduled after discussion at the multidisciplinary team meeting (MDT). Patients are mostly operated on within three months from the index procedure (ERCP/EPT).

Nevertheless, the optimal timing of cholecystectomy after an ERCP/EPT remains unclear. Despite the fact that an early cholecystectomy is recommended, there are no clear guidelines on how long the time interval should be. (2,10–13). Recommendations put forth in many guidelines are conflicting and often very unspecific, as is clearly shown in the review article, done by van Dyk and al. Literature recommendations for the time interval differ from a few hours to a few months, while some authors even favor a single-step management, where ERCP/EPT is done during the cholecystectomy. (2,3,7,12,14,15)

Salman et al in their paper recommend a very short time interval (<72h), due to a presumably decreased risk of conversions, duration of surgery as well as length of stay and postoperative complications. Same approach is recommended by Borreca et al, mainly due to decreased risk of symptoms reoccurrence. An early cholecystectomy does seem to decrease the risk for reoccurrence of biliary complications. Postponing the operation for about 6 weeks, on the other hand, provides for better operating conditions, due to less
inflammation in the gallbladder area. Mann et al argue, that a 6-week delay is safe for the patients and does not increase the risk of symptoms reoccurrence, postoperative complications, operation duration or conversion rates. Contrary to this, Schiphorst et al believe that the operation, performed within the first week after ERCP/EPT, leads to a decreased rate of symptoms reoccurrence, length of stay and rate of conversion. This is backed by a study done by De Varies et al, which shows that patients operated in less than 2 weeks after ERCP/EPT have a lower conversion rate than those operated on within 2-6 week.

It remains unclear if a one-step approach, where ERCP/EPT is done during cholecystectomy, is superior to a two-step approach (therapeutic splitting). Some authors argue, that the former approach decreases the length of stay, costs and is more comfortable for the patients. On the other hand, others report no differences in length of stay and operation time, with most noting one-step approach being technically and organizationally more challenging, and therefore requiring high level of experience.

The primary aim of our study was to evaluate our current practice where patients are mostly operated on one to three months after ERCP/EPT.

The secondary aim was to determine the optimal timing for the cholecystectomy after ERCP/EPT.

Methods

1. Participants

The electronic database of a tertiary referral medical center was searched for patients that underwent cholecystectomy between 1. 1. 2017 and 31. 12. 2017 at Department of Abdominal Surgery, University Medical Center Ljubljana. Patients that had undergone a
preoperative ERCP/EPT were intended to be included. All the patients with ERCP/EPT performed more than 180 days before the cholecystectomy were excluded from our study (Figure 1).

Data regarding the surgery (date, type of surgery, approach, duration, postoperative complications) was gathered from Quality control (Q1) form and the rest of the patient data (gender, age, BMI, ASA score) was collected from patient records. Data regarding ERCP/EPT procedures (date, indication, concrement extraction, stent placement, complications) was collected from the procedure notes.

2. Statistical tools

Means and standard deviations were calculated for numerical and frequencies and percentages for categorical variables. Median and interquartile range (IQR) was calculated for non-normally distributed numerical variables. For testing the normality of distribution Shapiro-Wilk test was used. Relationship between demographic characteristics, illness severity, type, duration of operation, operation conversion, operation complications and time interval from index procedure to operation were tested by using multiple linear regression. The existence of optimal interval of time between ERCP/EPT and cholecystectomy that would discriminate between patients having operation conversion or not was studied by drawing receiver operating curve (ROC) and studying the area under curve (AUC). ROC and AUC was also used to find the existence of optimal interval of time between ERCP/EPT and cholecystectomy that would discriminate between patients having postoperative complications and those not having them. Significance level was set to $\alpha = 0.05$. The analysis was performed using SPSS v. 23.0.

Results

A total of 117 patients were included in the statistical analysis. Clinical and demographic data is shown in table 1.
For 107 patients (91.5%) the indication for ERCP/EPT was choledocholithiasis, while 10 (8.5%) have undergone the procedure due to biliary pancreatitis. All the patients had an EPT performed during the ERCP. During the procedure stones were extracted in 100 (85.5%) patients. Stent placements was necessary in 10 patients. Apart from a small bleeding in 24 patients, there were no other complications during the ERCP.

Range of the interval between ERCP/EPT and cholecystectomy was between 0 and 179 day, with median of 56 days and IQR between 21 and 92 days.

Surgery was done in an elective setting in 81 patients (69.2%), rest of the were operated on as an emergency. Laparoscopic cholecystectomy was performed in 114 patients (97.4%). Among those there were 17 (14.5%) conversions, most of them (64.7%) due to unclear anatomy, the rest due to adhesions. Range of operating time was between 15 min to 190 min, with median of 57 min and IQR 40-82 min).

Postoperative complications occurred in 11 patients (9.4%), 5 patients had Clavien-Dindo score 2 complications, 6 patients Clavien-Dindo 3A. There was no mortality in the group.

| Male gender                        | n = 117                  |
|------------------------------------|--------------------------|
| Median age (IQR)                   | 61 (52.1)                |
| Median BMI (IQR) (n = 91)          | 67 (52 - 75)             |
| ASA                                | 26.9 (24.7 - 30.3)       |
| I                                  | 16 (13.7)                |
| II                                 | 67 (57.3)                |
| III                                | 33 (28.2)                |
| IV                                 | 1 (0.9)                  |

| Indication for ERCP                |                          |
|------------------------------------|--------------------------|
| Holedoholitiasis                   | 107 (91.5)               |
| Acute pancreatitis                 | 10 (8.5)                 |
| Laparoscopic operation             | 114 (97.4)               |
| Conversion                         | 17 (14.5)                |
| Complications                      | 11 (9.4)                 |

| Median no. of days till operation (IQR) | 56 (21 - 92) |
| Median length of operation (IQR) in min | 57 (40 - 82) |

**Table 1:** Patient's characteristics (data are shown as frequencies (percentages) if not otherwise indicated).

No statistically significant associations between any independent variable and time until operation were found (Table 2), all the p values for the calculated standardized regression
coefficient were significantly higher than 0.05. When controlling for other variables in the model, operation conversion, complications and operation duration were still not associated with the time interval from ERCP/EPT to the operation.

|                              | Std. reg. coef. (p - value) |
|------------------------------|----------------------------|
| Gender                       | -0.03 (0.759)              |
| Age                          | 0.17 (0.202)               |
| BMI                          | 0.11 (0.370)               |
| ASA I                        | 0.12 (0.447)               |
| ASA II                       | -0.15 (0.302)              |
| ASA III or IV                | Ref.                       |
| Choledocholithiasis          | 0.13 (0.276)               |
| Classic OP                   | -0.05 (0.652)              |
| Conversion                   | -0.06 (0.653)              |
| Complications                | -0.03 (0.798)              |
| Operation duration           | 0.01 (0.967)               |

**Table 2:** Relationship between time interval and patient characteristics, type of operation, duration of operation, operation conversion, post-operative complications (results of multiple linear regression). *Std. reg. coef. = standardized regression coefficient; ref. = reference group*

To find threshold of time until operation that best discriminates between operation conversion or operation complications, the receiving operating curve is plotted and area under the curve was calculated (Figure 2). In both instances, the AUC was not statistically significantly different from 0.5. No threshold value of time interval to the operation could be found that would discriminate whether a patient had a conversion or postoperative complications or not.

**Discussion**

ERCP with EPT, followed by a subsequent laparoscopic cholecystectomy, is currently a golden standard treatment for patients with common biliary duct stones. There is, however, no consensus in the literature, what the time interval from the index procedure to the operation should be. Some authors even argue, that ERCP/EPT should be performed during the same surgery, when the gallbladder is removed (one-step approach). Results of
our study show no statistical differences in the number of conversions to open surgery, duration of the operation or postoperative morbidity regardless of the time interval between cholecystectomy and ERCP/EPT. Our current practice where patients are usually operated one to three months after ERCP/EPT operated is, based on the results of our study, safe. No specific time interval that would decrease the possibility of a conversion to open cholecystectomy or the patient having postoperative complications can be proposed. There was no mortality in our group and the rate of postoperative complications in our sample was 9.4%, which is similar to those reported (5.3-14%) by other authors (2,9,27,30). It is an established fact, that the rate of conversion to open cholecystectomy is higher (8-55%) in patients with a complicated gallstone disease (i.e. gallstones present, previous ERCP/EPT, urgent surgery) compared to the conversion rates (3-5%) in uncomplicated cholecystectomies (7,17,26-29) In our study the conversion rate was 14.5%, which is comparable to the reported conversion rates in the literature. We found that the timing did not affect the rate of conversion, duration of the surgery or postoperative complication. It is hypothesized that ERCP/EPT causes inflammation in the gallbladder area thus making the subsequent cholecystectomy more difficult. Hence, surgery is often delayed, allowing the area presumably to cool off. Also, the delay allows the patient to recover from initial illness (10,16,27) Such a delay, however, causes an increased risk of biliary symptoms reoccurrence and disease progression, hence complicating the following surgery (12,17,27) Therefore two approaches to the timing can be considered, a very early cholecystectomy, avoiding the risk of symptoms reoccurrences or a delayed operation allowing for the gallbladder area to settle. Several published studies confirm equivalency of both therapeutic strategies (10,11,16,18,27), including the results of our study. Contrary to this, there are some studies that favour either one or the other approach. Our study has limitations. First of all, it has all of the inherent biases of a
retrospective study. Second, only a few patients were (N=3) operated within a very short period of time (<72h), in an interval, that many authors argue decreases the rate of conversions, postoperative morbidity and length of stay, outweighing the risk of an early surgery. (2,12,26). On the other hand, even though most of our patients were in fact operated on in a somewhat delayed fashion (median of a 56 days), in our analysis we did not find any statistical significance of such approach, positive or negative. This is not in line with a review done by Friis et al. in which authors argue that a delayed cholecystectomy increases the risk of conversion to open surgery (26). In our analysis we did not include some variables that are reported to have an effect on the patient outcome (eg. length of stay, reoccurrence of symptoms). Furthermore, there are other variables that could affect the rate of conversions (patient conditions, previous abdominal surgeries, adhesions, experience of the surgeon), duration of operation (pre-operative diagnosis, intraoperative complications, anatomical differences, surgeon experience) and the post-operative complications and were not included in the analysis. However, most of these variables were mostly not included in other studies, either. (2,7,12,27,31)

Conclusion

Based on the results of our study, the interval of one to three months between ERCP/EPT and cholecystectomy, is safe, as it did not affect the rate of conversions, duration of the operation or postoperative complications in our group of patients. With the lack of clear guidelines and conflicting recommendations for the optimal time interval in the literature, it is evident that further research is necessary, probably through larger prospective randomized studies.

Abbreviations

MRCP - Magnetic Resonance Cholangiopancreatography
ASA - American Society of Anesthesiologists
AUC - Area under the curve
EPT - Endoscopic papillotomy
ERCP - Endoscopic retrograde cholangiopancreatography
ERCP/EPT - Endoscopic retrograde cholangiopancreatography with endoscopic papillotomy
MDT - Multidisciplinary meeting
ROC - Receiver operating characteristic curve
IQR - Interquartile range
BMI - Body Mass index

Declarations

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Authors’ contributions
JG made a substantial contribution to the conception and design of the work and has also substantively revised it. MP has made a substantial contributions to the concept and design of the work. DP has done the acquisition, analysis and drafted the work. AT has made a substantial contribution to the conception of the work and has also substantively revised it.
All the authors approve the submitted version and have agreed to be personally accountable for the author's own contribution.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Approval for the study was obtained from the Medical Ethics Committee of the Republic of Slovenia (MZ 0120-436/2018).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
Participant selection

Figure 1

Figure 2

The ROC curve and area under the curve (AUC) with 95% CI for two binary classifiers with different thresholds of time until operation.