DOI 10.26724/2079-8334-2022-1-79-59-62
UDC 616.361–003.7–06:616.36–008.5–007.272–089.878/879.168.1–07

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RECURRENT BILIARY EVENTS IN PATIENTS, WHO UNDERWENT ENDOSCOPIC LITHOEXTRACTION DUE TO OBSTRUCTIVE JAUNDICE

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The purpose of our study was to analyze early results of successful endoscopic lithoextraction in patients with choledocholithiasis complicated with obstructive jaundice. We investigated case histories of 103 patients, who were treated with obstructive jaundice due to choledocholithiasis and have undergone endoscopic lithoextraction during last 6 months. We observed episodes of biliary pain in 29 patients, 20 cases of acute calculus cholecystitis and 3 cases of obstructive jaundice recurrence. After statistical data analysis, the following conclusions were made: 1) there is no correlation between age, sex and occurrence of acute calculus cholecystitis during first six month after endoscopic lithoextraction on account of obstructive jaundice; 2) episode of successfully treated biliary pain can be considered as a risk factor for acute calculus cholecystitis occurrence in patients after endoscopic lithoextraction; 3) time gap of four weeks after endoscopic lithoextraction seems to be relatively safe with regard to adverse biliary events occurrence and laparoscopic cholecystectomy should be performed during this interval.

Key words: choledocholithiasis, endoscopic retrograde cholangiopancreaticography, cholecystectomy.

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АНАЛІЗ ПОВТОРНІХ ЗАГОСТРЕНЬ ЖОВЧОКАМ'ЯНОЇ ХВОРОБИ У ПАЦІЄНТІВ, ЯКІ ПЕРЕНЕСЛИ ЕНДОСКОПІЧНУ ЛІТОЕКСТРАКЦІЮ ВНАСЛІДОК РОЗВИТКУ МЕХАНІЧНОЇ ЖОВТЯНИЦІ

Метою дослідження було проаналізувати ранні результати лікування пацієнтів, яким було виконано ендоскопічну літоекстракцію через розвиток механічної жовтяниці. Проаналізовано медичні карти 103 стаціонарних хворих, які проходили лікування протягом 2019–2020 рр з приводу механічної жовтяниці, що була викликана холедохолітіазом, або гострим холециститом з наявністю в анамнезі ендоскопічної літоекстракції протягом останніх 6 місяців. Епізоди біліарного болю спостерігалися у 29 пацієнтів, у 20 хворих виник гострий калькульозний холециститу, у 3х — рецидив обтураційної жовтяниці. Статистичний аналіз даних, що було отримано, дозволив зробити наступні висновки: 1) вік та стать пацієнта не є предикторами виникнення рецидивів жовчнокам'яної хвороби протягом 6 місяців після ендоскопічної літоекстракції; 2) напад біліарного болю в анамнезі є фактором ризику виникнення гострого калькульозного холециститу протягом 6 місяців після літоекстракції; 3) чотирьохтижневий період після літоекстракції є відносно безпечним щодо виникнення несприятливих біліарних подій та повинен використовуватися для виконання лапароскопічної холецистектомії.

Ключові слова: холедохолітіаз, ендоскопічна ретроградна холедохопанкреатографія, холецистектомія.

The work is a fragment of the research project "Validation of mini-invasive procedures applying in the structure of surgical pathology treatment" state registration No. 0121U113943.

According to the European Association for the Study of the Liver data up to 20 % of the adult population are affected with cholelithiasis in Europe [4]. From 10 to 20 % of patients in this subgroup suffer from choledocholithiasis [11]. This pathological condition is the most common indication for different types of endoscopic lithoextraction (EL) [8], which can be combined with laparoscopic cholecystectomy(LC) during single hospitalization or the latter procedure can be delayed [2]. There is a wide diversity considering the time gap between EL and LC ranging between 72 hours and 6 weeks or even "wait and see strategy" [1, 4, 10]. Obstructive jaundice (OJ) is a typical complication of choledocholithiasis. It significantly worsens patients' condition due to cholestatic hepatitis and a great probability of cholangitis uprising [5].

The purpose of the study was to analyze early results of successful endoscopic lithoextraction in patients with choledocholithiasis complicated with obstructive jaundice.

Materials and methods. A retrospective study was performed based on single-center data. We investigated case histories of 103 patients, who were treated in the Surgical Department of Municipal Enterprise "Poltava M.V. Sklifosovskiy Regional Clinical Hospital at Poltava Regional Council", during 2019–2020 years. Women predominated in our group (n=74; 71.8%), which is typical for gallstones disease in general. The majority of patients were between their 50^{th} and 70^{th} with a mean value of 50.5±12.93 years and data distribution close to normal (Shapiro-Wilk's test p=0.07).

The following inclusion criteria were established: 1) Age more than 18 years; 2) Presence of OB (total bilirubin >60 μmol/L) caused by choledocholithiasis at time of hospitalization followed by endoscopic retrograde cholangiopancreaticography (ERCP) and successful EL; 3) Presence of acute calculus cholecystitis(ACC) at time of hospitalization with OJ and ERCP with EL in recent (last 6 moth) medical history. The exclusion criteria were as follows: 1) Diagnosed oncological disease of any kind;

2) HIV–positive status; 3)Pregnancy at time of hospitalization or childbirth during last 6 months. Surveillance after patients who had undergone EL was performed during 6 months period or until LC was performed and all episodes of biliary pain (BP) attacks, ACC occurrence or OJ recurrence were documented. In the cohort of hospitalized with ACC careful acquisition of medical history was carried out focusing on OJ episode, EL time and attacks of BP.

We used Tokyo Guidelines 2018 to diagnose ACC and Rome IV criteria for diagnostic of BP [3, 15]. STATISTICA 6.0 (StatSoft, USA) and Microsoft Excel 2013 (Microsoft Corporation, USA) software were used for data statistical analysis. Chi-square and Mann-Whitney tests were used for qualitative and quantitative data comparison respectively. Kaplan-Maier analysis, Gehan's Wilcoxon test and proportional hazard Cox regression model were used to investigate BP, ACC and jaundice recurrence episodes.

Results of the study and their discussion. We observed attacks of BP in 29 patients (fig.1). The earliest episode was detected during the first week after EL and lower quartile on the 22nd week (standard errors 0.01 and 0.04 respectively).

A cut-off level of 95 % without BP emergence was noticed during 5th week. The largest number of BP episodes (n=5) occurred during 10th and 11th weeks.

All the events were successfully treated in the out-the-patient level (n=10), in the surgical department (n=4) or by the patients themselves without reference to medical professionals (n=15). None of the BP episodes required an operation to be cured. Standard treatment protocol for the out-the-patient department included antispasmodic and analgesic agents.

ACC arose in 20 patients from our group. The first two cases occurred during 5th week after EL (standard error 0.01). The frequency of ACC occurrence was relatively steady (fig.2).

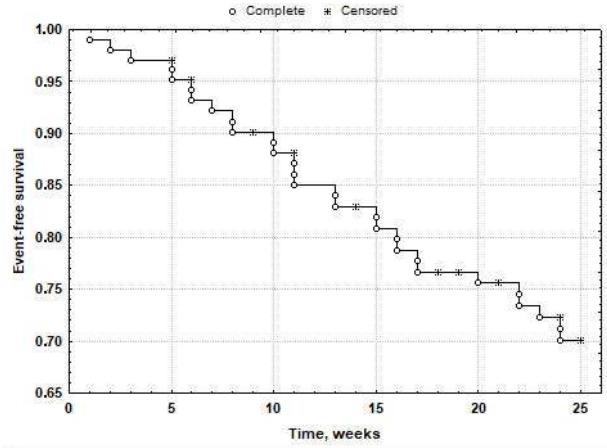

Fig. 1. BP episodes occurrence during surveillance period

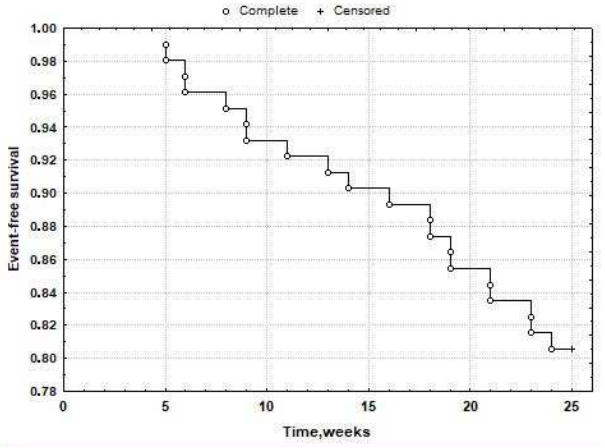

Fig. 2. ACC episodes occurrence during the surveillance period

None of ACC cases occurred during first four weeks after initial mini-invasive OJ treatment. In 9 cases LC was performed with no conversions. In one case the level of procedure complexity was evaluated as grade 1, in six cases – as grade 3, and in two cases – as grade 3 according to Nassar scale for cholecystectomy difficulty assessment. In 11 cases patients refused the operation and were successfully managed with medical treatment only.

We also observed recurrence of OJ in three patients during 9th, 15th and 18th weeks after EL. Repeated EL with subsequent LC throughout the same hospitalization was performed in two cases. One patient underwent a laparotomy procedure.

Considering ACC as one of the most dangerous endpoints, we provided further analysis of factors, which can be connected with its emergence. ACC occurrence in men (five ACC episodes) and women (15 ACC episodes) separately is shown in fig. 3. The curves are very similar from the start point until the 8–9 weeks. From this period ACC episodes are absent in the men's group up to the 19th week, while in the women's group new ACC arises every two or three weeks. Anyway, from the 19th week the groups resemble closely again with cumulative surviving in 24 from 29 men and 59 from 74 women. Gehan's Wilcoxon test shows no statistically significant difference between groups (p=0.72).

There was some difference in cumulative surviving considering ACC in patients with or without previous BP episode(fig.4). The curves start to deviate from the 13th–14th weeks of observation and patients without BP show better results. The overall incidence of ACC in patients, who suffered from BP previously, was 31 % whereas in group with no BP episodes this parameter was 15 %. We used Gehan's Wilcoxon and Chi-square tests to compare groups and both of them sowed trend to statistical significance (p=0.09181 and p=0.0621 respectively).

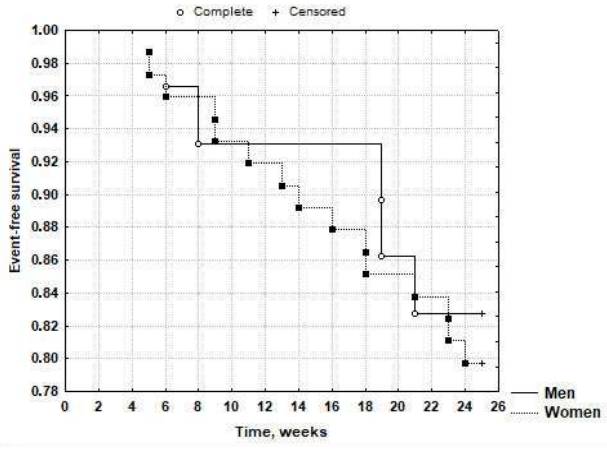

Fig. 3. ACC occurrence in men and women separately

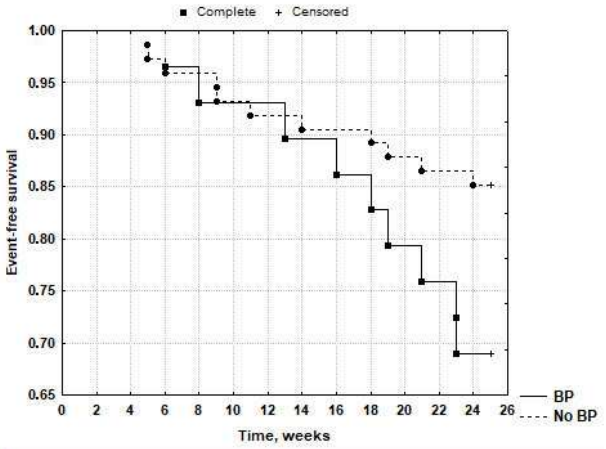

Fig. 4. ACC occurrence depending on previous BP episode

Investigating age structure in patients groups with and without ACC episode we found out prevalence of older people in the first group and more narrow values distribution in it (table 1).

Table 1

Age distribution in groups of patients with and without ACC episode

	Patients with ACC episode (n=20)	Patients without ACC episode (n=83)
Median	64.5	61
Minimum	44	26
Maximum	86	84
Lower Quartile	56.5	51
Upper Quartile	71	71
Quartile Range	14.5	20

Proportional hazard Cox regression model was used to evaluate connection between age and ACC cases and Mann-Whitney test was made to assess the difference between ACC and no ACC groups depending on age. Both of them showed no statistical significance (p=0.1228645 and p=0.3056789 respectively). Due to small number (n=3) of OJ recurrence in our study we did not make any statistic data processing regarding potential relation between abovementioned and other parameters.

Optimal timing of LC implementation after OJ treated with EL remains questionable. In situation when choledocholithiasis is not accompanied by OJ even one-stage approach (simultaneous EL and LC) seems feasible according to some papers [12]. This type of treatment allows to shorten time of overall hospital stay. Thus, it also reduces total cost of patients' management, though 'two-in-one' type of surgical intervention may demand more skills and resources. Simultaneous procedure takes more time, can be challenging for anesthesiologist and require coordinated work from surgical and endoscopic teams. Nevertheless, other authors recommend to perform LC as a second-stage procedure during first three days after endoscopic treatment or even after some weeks after EL [1, 4, 6, 7, 10]. Significant risk decrease for recurrent biliary events in patients, who underwent cholecystectomy during index admission, was noted in article by Huang et al. [9]. This large study contained information about more than four thousand patients from approximately 25 % of United States of America territory and different races. According to their data, early operation can lower relative risk of adverse biliary events by 92 % during first 60 days after EL. On the other hand, longer surveillance period showed only 1 % difference between early and delayed cholecystectomy (88 % versus 87 % lower risk compared with no gallbladder removal). Patients, who underwent cholecystectomy during initial admission, had similar rates of adverse events, including death, in comparison with those, who were operated during 60 days after discharge (1.4 % and 1.3 % respectively). Furthermore, inclusion criteria for this paper required only sphincterotomy or endoscopic stone extraction due to choledocholithiasis, presence of OB in those patients was not obligatory. Another more recent study by Wang et al. controversially shows benefits of delayed cholecystectomy [14]. The authors found no dissimilarity in early and deferred cholecystectomy groups regarding adverse biliary events during 60 days gap after EL. Furthermore, recurrent biliary events-free survival rates during one year period were higher in delayed cholecystectomy group (89.54 %) than in early cholecystectomy group (85.04 %). Surprisingly, medical expenses for treatment in the delayed cholecystectomy group was by 1.8 time lower than in patients, who underwent procedure of gall bladder removal during index admission. This phenomenon could be explained by the relatively high (48.84 %) frequency of open cholecystectomies performed in the investigated group, which prolonged time of hospital stay. The third study by Terauchi et al. stydied results of gallstones–associated cholangitis treatment with initial EL in early and delayed cholecystectomy groups [13]. The majority of patients showed clinical and laboratory signs of OJ at the

time of admission. The second feature of the study was relatively long period before cholecystectomy in the delayed group (from 62 to 206 days with 98 days median). Despite of severe type of initial pathology, the majority of gallbladder removal procedures were accomplished during initial hospitalization. Results of this study showed no differences in procedure duration, postoperative complications and postoperative length of stay after comparison early and delayed strategy for cholecystectomy. In addition, there were no elective laparotomies and conversions in the delayed cholecystectomy group.

Taking into account the main guidelines recommendations, the tendency to early LC is clear and stays on well-proved basis. On the other hand, as it could be seen from three abovementioned studies from different geographic and economic regions, local conditions, experience as well as cost issues and patient preferences play important role in the management of gallstone disease after EL on account of OJ. We think, that our results can provide some additional information for proper decision making in different clinical situations. As for study limitations, we want to underline all potential biases, which are connected with its retrospective single-center design. We also want to admit that patients with incomplete EL but successful OJ treatment after endoscopic common bile duct stenting were not included in this study. COVID–19 pandemic with its negative impact on logistic, access to family physicians and hospitalization for none-urgent conditions also could be considered as modifying factor, which had some influence to this study.

Conclusion

Early cholecystectomy is the most preferable scenario for patients, who underwent EL due to choledocholithiasis, especially in case of bad compliance, which is a risk factor for loss of follow-up and increase of biliary adverse events probability. Nevertheless, timing of this procedure can be rather difficult decision influenced by severity of patient status, age, concomitant diseases and individual patient preferences and sometimes delayed cholecystectomy can be a good option. Data obtained in this study can provide some suggestions for further risk management in such cases. Our main findings are the following: 1) there is no correlation between age, sex and occurrence of ACC during first six month after EL on account of OJ; 2) episode of successfully treated BP can be considered as a risk factor for ACC occurrence in patients after EL; 3) time gap of four weeks after EL seems to be relatively safe with regard to adverse biliary events occurrence and LC should be performed during this interval.

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Стаття надійшла 20.02.2021 р.