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A review of the literature

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AIM: *Laparoscopic cholecystectomy for gallstone disease is the most common surgical procedures performed in Western countries and bile leaks remain a significant cause of morbidity. A recognized treatment for minor biliary injury is internal biliary decompression by endoscopic retrograde cholangiopancreatography. The aim of this study was to assess the effectiveness of endoscopic strategy in the management of minor biliary injuries.*
MATERIAL OF STUDY: *Twenty-two patients with a bile leak following laparoscopic cholecystectomy were recorded consecutively between 2007 and 2017 and they were all treated with endoscopic approach, with ERCP in order to confirm the nature of the injury and decompress the bile duct with sphincterotomy, stent insertion, or the placement of nasobiliary drains. In 15 patients, the leak was diagnosed by persistent bile drainage, in the other 7 patients without a drain the biliary leak was suspected because of symptoms in the immediate postoperative period.*
RESULTS: *Controlled biliary fistulae were established in all 22 patients (100%), without further intervention. A complete cholangiogram was obtained in all patients (100%). The most common sites of minor leak were the cystic duct stump and the Luschka duct, but in one patients the site of the leak was unclear.*
DISCUSSION: *Early in the series, sphincterotomy alone or nasobiliary tube placement was performed. Subsequently patients underwent sphincterotomy with stent insertion, in order to promote preferential drainage of bile into the duodenum. The median time to resolution after successful ERCP was 4 days. Two patients underwent ERCP complicated by mild pancreatitis. The median hospital stay was 15 days (range, 10–31 days) post-laparoscopic cholecystectomy. ERCP was performed 4-6 weeks later to document healing of the leaking point and to remove the stent. Routine follow was at median 50 days.*
CONCLUSIONS: *This review confirms that postoperative minor biliary injuries can be successful managed by endoscopic ERCP biliary decompression.*

KEY WORDS: Bile leak, Bile duct injury, Biliary fistula, Endoscopy, ERCP, Laparoscopic cholecystectomy

Introduction

Bile duct injury occurs in 0.3–2.7% of patients, it represents an uncommon but potentially serious complication after cholecystectomy [1,2] .

Biliary fistula is defined as the persistent leakage of bile from the biliary tree. This can arise from an injury to the common bile or hepatic duct but the vast majority arise from the cystic duct stump or a sub-vesical duct of Luschka [3].

Different types of biliary injuries, management modalities, therapeutic strategies and prognosis are described according to several classifications of bile duct injury (BDI) [4].

Minor injuries are usually defined as those of the cholecystohepatic duct (duct of Luschka), injuries to small subsegmental ducts in the gallbladder bed and cystic duct

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stump leaks. Major biliary injuries are those of the common hepatic duct, common bile duct (CBD), right hepatic duct and transection of the right posterior sectoral duct.

Since the introduction of laparoscopic cholecystectomy (LC), a higher incidence of biliary injuries was reported by many authors [5,6]. In the last decade large studies demonstrated incidences of major and minor biliary injury of 0.25–1.90% and 0.38–1.20%, respectively [7,8] .

A bile leak may result in a biliary fistula, a subhepatic or subphrenic collection and localised or generalised peritonitis. Clearly, this can be associated with significant morbidity and even mortality, particularly if it is not diagnosed and treated at an early stage.

So, biliary fistula is one of the common presentations of BDI and it is included in many of the most widely used classifications of BDI [9-11].

In the first few postoperative days, a postoperative bile leak is usually diagnosed because of excessive postoperative pain or bilious drain tube output [12].

The management and the therapeutic strategy of bile leaks are changed during the last years. In fact, bile leaks were managed conservatively in the early 1990s when both minimally invasive techniques and laparoscopic cholecystectomy were in their infancy; instead a laparotomy was often performed when the patient did not improve.

Management was still anecdotal and based upon the experience of the surgeon. However, the current trend is to manage bile leaks in a minimally invasive manner as a result of the advent of therapeutic endoscopic retrograde cholangiography (ERCP) [13,14] improved radiological percutaneous drainage, and increased confidence with laparoscopic techniques including suturing [15,16], potentially reducing morbidity and mortality.

The possibility of a prompt access to the full range of techniques is fundamental as well as a structured approach is necessary.

Endoscopic modalities, including stenting, endoscopic sphincterotomy (ES), and the placement of nasobiliary drains (NBT), have replaced surgery as a first-line approach to the management of minor BDI [17-19], whereas surgical reconstruction is the standard treatment for major BDI [20,21].

In line with other groups, we have applied endoscopic management to treat minor post-cholecystectomy biliary injuries. We report the outcomes of this approach in a consecutive series of 22 patients over a 10-year period.

Material and Method

Twenty-two patients were managed in our Department for symptomatic bile leak after laparoscopic cholecystectomy (LC) in the period between January 2007 to January 2017. There were 15 women and 7 men, median age 52 years (28-90 yr). The major presenting symptoms were persistent bile drainage, pain, nausea and abdominal distension. In 15 patients, the leak was diagnosed by persistent bile drainage through a drain tube inserted at the time of the operation. The other 7 patients without a drain developed symptoms in the immediate postoperative period. The overall time for presentation in the 22 patients was a median of 4 days [1-8].

In according to the magnitude of bile leak daily, we subdivided the patients in two groups: a) < 180 ml/daily,

TABLE I - *Patient demographics, indications for surgery and operative details.*

	Group A with drainage N° 15	Group B without drainage N° 7
Sex n°		
Male	3 (20%)	2 (28%)
Female	12 (80%)	5 (72%)
Age, y		
Mean (SD)	54 ± 18,16	49 ± 19,46
Median (range)	50 (30-90)	45 (28-85)
ASA grade n°		
I	10 (67%)	5 (72%)
II	4 (27%)	2 (28%)
III	1 (6%)	0
Indication for surgery n°		
-Biliary colic/chronic cholecystitis	7 (47%)	4 (58%)
-Acute cholecystitis	4 (27%)	1 (14%)
-Empyema	1 (6%)	0
-Previous obstructive jaundice	2 (14%)	1 (14%)
-Pancreatitis	1(6%)	1 (14%)
Pre-operative ERCP with stone removal n°	2(14%)	1 (14%)
Timing of surgery n°		
Elective	10 (67%)	6 (86%)
Emergency	5 (33%)	1 (14%)
Operative time of LC		
Mean (SD)	45,3+15,37	35,2-8,56
Median (range of min)	45 (25-70)	30 (27-50)
Operative findings n°		
Quiescent GB	10 (67%)	5 (72%)
Inflamed GB	5 (33%)	2 (28%)
Gangrenous GB	0	0
Symptoms of biliary fistula		
Pain	9 (60%)	4 (58%)
Jaundice	2(14%)	0
Fever	1(6%)	1 (14%)
Abdominal distension	3 (20%)	2 (28%)
Severity of bile leak *		
Low grade	11 (73%)	/
High grade	4 (27%)	/

*LC laparoscopic Cholecystectomy; GB, gall-bladder; *> or <180 ml/daily.*

and b) > 180 ml/daily. We considered a biliary drainage upper of 180 ml/daily as cut off between minor and major leaks, in order to evaluate eventual differences in management or outcomes.
All patients initially had a standard 4-port procedure [22] performed mainly by consultant surgeons, and no conversion was taken. An abdominal drain was placed in all cases, as routinely.
On table, cholangiography was not undertaken in these cases. Pre-operative demographics, indications for surgery and operative details are shown in Table I.
The subdivision of patients into two groups, group A patients with drainage and group B patients without drainage, does not show statistical differences ($p > 0.05$) between them according to sex, age, ASA score, clinical and histological diagnosis, timing and type of previous surgery, type of fistula and related symptoms.
Three patients affected by acute pancreatitis and obstructive jaundice underwent in the preoperative phase to firstly magnetic resonance cholangiopancreatography, like our diagnostic standard protocol and then endoscopic-retrograde-colangio-pancreatography (ERCP) with sphincterotomy for clearance of biliary duct before cholecystectomy [23].

Statistical Analysis

Data are expressed as raw numbers (%) or median values (range). Continuous variables were analyzed using the Student-t-test. Categorical data were compared using the chi-squared test. A P-value < 0.05 was considered to be significant.

Results

After clinical evaluation all patients were investigated with routine hematological and biochemistry tests, including liver function tests and abdominal US.
In 11 cases the biliary drainage was < 150 ml/daily (110-170 ml/daily). In the remnant 4 cases it was 230 ml/daily (180-400 ml/daily).
The patients without drainage showed a subhepatic bile collection (biloma), accessible, well-localized ultrasound (USS) without evidence of systemic sepsis. All the seven patients with biloma underwent to USS-positioning a percutaneous drainage and a catheter was left in place to drain the bile.

Table II - *ERCP management details and post-ERCP outcomes.*

	Group A With drainage N° 15	Group B Without drainage N° 7	Total N° 22	*P value*
Time to ERCP				
Mean (SD)	4.5 + 1.8	7.1 + 1.95	5.3 + 2.26	p 0.011
Median (range of days)	5 (2-7)	7 (4-10)	5 (2-10)	
Percutaneous USS-guided aspiration/drainage	–	7 (100%)	7 (32%)	p >0.05
Feasibility rate of ERCP (Successful Cannulation)	15 (100%)	7 (100%)	22 (100%)	–
Diagnostic Rate of ERCP (Diagnosed site of bile leak)	15 (100%)	6 (86%)	21 (95,5%)	p >0.05
Cystic duct stump	11 (73%)	4 (57%)	15 (69%)	
Luschka duct	4 (27%)	2 (28%)	6 (27%)	
Unclear	0	1 (15%)	1 (4%)	
Ercp Intervention				
Nasobiliary tube	2 (13%)	1 (14%)	3 (14%)	p >0.05
Sphincterotomy	14 (94%)	6 (86%)	20 (90%)	
Stent insertion	11 (74%)	5 (72%)	16 (73%)	
Stone extracted	2 (13%)	2 (28%)	4 (18%)	
Therapeutic Rate of ERCP	15 (100%)	7 (100%)	22 (100%)	–
ComplicationsPost-ERCP pancreatitis	2 (13%)	–	2 (9%)	p >0.05
Hospital stay (days)				
Mean (SD)	13,5 + 2,30	21,12 + 6,46	15,9 + 5,47	
Median (range of days)	14 (10-18)	20 (12-31)	15 (10-31)	p < 0.001

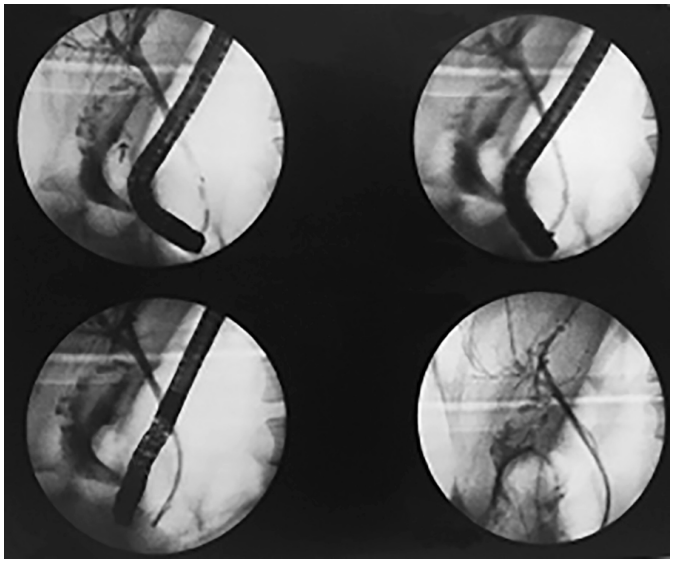

Fig. 1: Endoscopic retrograde cholangiopancreatography (ERCP) of a patient of our study showing biliary leak of the cystic duct stump. Thick arrow indicates a likely dislocated endoclip. An endoscopic stent of 8,5 F (10cm) is positioned in biliary duct with a good final cholangiography.

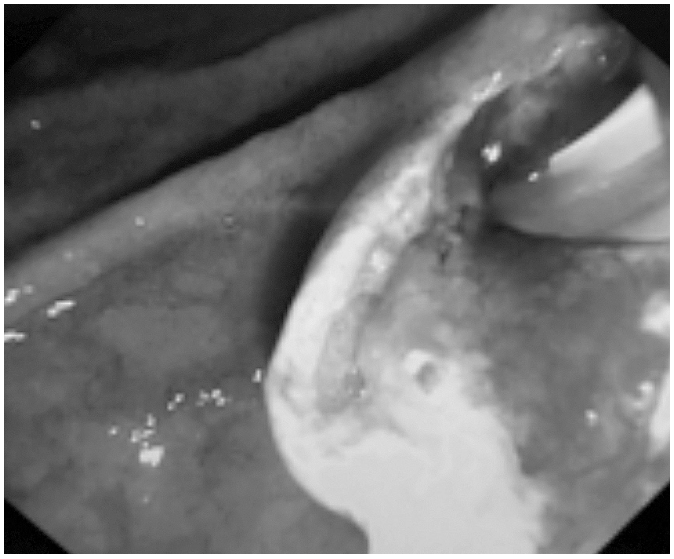

Fig. 2: Sphincterotomy during the endoscopic retrograde cholangiopancreatography (ERCP).

All patients underwent to ERCP because of a persistent bile fistula in order to delineate the biliary tree anatomy, make diagnosis and therapy.
ERCP management details and post-ERCP outcomes are reported in Table II.
Median time from surgery to ERCP was 5 (range 2-7) and 6 (range 7-10) days in patients with drainage and without drainage, respectively ($p < 0,05$). A complete cholangiogram was obtained in all patients (100%).
The most common site of minor leak was the cystic duct stump (17/22 patients = 77%), and the Luschka duct in 4 patients (19%), but in one patients (4%) the site of the leak was unclear.
After documentation of the leaking point, an endoscopic sphincterotomy was performed; in 4 patients bile duct stones were present and they were removed.
Early in the series, sphincterotomy alone or nasobiliary tube placement was performed. However, subsequently patients underwent sphincterotomy with stent insertion, usually with a 8,5-10F stent 7–12 cm in length in order to promote preferential drainage of bile into the duodenum attenuating the leak and allowing it to stop (Fig. 1).
Sphincterotomy represents the fundamental therapeutic intervention of these minor biliary fistula because of the internal biliary decompression, in fact it was performed in our study in 90% of cases (Fig. 2).
Endoscopic management leads to resolution of the biliary fistula with a median time of 4 days (range 2-15 days) from ERCP.
There were no complications directly relating to ERCP, unless two cases of mild pancreatits after-ERCP in the group A ($p>0,05$). Provided there was no clinical or radiological evidence of further leaking, patients were discharged. The median hospital stay was 15 days (range, 10-31 days) post-laparoscopic cholecystectomy, slightly longer in this latter group ($p< 0,001$).
ERCP was performed 4-6 weeks later to document healing of the leaking point and to remove the stent.
Routine follow was at median 50 days (range, 40-120 days), with no differences between the two groups.

Discussion

Laparoscopic cholecystectomy is currently the procedure of choice to treat symptomatic gallstones. Over the last 20 years it has evolved from an innovative, but time-consuming, novelty to a routine day-case procedure [24,25].
Minor biliary tree injury is a complication of laparoscopic cholecystectomy, that occurs with an incidence of up to 1.2% [26]. With unsuccessful treatment, these injuries represent an iatrogenic catastrophe that reduces the patient's quality of life and causes serious long-term morbidity and mortality.
The main causes of bile ducts injuries are the anatomic alterations (i.e.: acute cholecystitis [27], previous surgery), and the mechanical difficulty (i.e.: electrosurgical injury, misplacement or displacement of the surgical clips at the level of the cystic-duct stump, or ischemic injury by disruption of the biliary duct blood supply) [28,29].
However, it is possible to individualize patient's risk factors like as empyema, acute and chronic cholecystitis, porcelain or intrahepatic gallbladder, obesity, previous surgery and previous ERCP in order to treat choledocholithiasis [30,31].
But there are also surgeon related risk factors; in fact, a surgeon must to have some precautions to avoid the leak, as a good visualization, complete demonstration of anato-

TABLE III - *Endoscopic management of minor post-cholecystectomy biliary fistula.*

Study	*n*	Successful ERCP	Days to resolution	Complication rate	Further intervention
Present study	22	n = 22	4	n = 2/22	0%
Katsinelos et al. [48]	60	94%	NA	13%	1.6%
Donnellan et al.[44]	48	n = 44	5	n = 0	n = 0
Mavrogiannis et al.[43]	52	100%	2–4	7.7%	0%
Familiari et al. [47]	85	96.3%	NA	2.9%	2.3%
Tzovaras et al.[49]	20	n = 19	NA	n = 1	n = 1

NA, not available

my, minimal diathermy, early experienced help/conversion and intra-operative cholangiography (IOC) when in doubt, fundal traction, and keep close to gallbladder wall.

Leaks arise most commonly from the cystic duct stump and secondly from duct of Luschka, both of them included in the Strasberg's Classification in injury type A.

The goal at ERCP is twofold, both diagnostic and therapeutic. It allows identification of both the site of the leak as well as any residual stones within the bile duct that may be contributing to it.

The principle of therapy is a reduction in the transpapillary pressure gradient across the sphincter of Oddi [32] leading to preferential flow through the papilla into the duodenum, thus attenuating the bile leak and allowing the site to heal [33].

The management of bile leaks following laparoscopic cholecystectomy has changed in the last decade in favor of an endoscopic approach, which success therapeutic rate is reported in the literature to be in the range of 66 % to 100%. Different techniques are described, including nasobiliary drains, endoscopic sphincterotomy (ES) and stent placement. Endoscopic sphincterotomy has a higher complication rate, while nasobiliary drains are not particularly well tolerated by patients and can easily become displaced [34]. The therapeutic modalities consist of nasobiliary tube alone, sphincterotomy alone, or placement of a biliary stent with or without sphincterotomy.

ERCP with ES and stent has become the treatment of choice, and in experienced hands, its efficacy is upper 80% and it represents the treatment of choice of our study, with a significantly higher rate of success [35].

Davids et al. reported a successful rate of endoscopic management in 90% of cases [36].

Ryan et al. in the 88% of patients who underwent ERCP resolved the leak [37]. Kaffes et al. [38] found significantly more patients in the group treated by ES alone required further intervention to control the leak, compared with ones in which other endoscopic strategies.

Stent insertion was superior to sphincterotomy alone without any influence on the diameter of the stent.

From this data, that is evident that there is little consensus on the role of sphincterotomy in combination with stent insertion. When possible, avoiding a sphincterotomy minimizes risk for perforation or bleeding, because of sphincterotomy is associated with an increase in complication rates of 7.3-9.8% [39,40] and a mortality of up to 1.3% [41,42]. In addition, sphincterotomy cannot be performed in patients with coagulopathy.

Mavrogiannis et al. [43] found no additional benefit from sphincterotomy in terms of leak resolution; however, they and other authors demonstrated there may be a higher rate of pancreatitis in cases without sphincterotomy [44,45].

Aksoz et al. with an earlier publications have reported sphincterotomy alone as a means of negate ampullary pressure, but with a quoted leak resolution rate of only 87.1% [46]. This is inadequate when compared with the findings of other reports using stents (Table III) and Familiari et al. report that up to 12% of patients after sphincterotomy alone require subsequent stent insertion[47]. The importance of stent size remains controversial. Theoretically, a larger stent provides improved biliary drainage. A single randomized trial comparing 7-Fr and 10-Fr stents showed a non-significant trend towards bile leak resolution with larger stents [48]. In addition, some cases, with 7-Fr stents that didn't show resolution, was consequently treated by the insertion of a larger stent. It is difficult to draw definitive conclusions from these data, but the current study shows as these findings and choices depends only by endoscopist experience.

So, endoscopic management of minor biliary tree injuries has a very high rate of success with minimal additional morbidity, without the need for an additional operation, as our current study and previously published data show, (Table IV).

In addition, they confirm that the most common locations are the cystic duct stump and gallbladder fossa, (Table IV)

TABLE IV - *Distribution of site of minor biliary injuries*

Study	Cystic duct stump	Segment VI/V leak
Present study	n = 17/22	n = 4/22
Donnellan *et al.*[44]	n = 19/44	*n* = 11/44
Mavrogiannis *et al.*[43]	71.2%	NA
Familiari *et al.*[47]	75%	22.3%
Tzovaras *et al.* [49]	n = 16/20	NA
Pinkas & Brady [50]	n = 15/20	*n* = 5/20

NA, not available

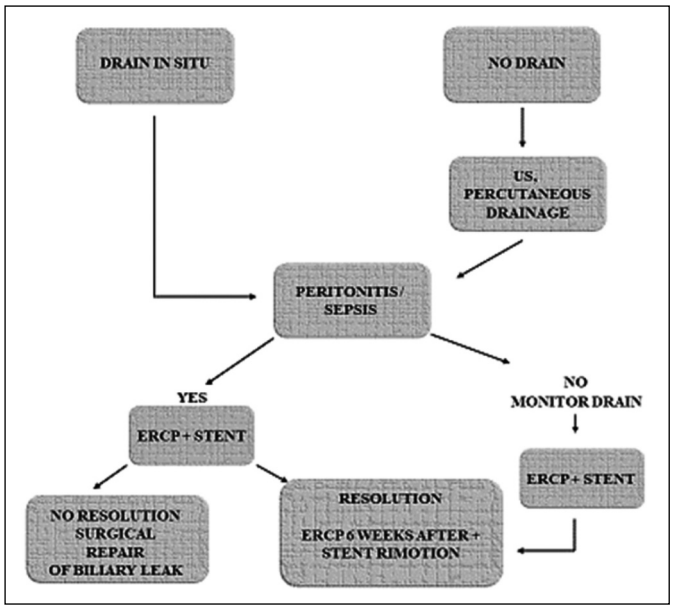

Fig. 3: Structured stepwise approach to the current management of minor post-cholecystectomy biliary fistula.

Cystic stump leaks occur from faulty clip application, slipping of the clips or necrosis of the cystic duct stump proximal to the clip, probably related to diathermy injury [51]. Retained CBD stones can increase intraluminal pressure and therefore promote bile leakage [52], as seemed to be the case in our four patients.

Patients with missed stones were managed with endoscopic sphincterotomy and stone extraction alone if the leak appeared minimal, or in many cases of our practice with a combination of endoscopic sphincterotomy, stone extraction, and stent placement, bypassing the site of the leak, if the leak appeared to be significant during cholangiography. With this approach, we have reached a success rate of 100 %.

If a major biliary injury is identified at ERCP, the patient should be referred for consideration of biliary reconstruction.

If ERCP fails or if bile collections persist, relaparoscopy can be an alternative therapeutic strategy, with a successful rate of only 70% because of the possibility of diffuse bile peritonitis and delayed diagnosis [53,54]. In these difficult cases, with a high risk of sepsis, laparotomy is mandatory with good final outcomes [55,56].

In presence of alteration of gastro-duodenal anatomy, like Billroth II gastrectomy or Roux-en-Y biliary-enteric anastomoses, ERPC is unsuitable [57].

USS guided percutaneous biliary drainage can be successful performed but it is not free from complications including fistula formation, haemorrhage and bile leak secondary to liver puncture [58]. Although there were no ERCP-related complications in this study, except two post-ERCP pancreatitis, these are always a concern and can, rarely, be life-threatening.

The plastic stents inserted need removal after 6 weeks, exposing the patient to a second ERCP and hospital visit, that explains the longer follow-up of this study.

In our practice bile leak remains an unusual problem, that explains that it has taken 10 years to accumulate the relatively small series of this study.

Nonetheless, this study provides a useful analysis of our experience and we think that a structured stepwise approach to the current management of uncommon complications such as bile leaks is advantageous (Fig. 3).

Conclusion

Bile duct injury represents an uncommon but potentially serious complication after laparoscopic cholecystectomy. Endoscopic treatment by means of ERCP is the cornerstone of management, supplemented by either interventional radiological or laparoscopic procedures. ERCP can be used to diagnose the site of biliary leakage and to overcome the pressure gradient at the ampulla of Vater in order to allow bile to flow into the duodenum and away from the site of bile leak. This allows for the healing of the affected biliary segment. The ideal endoscopic approach – whether endoscopic sphincterotomy, long versus short stent placement or naso-biliary tube drainage – has not yet been established. It largely depends on personal experience.

Riassunto

OBIETTIVO: La colecistectomia videolaparoscopica per il trattamento della colelitiasi è la procedura chirurgica più comune eseguita nei paesi occidentali e le fistole biliari rimangono una causa significativa di morbilità (0,2-2%). Una valida strategia terapeutica per le fistole biliari minori è la decompressione biliare interna mediante ERCP e sfinterotomia endoscopica. Lo scopo di questo studio è quello di valutare l'efficacia della strategia endoscopica nella gestione delle lesioni biliare minori.

PAZIENTI E METODI: Ventidue pazienti con fistola biliare post-colecistectomia videolaparoscopica sono stati arruolati consecutivamente tra il 2007 e il 2017; tutti trattati con approccio endoscopico, con ERCP per confermare la natura della lesione, nonché decomprimere il dotto biliare con sfinterotomia, con il posizionamento di endostent o drenaggio nasobiliare.

In 15 pazienti, la perdita biliare è stata diagnosticata mediante il drenaggio addominale, negli altri 7 pazienti la perdita biliare è stata sospettata per l'insorgenza di un tipico quadro sintomatologico nell'immediato periodo postoperatorio.In base all'entità della perdita biliare giornaliera, abbiamo suddiviso i pazienti in due gruppi: a) <180 ml / giorno e b)> 180 ml / giorno.

RISULTATI: Iltrattamento endoscopico è stato efficace in tutti i 22 pazienti (100%), senza ulteriori interventi. Un

colangiogramma completo è stato ottenuto in tutti i casi (100%). I siti più comuni di perdita biliare minore registrati sono stati il moncone del dotto cistico e il condotto di Luschka, in un unico caso il sito della perdita non è stato riconosciuto. All'inizio della serie, è stata eseguita la sfinterotomia da sola o il posizionamento del sondino nasobiliare. Tuttavia, successivamente i pazienti sono stati sottoposti a sfinterotomia con inserimento di stent, al fine di favorire il drenaggio preferenziale della bile nel duodeno attenuando la perdita, fino alla sua completa risoluzione, che in media veniva raggiunta in 4 giorni.
Due pazienti hanno mostrato dopo ERCP una lieve pancreatite; non sono state osservate altre complicaze. La degenza ospedaliera mediana era di 15 giorni (range, 10-31 giorni).
A 4-6 settimane è stata eseguita una ERCP di controllo per la rimozione dello stent.
Il follow-up routinario è stato nella media di 50 giorni.
CONCLUSIONI: Questa revisione conferma che le lesioni biliari minori postoperatorie possono essere gestite con successo mediante trattamento endoscopico.

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