Post-ERCP pancreatitis
A single center experience and an update on prevention strategies

Ann. Ital. Chir., 2015 86: 234-238
pii: S0003469X1502374X
www.annitalchir.com

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OBJECTIVES: *Pancreatitis is the most frequent complication of the ERCP; in unselected patients the incidence is 3.5%, reaching 25%, and is mild-moderate in 90%. A stratification of patients into low or high risk is important to provide adequate information to patients and to decide when refer them to tertiary centers; moreover, many prophylactic measures have been proposed over years. Our aim was to select risk factors for PEP and compare them with current literature in order to propose adequate preventive strategies.*
METHODS: *It was analyzed the occurrence of Post-ERCP Pancreatitis in a series of 492 consecutives patients treated with ERCP by two expert interventional endoscopists. The possible risk factors were evidenced by a multivariate analysis, were states our proposals for Post-ERCP Pancreatitis prevention and compared them to the current literature.*
RESULTS: *We observed 14 PEP (2.8%), 6 mild, 4 moderates and 4 severe. The multivariate analysis evidenced as risk factors the high number of attempts of cannulation and the pancreatic injection of contrast medium and found a protective role for pre-cut sphincterotomy. Our mortality rate was 0.4%.*
CONCLUSIONS: *The guide-wire cannulation technique and, in selected cases, the pre-cut permit to minimize the number of cannulation attempts and to increase the success rate of primary cannulation; we promote their use to reduce PEP occurrence.*

KEY WORDS: Endoscopic retrograde cholangiopancreatography, Pancreatitis

Introduction

ERCP recognizes nowadays a prevalent role in the treatment than in the diagnosis of pancreato-biliary diseases, thanks to the development of alternative diagnostic tools as MRCP and EUS that better follow the scope.

The procedure's complications include bleeding, cholangitis, cholecystitis, perforation and pancreatitis and can lead to severe or fatal outcomes.
The post-ERCP pancreatitis (PEP) is the most frequent complication and its occurrence is nowadays difficult to manage [1]. The diagnosis of pancreatitis according to Cotton's criteria includes three main factors: clinical, laboratoristics and imaging [2]. The upper quadrants' abdominal pain is need. Biochemically an elevation of the amylase or lipase serum levels over three times the upper normal level (UNL) is the second element in diagnosing. The CT, MR or EUS can aid in the diagnosis. As proposed by Freeman in PEP these have to be present at 24 hours from the procedure determining a hospital admission or a prolongation of the planned [3].

Pervenuto in Redazione Febbraio 2015. Accettato per la pubblicazione Febbraio 2015
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CT examination to establish the grading of pancreatitis in accordance to Balthazar score must be used in uncertain diagnoses, to confirm the severity basing on clinical data, if there was an inefficient treatment, to confirm the failure of the therapy or if is planned an invasive attempt of treatment.
Were found patient related and procedure related risk factors for PEP.
We attempt to analyze the occurrence of this complication in our series comparing this to literature data to analyze the proposals for its prevention.

Methods

A retrospective study was carried out through the analysis of patients treated with ERCP for pancreato-biliary diseases by the General and Urgent Surgery Operative Unit of the Policlinico "Paolo Giaccone" of Palermo from January 2012 to November 2013 to evaluate the occurrence of PEP. All procedures were executed by two expert interventional endoscopists.
Patients' anamnesis and admission diagnoses were analyzed. The elevation of serum amylase values more than 3 or 5 times the UNL at 4-6 hours post-ERCP, the occurrence of pain documented by clinical diaries and radiological investigation by CT scan were collected in all patients to evaluate the occurrence of PEP.
The presence of patients-related and procedure-related risk factors for PEP was analyzed.
Data were collected using frequencies and percentages and those about risk factors were then analyzed with a multivariate analysis using STATA software for the OLS regression and SPSS software for the binary logistic regression to evaluate the impact of the different risk factors proposed by the ESGE guidelines 2010 in our series. It was verified the relation between variables with the "correlate" command and all variable were found independents; the absence of multicollinearity between variable was tested with VIF and so could be performed the regression.
For the OLS regression it was done a linear regression that includes as variables: SOD; female gender; previous pancreatitis; younger age; non dilated bile ducts; absence of chronic pancreatitis; normal serum bilirubin; pre-cut; pancreatic injection of contrast; high number of attempts; Pte; biliary balloon extraction; failure to clear bile duct; then, it was done a STEPWISE regression (a normal linear regression) that permitted to evidence the relevant risk factors for our series.
It was done a test to understand which model was better for our database using the Fisher's F and it was found preferable the STEPWISE regression.
The logistic binary regression, even though the small number of cases analyzed, was conducted, too, for risk factors analysis. Data on hospital stay to assess the morbidity and mortality rates were finally collected.

Results

By the interventional endoscopy group of the General and Urgent Surgery O.U. of the Policlinico "P. Giaccone" of Palermo in the years 2012-2013 were executed 492 ERCP. The average age of patients treated was 70 years old with a standard deviation of 14 years. The diagnoses are summarized in Table I.
The Freeman's criteria for the diagnosis of pancreatitis presented at 24 hours from procedure that occurred in our patients are summarized in Table II. We had 14 PEP accounting for 2.8 % of our patients. The admittance diagnoses in patients with PEP were lithiasis in 6 patients, malignancies of biliary tract in 6 patients and pancreatic neoplasms in 2 patients.
Presence of risk factors for PEP, according to ESGE guidelines 2010, presented by patients was analyzed with a univariate analysis and is reported in Tables III and IV. The multivariate analysis with the STEPWISE regres-

Table I

Diagnosis	N. patients	%
Lithiasis	244	49,6
Pancreatic malignancies/ Chronic pancreatitis	58	11,8
Malignancies biliary tract	90	18.3
Sump syndrome	36	7.3
Acute biliary pancreatitis	24	4.9
Others	40	8.1
Tot.	492	100

Table II

Freeman's criteria for pancreatitis	N. patients/Tot.	%
Serum amylases or lipases > 3 upper normal limit (UNL)	64/492	13
Pain + Serum amylases or lipases > 3 UNL	14/492	2.8
CT-scan confirmation	2/492	0.4

Table III

Patient-related risk factors	N.	%
Definite risk factors		
Suspected SOD	0	0
Female gender	242	49.2
Previous pancreatitis	1	0.4
Likely risk factors		
Younger age	20	4.1
Non-dilated extra hepatic bile ducts	106	21.5
Absence of chronic pancreatitis	470	95.5
Normal serum bilirubin	108	22

Table IV

Procedure-related risk factors	N.	%
Definite risk factors		
Precut sphincterotomy	18	3.7
Pancreatic injection	114	23.2
Likely risk factors		
High number of cannulation attempts	40	8.1
Pte	292	59.3
Biliary balloon sphincter dilation	6	1.2
Failure to clear bile duct stones	40	8.1

Table V

Prob > F = 0.0192
R-squared = 0.2507
Root MSE = .15513

PEP	Coef.	Robust Std. Err.	t	P>|t|	[95% Conf.	Interval]
MARKERS	.2503705	.0751269	3.33	0.001	.1023813	.3983597
PRECUT	-.0995333	.0510408	-1.95	0.052	-.2000764	.0010097
HIGHNATTEMPTS	.0987419	.0597659	1.65	0.100	-.0189883	.216472
FAILURETOCLEAR	-.0546698	.0274475	-1.99	0.048	-.1087375	-.0006021
_cons	.0000102	.0031184	0.00	0.997	-.0061325	.0061529

Table VI

	B	E.S.	Wald	df	Sig.	Exp(B)	95% CI per EXP(B) Inferiore	Superiore
FEMALE(1)	-,150	1,418	,011	1	,916	,861	,053	13,855
previouspancreatitis(1)	31,080	40590,924	,000	1	,999	3,147E+13	,000	.
YOUNGERAGE(1)	-,321	9937,727	,000	1	1,000	,725	,000	.
NONDILATATEBILEDUCTS(1)	-1,075	1,654	,422	1	,516	,341	,013	8,736
ABSENCECRONICPACREATITIS(1)	1,763	10601,299	,000	1	1,000	5,828	,000	.
NORMALBILIRUBIN(1)	-1,126	1,707	,435	1	,509	,324	,011	9,209
PRECUT(1)	-35,593	9884,868	,000	1	,997	,000	,000	.
CONSTRAST(1)	2,781	1,778	2,448	1	,118	16,137	,495	525,945
HIGHNATTEMPTS(1)	18,314	9789,225	,000	1	,999	89901815,36	,000	.
SPHINCTEROTOMY(1)	-18,479	3026,311	,000	1	,995	,000	,000	.
BILIARYBALLOON(1)	-2,394	20566,003	,000	1	1,000	,091	,000	.
FAILURETOCLEAR(1)	-18,661	7187,409	,000	1	,998	,000	,000	.

Table VII

Cotton's criteria	N. patient	%
Mild pancreatitis: 2-3 days of hospital stay	6	42,8
Moderate pancreatitis: 4-10 days of hospital stay	4	28,6
Severe pancreatitis: More than 10 days	4	28,6
Tot.	14	

sion, a normal linear regression, preferred to the complete one, according to the F of Fisher, is reported in Table V. The logistic binary regression conducted even though the small number of cases is showed in table VI. 28% of our patients were high risk patients; among them 7.2% suffered PEP. The average hospital stay was of 1.3 days with a standard deviation of 3.4 days.

PEP according to Cotton's criteria of hospital stay and appearance of organ failure or MOF are in table n. 7. 71% of our PEP were mild-moderate.
Our Mortality rate was 0.4%.

Discussion

PEP is a current problem in an interventional endoscopy O.U. According to Freeman, PEP is a clinical pancreatitis with amylase at least three times normal at more than 24 hours after the procedure, requiring hospital admission or a prolongation of planned admission [3].
PEP was classified in mild, moderate and severe according to hospital stay. Mild PEPs require 2 to 3 days of hospitalization, moderates 4 to 10 days and is considered severe more than 10 days or if occur hemorrhagic pancreatitis, phlegmon or pseudo cyst or if there is the need of intervention (percutaneous drainage or surgery) [2].
PEP has, in unselected patients, an incidence of 3.5% and is mild or moderate in about 90% of patients [1].
In the Cotton's large series of 2009, including 11000 patients, the occurrence of PEP was 2.6%, classified as mild in the 75%, moderate in 19%, severe in 6% and fatal 0.3% [4].
The severe pancreatitis leads to the impairment of the gland that is better evaluable with CT that has to be done at 72 hours. Abdominal compartment syndrome, sepsis, respiratory failure, MODS until in some cases death are possible [5].
We had 14 PEP accounting for 2.8% of our patients; 71% were mild-moderate.
All patients were initially treated with fluid infusion, PPI, NSAIDs and fasting.
In cases that suffered severe PEP (4 patients) gastric decompression, octreotide, TPN and antibiotics were administered and they have needed ICU admittance; two of these developed MOF and successively died. Our mortality rate was 0.4%.
To reduce the risk of PEP are important a risk stratification, the administration of drugs and some technical aspects [6]. In order to provide adequate pre-procedure information to the patient and to decide when to refer patients to a tertiary center it was proposed to stratify patients into low-risk or high-risk. Were evaluated various prognostic factors related with its occurrence; these are patient-related and procedure-related.
After the proposals of Freeman, the European Society of Gastrointestinal Enodoscopy, in 2010, have established as independent definitive patient-related risk factors: suspected SOD, female gender and previous pancreatitis; and as independent definitive procedure-related risk factors: pre-cut sphincterotomy and pancreatic duct injection of contrast; considering as likely risk-factors: younger age, non-dilated extra hepatic bile ducts, absence of chronic pancreatitis, normal serum bilirubin, high number of cannulation attempts, pancreatic sphincterotomy,

biliary balloon sphincter dilatation, failure to clear bile duct stones [1,7].

In June 2014 an update of these guidelines includes, as definitive procedure-related risk-factors: cannulation attempts duration > 10 minutes and pancreatic guidewire passage> 1, in addition to the pancreatic injection of contrast; moving pre-cut sphincterotomy to the likely, but not-definitive, risk-factors [8].

In our multivariate analysis, using the STEPWISE regression, the only risk factor for PEP is the high number of cannulation attempts, while are favorable factors the pre-cut and failure to clear bile duct (Table V). The logistic binary regression, performed even though the small number of case, reveals, as only risk factor, the pancreatic injection of contrast (Table VI).

Four patients (10%) among those presenting high number of attempts and 8 patients (7%) among those presenting pancreatic injection of contrast have suffered PEP. Nobody of the patients in whom it was used pre-cut has showed PEP. Many prophylactic measures, as procedural tricks and various drugs were proposed over the years. Non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the incidence of PEP. 100 mg of diclofenac or indomethacin administered rectally immediately before or after ERCP are recommended [1,8]. Even if, Dobronte reports that indomethacin did not prove effective in preventing PEP and Li reports that NSAIDs effectively reduce the incidence of PEP but not that of moderate to severe pancreatitis [9,10]. We didn't use NSAID in the analyzed patients but their use seems to have found a large consensus, and being an easy and cost effect measure, we agree that it have to be enterprise.

Zhao proposes pre- ERCP somatostatin in reducing the risk of PEP in high-risk patients, but not in low-risk ones; however in this regard there is no consensus [8,11]. Cotton found a reduced risk for overall complications after prophylactic pancreatic stent (PS) placement but not specifically for pancreatitis [4]. Mazaki affirms that PS reduces the risk of PEP and is beneficial for patients with high risk [12]. In high risk patients prophylactic PS is, also, recommended by ESGE guidelines 2014; although, Takenaka affirms that it is not apparent which group receives the most preventive effects from PS within the high risk group of PEP, especially in the procedure-related group which is affected by intraoperative decision [8,13]. However, Elmunzer reports that patients receiving Indomethacin alone appear to have a lower risk of PEP compared to those receiving a stent alone or a stent in combination with indomethacin [14]. Failure of pancreatic stent placement is associated with high rates of PEP [15]; we don't use its and concord to Abu Dayyeh in that it seems not an ideal solution for PEP for multiple reasons: failure rate in stent placement > 65% PEP, adverse events, substantial costs and inconvenience to the patient [16]. Trauma resulting from repeated attempts of biliary cannulation has been proven to be a risk factor for the development of PEP. High number of cannulation attempts is a risk factor also in our multivariate analysis. The number of cannulation attempts should be minimized [8]. Injection of contrast medium into the pancreatic duct is an independent predictor of PEP and, if it occurs, the number of injections and the volume of contrast medium injected into the pancreatic duct should be kept as low as possible [8]. Tse, in a large meta-analysis, reports that the guide wire cannulation technique reduces PEP facilitating selective biliary cannulation, limiting papillary trauma, and minimizing inadvertent contrast injection into the pancreatic duct or the papilla itself; he propose to put the guide wire in a sphincterotome as the most appropriate first-line primary cannulation technique in the era of therapeutic ERCP.[17] The guide wire cannulation technique increases the success rate of primary cannulation when compared with the contrast assisted method and is recommended for deep biliary cannulation [1,8]. We agree on this technique to reduce the number of cannulation attempts and use it several times.

In the past, pre-cut sphincterotomy was considered a risk factor for PEP while recently this role was attributed most to the high number of attempts prior to pre-cut, than to the pre-cut itself. In a meta-analysis Navaneethan reports that precut sphincterotomy and persistent attempts at cannulation are comparable in terms of overall complication rates; early pre-cut prevent excessive and repetitive papillary trauma which may in turn increase the risk of PEP [18]. Choudhary suggests that early precut done within 5-10 min of failed cannulation decrease the odds of PEP without compromising cannulation rates or increasing other complications [19]. We used it, in selected cases, without PEP occurrence and our data, in accordance with the recent literature, support this choice, finding it as a favorable factor.

Conclusion

In conclusion, the diffusion of MRCP and EUS as diagnostic tools and the strictly therapeutic intent for ERCP can prevent unnecessary procedures. Guide-wire cannulation technique and the early pre-cut can reduce the trauma to the papilla caused by high number of attempts and promote selective biliary cannulation reducing pancreatic duct contrast injection. The use of prophylactic drugs can reduce the inflammatory process. Even if PEP is an ineludible complication of the ERCP with these measures it seems to be possible to reduce the procedure's complication rate.

Conflict of interest: Francesco D'Arpa and other co-authors have no conflict of interest.

Riassunto

La pancreatite rimane ad oggi la maggiore complicanza dell'ERCP nonostante numerose misure tese alla sua pre-

venzione siano state proposte negli anni. La sua incidenza è del 3.5% e raggiunge in alcune serie di casi anche il 25%; solitamente è lieve-moderata nel 90%.
La stratificazione dei pazienti in base al grado di rischio è necessaria per destinare i casi più complessi a centri di terzo livello presenti nel territorio; per far questo, un'analisi dei possibili fattori di rischio è stata originariamente proposta da Freeman ed è poi stata modificata dall'ESGE sulla base dei contributi dei singoli centri, con importanti modifiche.
Il presente studio analizza l'incidenza di pancreatite post-ERCP in un centro di terzo livello analizzando, sulla scorta dei fattori di rischio proposti, l'aderenza dei dati. Negli anni 2012-2013, 492 pazienti sono stati sottoposti ad ERCP da due esperti endoscopisti.
Secondo le classificazioni di Freeman e Cotton sono state osservate 14 PEP (2.8%), di cui 6 lievi, 4 moderate e 4 severe. È stata condotta un'analisi multivariata che ha evidenziato come fattori di rischio l'elevato numero di tentativi di incannulamento della via biliare e l'iniezione di mezzo di contrasto nel dotto pancreatico; sono risultati fattori protettivi l'early pre-cut e il fallimento della procedura con la sua interruzione.
Nella discussione sono state inoltre brevemente analizzate le varie misure profilattiche, quali il posizionamento di protesi pancreatiche e l'utilizzo dei FANS.
È interessante notare come i nostri risultati rafforzino gli ultimi orientamenti nel management dell'ERCP, circa l'utilizzo della tecnica di incannulamento filo-guidato e del pre-cut; questi infatti riducono il numero di tentativi di incannulamento ed il conseguente trauma alla papilla promuovendo un incannulamento biliare selettivo e prevenendo l'iniezione di mezzo di contrasto nel dotto pancreatico. Nonostante la pancreatite sia un'ineludibile complicanza dell'ERCP, reputiamo che questi accorgimenti tecnici possono essere utili nel prevenire la sua insorgenza.

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