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Why the Incidence of Post-ERCP Pancreatitis Varies Considerably? Factors Affecting the Diagnosis and the Incidence of This Complication

Pier Alberto Testoni

Division of Gastroenterology and Gastrointestinal Endoscopy, University Vita-Salute San Raffaele, IRCCS San Raffaele Hospital. Milan, Italy

Summary

The reported incidence of post-ERCP/sphincterotomy pancreatitis ranges between 1.3 and 24.4% in non-selected series. This varying incidence likely reflects on the one hand difference in patient populations, indications and endoscopic expertise and, on the other hand, different definitions of pancreatitis and methods of data collection. Among a number of patient-related factors recognized at risk for post-ERCP pancreatitis in four recent large prospective studies, the combination of female gender, normal serum bilirubin levels and recurrent abdominal pain suggesting sphincter of Oddi dysfunction and previous post-ERCP pancreatitis placed patients at an increasingly higher risk of pancreatitis. Among the technique-related risk factors for post-ERCP pancreatitis, biliary sphincter balloon dilation, difficult cannulation, sphincter of Oddi manometry and pancreatic sphincterotomy have also been recognized as significant risk factors. However, since the case mix in non-selected series does not significantly differ in the different studies, it is logical to assume that the different criteria adopted for defining the post-ERCP pancreatitis play a key role in the reported wide variation of incidence reported for this complication. The occurrence and duration of pain and the amplitude of serum amylase after ERCP are critical points in the definition of post-ERCP pancreatitis. Although a consensus conference identified 24-hour persisting pain associated with hyperamylasemia greater than 3 times the upper reference limit as an indicator of pancreatitis, these two parameters are however considered in a different manner in the studies available up to now. In a prospective study where we calculated the incidence of post-ERCP pancreatitis by using the most widely used criteria, for both occurrence and duration of pancreatic pain and serum amylase amplitude, the incidence of post-procedure pancreatitis ranged from 1.9 to 11.7% depending on the criteria adopted.

Background

Acute pancreatitis is still the most common and most feared complication after endoscopic cholangiopancreatography (ERCP) and endoscopic sphincterotomy; a meta-analysis found an average overall frequency of 5.2% and 4.1% after diagnostic and therapeutic procedures, respectively [1]. However, prospective series of non-selected patients reported a frequency of post-ERCP pancreatitis that ranged between 2.1 and 24.4% [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. This varying incidence was further confirmed in the four largest prospective studies available up to now which reported an incidence of post-ERCP pancreatitis ranging from 1.3 to 6.7% [16, 17, 18, 19].

It is surprising that the same procedure (ERCP) performed in different series of consecutive, non-selected patients, approximately in the same decade (1990-2002), gives such a high rate of post-procedure pancreatitis. Since potential mechanisms of pancreatic injury during ERCP (mechanical, thermal, chemical, enzymatic and microbiological) probably do not differ significantly in the procedures performed in these studies, it seems logical to assume that the varying incidence of post-procedure pancreatitis may reflect, on the one hand, differences in patient populations, kind of therapeutic procedures or endoscopic expertise and, on the other hand, different definitions of pancreatitis and methods of data collection.

Technique- and Patient-Related Conditions as Factors Affecting the Incidence of Post-ERCP Pancreatitis

The case mix could markedly affect the incidence of post-procedure pancreatitis. In previous prospective investigations, it has been documented that post-procedure pancreatitis occurs with a higher incidence (up to 57%) in young patients [16] and in cases with suspected or documented sphincter of Oddi dysfunction [20, 21, 22, 23, 24], pancreatic sphincter hypertension [25], previous episodes of pancreatitis [16, 17] and small-diameter bile ducts [21, 22]. Technique-related risk factors such as difficult cannulation or multiple injection of the pancreatic ducts [9, 16, 17, 19, 26], and the use of precutting techniques or balloon dilatation have also been shown to be associated with an increased risk of pancreatitis. The last multicenter prospective study available up to now, carried out on a series of 1,963 consecutive ERCPs using multivariate analysis, demonstrated that female gender, normal serum bilirubin, recurrent abdominal pain and previous post-ERCP pancreatitis were at an increasingly higher risk of pancreatitis, regardless of whether ERCP was diagnostic, therapeutic or associated with ancillary procedures as sphincter of Oddi manometry [19]. The results of this study showed that the risk of post-ERCP pancreatitis is determined as much by patient characteristics as by endoscopic technique-related factors. The incidence of pancreatitis in the different series could therefore be correlated with the percentage of patients included in the studies having a high risk for this complication; in fact, the incidence of complication can increase up to 31% in series with high-risk cases.

The assumption that the skill of endoscopist is an important factor in the outcome of ERCP is difficult to document. Few studies provide substantial information about a possible relationship between the expertise of the endoscopist and the incidence of post-ERCP pancreatitis [16, 17, 19, 27, 28, 29, 30, 31, 32].

Although in studies with a preponderance of patient-related risk factors for post-ERCP pancreatitis such a dependence failed to be proven [16, 19], however when non-selected cases are investigated, there is evidence of some correlation between case volume and incidence of post-ERCP complications [17, 27].

In fact, apart from a few studies in selected series of high-risk patients for post-procedure pancreatitis, most studies involve a variety of patients (at either higher or standard risk of developing post-procedure pancreatitis – mostly the latter) and are done by skilled endoscopists. Therefore, the differences in the rate of post-ERCP pancreatitis seem to depend as much on differences in data collection methods or the definition of pancreatitis as on patient- and technique-related risk factors.

Definition Criteria as Factors Affecting the Incidence of Post-ERCP Pancreatitis

The definition of post-procedure pancreatitis still remains a controversial issue in the field of post-ERCP/sphincterotomy complications, due to the different parameter criteria adopted; the occurrence and duration of pancreatic-type pain and the amplitude and duration of serum amylase increase are both

crucial points in the definition and grading of the pancreatic reaction. The differences in definition criteria and in the timing of the data collection are likely major factors leading to the varying incidence of pancreatitis in published series. The continuing search for reliable criteria in defining pancreatitis probably reflects the difficulty of the endoscopist to establish which parameters satisfy the need to identify cases with real pancreatic damage.

It is generally agreed that epigastric pain irradiating to the back in the post-procedural period, with or without abdominal tenderness, is a reliable indicator of some pancreatic involvement, whereas the amplitude of the serum enzymatic increase, whether associated or not with pain, is still a more questionable issue.

The duration of pain is crucial for defining post-procedure pancreatitis, since pain disappearing within 24 hours is unlikely to indicate clinical pancreatitis**,** and is more probably due to some transient pancreatic reaction or other causes, such as intolerance to the air inflated during the procedure. Moreover, pain persisting at 24 hours, but disappearing within the subsequent 12-24 hours and not requiring a prolonged hospital stay, probably does not likely satisfy the criteria for defining pancreatitis. In fact, excluding those few cases of moderate to severe pancreatitis requiring a hospital stay of longer than three days or those with complications, the distinction between clinical mild pancreatitis and hyperamylasemia with transient abdominal discomfort (occurring in a larger number of cases) seems to be more elusive.

The severity of pain could also be a parameter for classifying pancreatitis. However, in most reports, it has been neither graded nor standardized and its reliability remains uncertain since the subjective evaluation makes it difficult to exactly classify the degree. One aspect could be the need for narcotics, whose request is again patient-dependent.

Attempts were made a few years ago [2] to establish reliable criteria for defining post-ERCP pancreatitis, leading to a consensus statement based on more than 15,000 procedures; pancreatic-like pain associated with at least a three-fold increase in serum amylase value still persisting 24 hours after the endoscopic procedure was considered an indicator of pancreatitis. However, the criteria proposed have not been widely adopted since then, even in some of the largest series published.

Although epigastric pain persisting for at least 24 hours has been considered as an indicator of pancreatitis in the post-procedure period in the majority of studies, however, other investigators considered pain occurring 4 hours after the procedure [12] or only pain persisting for at least 48 hours [16, 23, 25] or requiring a hospital stay of more than 48 hours consistent for pancreatitis [4, 14, 26]. In another study, no mention is made of the duration of pain and the length of the hospital stay in cases classified as having post-procedure pancreatitis [6], while, in other reports, pain had to require narcotic analgesics to be consistent for pancreatitis [3, 21].

The amplitude and duration of post-procedure serum enzymatic increase associated with pancreatic pain are further points in the definition and grading of a pancreatic reaction. Hyperamylasemia occurs in about 70% of cases within 2 to 4 hours after endoscopic procedures involving Vater's papilla but, in most of them, values are normal after 24 hours, so this per se cannot be considered a complication, unless the patient also has pain and other signs of pancreatitis. The increase in serum enzymes may vary considerably without clinical significance.

Several prospective studies have suggested that, besides pancreatic pain, a 24-hour serum enzymatic increase either twice the upper reference limit [5, 9, 16], or three times [2, 10, 12, 17, 22, 23, 25, 27, 33] or four times [3, 21] or five times the upper reference limit [4, 6, 8, 11, 18] is enough to define pancreatitis.

This leads to some confusion about which findings should be really considered consistent for pancreatitis.

In a prospective study [11] performed in 1,185 consecutive procedures, either diagnostic or therapeutic, only 29% of patients with 24-hour serum enzyme increase between three and five times the upper reference limit had pancreatic-type pain, while it was reported in 56% of patients with serum amylase level greater than five times the reference limit. However, none of patients with 24-hour pain associated with serum enzymatic increase between three and five times the upper reference limit showed an elevated white blood cell count and still had pain 48 hours after the procedure; at this time, the serum amylase level was markedly reduced or within the normal range in all cases. CT scan findings were also normal in all cases. These findings therefore still refer to transient minimal pancreatitis which disappears within 36-48 hours and does not likely need any further follow-up.

In contrast, among those patients with 24-hour pain associated with hyperamylasemia greater than five times the upper reference limit, leukocytosis occurred in 41.7% of cases; in the same percentage of cases, pain and hyperamylasemia still persisted 48 hours after the endoscopic procedure; CT scan examination documented some pancreatic involvement only in this group of patients. In fact, only among those patients with 24-hour pancreatic-like pain and hyperamylasemia greater than five time the upper reference limit, was an elevated white blood cell count documented, CT scan findings showed some pancreatic involvement and pain persisted over a period of 48 hours after the procedure. These patients therefore developed acute clinical pancreatitis.

As a consequence of the above criteria, the incidence of post-procedure pancreatitis varies in reported studies from 1.3 to 16.9%, the latter in high-risk patients for pancreatic reaction (sphincter of Oddi dysfunction). Earlier studies, mostly retrospective, reported an incidence of pancreatitis ranging from 0.9 to 3.3%. The higher incidence and its wider range in more recent studies very likely reflect a more detailed attempt at defining the parameters indicative for this complication.

A prospective study carried out by us [34] confirmed that, using different criteria to define post-procedure pancreatitis in the same series of consecutive patients, the incidence of this complication has a considerable range, from 1.9% to 11.7%. Pancreatic reaction was recorded using criteria reported in the literature to define acute post-procedure pancreatitis, applied either 6-8 or 24 hours after the endoscopic maneuvers. The incidence of pancreatitis was therefore calculated on the basis of the presence of: a) 6- to 8-hour pancreatic-like pain associated with a serum amylase level either greater than three times or five times the upper reference limit; b) 24-hour pancreatic-like pain associated with a serum amylase level greater than two, three, four or five times the upper reference limit, irrespective of CT scan confirmation; c) CT scan confirmation of pancreatitis in patients with 24-hour pancreatic-like pain and with a serum amylase value either three or five times the upper reference limit. If post-procedure pancreatitis is defined on the basis of pancreatic pain still persisting 24 hours after the procedure, associated with a serum amylase level three or five times the upper reference limit, the incidence of such a complication has varied slightly, from 5.1 to 6.6%, respectively. However, the amylase levels were within the normal range 36 to 48 hours after the procedure and pain disappeared in all the cases with 24-hour enzymatic increases between three and five times the upper reference limit, so that only pancreatic pain associated with a serum amylase increase greater than five times the upper reference limit has been clinically consistent for pancreatitis in our series. Evaluation of the same parameters 6-8 hours after the procedure has considerably overestimated the incidence of pancreatitis (7.4% to 11.7%; $P<0.001$). However, when pancreatic-like pain was associated with serum amylase value five times the upper reference limit or higher, the difference between the 6- to 8-hour and the

24-hour evaluation did not substantially change the incidence of post-procedure pancreatitis (7.4% at 6-8 hours; 5.1% at 24 hours). If CT scan is used to confirm the presence of acute pancreatitis, the presence of some pancreatic involvement was documented only among those subjects with serum amylase values higher than five times the upper reference limit. The incidence of post-procedure pancreatitis was therefore reduced to 1.9%.

A procedure-related hospital stay has also been considered in defining the occurrence and severity of pancreatitis; prolongation of planned admission by 2-3 days is generally considered an indicator of post-procedure pancreatitis, and its severity is based on the duration of the hospital stay [2]. On the other hand, the Atlanta classification for pancreatitis severity classifies such a complication as mild or severe on the basis of the absence or the presence of local (documented by CT scan) or systemic complications, independently of the duration of the hospital stay [35]. The different modalities of follow-up for patients or the different clinical significance attributed to pain and severe hyperamylasemia could account for the variable prolongation of the hospital stay and therefore for differences in the incidence of cases considered to have pancreatitis.

Conclusions

The varying incidence of post-ERCP pancreatitis seems to depend on either the case mix or the criteria for defining acute pancreatitis. In the studies published so far, the different criteria adopted to define post-procedure pancreatitis probably play a major role in the variable rates reported for this complication. Despite the presence of several studies published up to now, the definition criteria used to assess the occurrence of post-ERCP pancreatitis are still not standardized. Although a consensus conference has attempted to establish reliable criteria for defining this complication, personal experience and data obtained in some prospective studies have however allowed the investigators to use different parameters. The presence of pancreatic-type pain persisting 24 hours after the procedure associated with serum amylase increase, irrespective of the amplitude of enzyme elevation, could be the only practical criterion to make the definition of pancreatitis uniform. Besides the 24-hour pancreatic-type pain associated with hyperamylasemia, the attempt to give some clinical significance to the amplitude of serum enzymes increase appears, in fact, theoretical and may be a confounding factor; however, our experience indicated that none of the patients who developed 48-hour persisting pain and hyperamylasemia (consistent with a clinically relevant pancreatitis) had 24-hour serum amylase levels less than 5 times the upper reference limit.

Key words Acute Disease; Amylases; Cholangiopancreatography, Endoscopic Retrograde; Epidemiology; Sphincterotomy, Endoscopic; Pancreatitis; Risk Factors

Correspondence
Pier Alberto Testoni
University Vita-Salute San Raffaele
Division of Gastroenterology and
Gastrointestinal Endoscopy
IRCCS San Raffaele Hospital
Via Olgettina, 60
20132 Milano
Italy
Phone: +39-02.2643.2756
Fax: +39-02.2152.559
E-mail address: testoni.pieralberto@hsr.it

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