Endoscopic therapy of chronic pancreatitis

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Introduction

Chronic pancreatitis (CP) is a rare disease in western countries (incidence 2-10/100.000/year). It ultimately leads to irreversible damage of the pancreas with exocrine and endocrine insufficiency. Pain is the major clinical symptom and is present early in the course of the disease in most of the cases (1-3).

With the exception of the rare hereditary CP which is associated with a mutation in the cationic trypsinogen gene on chromosome 7 (4,5), the etiology of CP has not already been demonstrated. Chronic alcoholism is a precipitating factor and it dramatically increases the probability of CP development but the disease can develop in non-alcoholic subjects and is then qualified of "idiopathic" CP.

The pathophysiology of CP is still discussed including "stone theory" in which the primary abnormality is the protein plugs formation due to a congenital tack of lithostatine (6) which is currently becoming obsolete, and the "necrosis fibrosis" theory in which fibrosis and ductal stricture are the consequence of focal inflammation and necrosis (7-9). Pain is most often associated to interstitial hypertension and further ischemia resulting of both ductal hypertension and a lack of compliance of the diseased pancreas (10).

It is also probable that, when CP is established, these repeated episodes of ischemia participate to the irreversible process of fibrosis and further worsening of the disease ultimately leading to the burn out of the gland.

Until recently, endoscopic retrograde cholangiopancreatography (ERCP) has been a goldstandard for the morphological diagnosis of CP. The main features of ductal abnormalities observed have been described in different classifications using ERCP as a criteria of severity (11-13). These classifications are useful for the differential diagnosis of CP but also as a guide to choose the most adequate management.

Magnetic resonance cholangiopancreatography (MRCP) is a major advance in depicting ductal anatomy of the pancreas. This technique gives satisfactory pancreatograms in most of the cases with CP without the need of any ductal or intravenous contrast medium injection and without irradiation (14). Furthermore, the development of the dynamic secretin MRCP (DSMRCP) has improved the quality of the morphological information especially for patients without abnormalities at CTScan or ultrasound (15). It also detects anatomical variations and the presence of a dominant dorsal duct which implicates the necessary approach to the minor papilla if a stricture is evidenced and endotherapy required. DSMRCP allows the clinician to decide if endotherapy is needed and to choose the appropriate treatment without any morbidity related to the diagnostic procedure. These informations could become an important tool to detect, before endoscopic retrograde cholangiopancreatography (ERCP), those patients with painful pancreatitis who could benefit from drainage procedures. With the development of these techniques, it is highly probable that within the next few years, it will become contraindicated to perform an ERCP just for imaging the pancreas.

Despite these sophisticated improvements on imaging techniques, the plain film of the pancreatic area remains mandatory to detect small or large calcified calculi responsible for the obstruction of the main pancreatic duct (MPD). For diagnostic purposes, the detection and location of tiny calcifications in only possible using CTScan without contrast injection. In patients presenting with a quite normal pancreatography, the presence of tiny calcification on the "CTScan plain film" is the best criteria for the differential diagnosis between acute pancreatitis and CP at the early stage.

This chapter discuss endoscopic treatment of CP. It is important to note that these drainage procedures are indicated for patients with pain and marked morphological changes of CP (12,13) and do not concern patients with anatomical variants or mild pancreatitis in whom no stone or stricture are evidenced in the MPD. In these patients with morphological evidence of MPD obstruction, improving MPD drainage has the most chances to improve the pain syndrome. In the other cases, only a papillary dysfunction is advocated and the main pancreatic duct is normal. Then, not only the risk of manipulation on normal ducts is higher but the results if these manipulations are largely inconstant (16) and the implantation of material in normal MPD could precipitate the development of morphological lesions of CP (17). Therefore in the absence of demonstrable MPID stone or stricture, the endoscopic manipulations of the pancreas remain largely experimental.

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Endotherapy for chronic pancreatitis

Pain management

The aim of endotherapy in painful CP is to decompress the MPD. Similarly to that of surgical drainage procedures that have been performed for many years. Another goal of MPD drainage might be slowing the evolution of atrophy and pancreatic insufficiency by decreasing the chronic ischemia process of the pancreas, and improving steatorrhea by restoring the residual pancreatic juice flow to the duodenum. Currently, the single major indication for endoscopic treatment remains the elective treatment of pain.

The rationale for proposing endoscopic approach as a first choice treatment before surgery includes the fact that ductal decompression is able to ensure pain control, that it may avoid resection and that this technique of MPD drainage provides the simultaneous delivery of pancreatic juice and bile into the duodenum.

The development of endotherapy for CP around the world has been much slower than that of endotherapy for biliary diseases for several reasons : the rarity of the disease, the heterogeneity of its morphological presentation, the technical requirements (lithotriptor with precise X ray focusing, medical surgical and radiological experienced team, sophisticated accessories) and perhaps also the medical social approach to patients with alcoholic related diseases.

Although we performed the first endoscopic pancreatic sphincterotomy twenty years ago (18) for a patient presenting with CP and an impacted calcified stone at the level of the papilla, most developments of endotherapy for CP started only ten years ago (10,19,20) with the availability of extracorporeal shock wave lithotripsy (ESWL) which provides millimetric disintegration of calcified calculy in nearly all cases and facilitates their extraction. Many centers are presently involved in the endoscopic management of CP, with good immediate technical results and data are now available for the long-term follow-up that can be compared with surgical series (21-27).

Methodology for endotherapy

The endoscopic treatment of CP has to be guided by the morphological informations obtained before ERCP, by various imaging techniques (plain film, MRCP or spiral CT).

For patients with mild or moderate CP in the Cambridge classification (type I A or B in our classification), the question is open to decide whether any decompression would be beneficial for a patient presenting with acute relapsing clinical attacks of pancreatitis. Only control trials may allow to give the answer of the long-term effectiveness of pancreatic sphincterotomy as the treatment of the earliest stage of primary CP. We think that the treatment of these patients remains currently experimented. It is possible that the routine use of DSMRCP might help, in the near future, to select those patients with the highest probability to benefit from endoscopic therapy.

For patients with type II CP (pseudocyst without gross abnormality of the MPD), one must be prepared to perform a cyst duodenostomy or a cyst gastrostomy after having recognized the bulging of the cyst against the upper GI tract. If the cyst has a relatively suitable size (< 5 cm) and communicates with the MPD, a pancreatic endoscopic sphincterotomy (EPS) combined with nasopancreatic drain placement is often sufficient to achieve cyst resolution.

Extracorporeal shock wave lithotripsy (ESWL)

Since most of the patients referred with severe CP of type III to V have embedded calculi obstructing the MPD. The principle in these cases is to remove stones and treat strictures is necessary. If calcified stones are present, ESWL may be performed as the first procedure before sphincterotomy. Good quality plain films of the pancreatic are taken in left and right oblique position are mandatory to decide of this preliminary treatment. Without previous ESWL, the deep cannulation of the MPD fails in 50% of these patients. On the other hand, ESWL is usually not necessary for patients with radiolucent stones. These “protein plugs” are usually friable and can be extracted immediately after sphincterotomy or they are spontaneously eliminated if their size is limited.

It is of major importance to use a lithotriptor using a focusing system including two X ray generators. The ultrasound localization of stones lacks precision and efficacy. The high quality of the fluoroscopy obtained in two axes at a 45° angulation (Lithostar, Siemens, Erlangen, Germany) is mandatory for small calculi and for stones of less calcified density. This is the key point for reaching a 99% success of disintegration. Analgesia using Midazolam and Meperidine is usually sufficient to perform the procedure but general anesthesia is sometimes necessary for less compliant patients and, in these cases, ESWIL and therapeutic ERCP may be performed consecutively. During ESWL, hundred SW per minute are delivered at an electric power of 19 KV during sessions of about 30 minutes with a mean required number of 1500 SW/stone. Quality of fragmentation is evaluated by fluoroscopic control. Multiple or very large stones sometimes require repeated ESWL sessions.

A Japanese group (28) applied ESWL without subsequent endoscopic approach in 32 patients with MPD stones. Complete disintegration was obtained in all cases with further ductal clearance in 24 patients, without the need for endoscopic extraction. Pain relief was obtained in 79% of the patients after a mean period of 44 months. Although this option is probably limited to patients without associated stricture, it deserves further investigations as a first line treatment for these patients.

Endoscopic pancreatic sphincterotomy (EPS)

It is the cornerstone technique of pancreatic endoscopy which finally provides access to the MPD (29). The aim of EPS in CP is not only to decrease the pancreatic duct pressure but mainly to facilitate the extraction of calculi. The EPS is performed at the major papilla for most of the patients and at the minor papilla for patients having a pancreas divisum anatomy but also for those having a "dominant" dorsal duct in whom the therapeutic access to the MPD is much easier through the accessory papilla.

The pancreatic sphincterotomy may be done directly by inserting a papillotome (most often over a guide wire) into the pancreatic duct and directing the cut (using pure cutting current to avoid further fibrosis) between 11 a 10 o'clock. This has the potential limitation of further difficult access to the bile duct and, mainly, of difficult evaluation of the extent of the pancreatic cut. Therefore, EPS is usually performed in 2 steps : first biliary papillotomy and then pancreatic septotomy. Endoscopic biliary sphincterotomy (EBS) as the first approach may also have the advantage to avoid the rare biliary complications occurring after primary EPS : some patients presented with jaundice the day after EPS probably due to some edema occurring at the level of the biliary sphincter. After biliary sphincterotomy, the pancreatic orifice is usually seen at 5 o'clock on the margins of sphincterotomy. Its orifice can often be better visualized by sucking a little bit the air into the duodenum, inducing its transient opening. When deep cannulation of the MPD has been achieved, pancreatic sphincterotomy or "septotomy" is performed using pure cutting current. The cut is done with the distal part of the cutting wire, at 12 o'clock, over a length of 5 to 8 cm (depending on the diameter of the MPD) to create the largest access.

For minor papilla sphincterotomy, a similar technique is used. The access to the duct is however sometimes more difficult, requiring the use of special cathether (cannula, needle, Wilson-Cook) or the help of an hydrophilic guide wire (Terumo). In very difficult cases, the technique of pancreatic rendez-vous can be chosen to gain access to the minor papilla (30).

EPS is sometimes the single endoscopic technique required in case of pancreatic stones impacted at the papilla or of relatively small floating stones or protein plugs into the MPD that can pass spontaneously to the duodenum. These settings are unusual and, most often, sphincterotomy has to be followed by stones fragments removal, stenting or both.

Extraction of pancreatic calculi

The ability to remove a stone is related to its size, degree of impaction and the presence of downstream stricture. Most often stones are very hard and impacted into the MPD wall or the emergence of secondary ducts. Therefore, ESWL is often mandatory prior to any attempt at extraction. It provides a millimetric fragmentation of the stones making the extraction much easier.

For stones fragments extraction, we usually use first a small dormia basket. It is passed opened into the pancreatic duct. When the stones are visible on the plain film, a good trick is to introduce the dormia basket without contrast medium injection. The localization of the residual fragments is easier and the basket can be "fiddled" at their level to trap them. Another trick is to pass the basket opened in the duct, turning it on its axis in the sheet, and perfusing the sheet with saline : we call this the "rotation perfusion", useful for elimination of small fragments. Finally, slightly inflated balloon catheters may be used in some cases but are of limited help in the pancreas.

If multiple sessions of endoscopy are necessary, a nasopancreatic catheter is left in place between the sessions, perfused with saline or drained according to the presence or not of an associated stenosis.

This can also be used as a clinical indication for the need of further pancreatic stenting. Indeed, if a patient tolerates, without pain, the perfusion of a nasopancreatic catheter, it highly suggests the absence of significant stricture. On the contrary, if perfusion of the NPC is painful, it has to be placed in drainage and further stones extraction and/or stenting must be considered (29).

Pancreatic stenting

It will be ultimately required in about 60% of patients with advanced CP. Stent implantation is decided on clinical (see above) and morphological basis. This latter is the presence of an MPD stricture in the head of the pancreas with upwards dilatation. The methods of insertion include EPS followed by bougienage (up to 11 F). If dilatation is difficult, a NPC can be left in place for 24 hours and makes easier further dilatation. Only large caliber (10 F) stents are used in this indication, their design is adapted to the pancreatic duct morphology. Usually, after stenting, pain disappearance correlates with MPD size reduction and is observed in a large majority of the cases (table 1). However, if plastic stents are able to relieve MPD stricture and to induce symptomatic improvement, their ability to calibrate the stricture and to maintain the patient free of symptoms after removal is only observed in a minority of patients after prolonged stenting. Therefore, stenting requires a careful follow-up and stent have to be exchanged either systematically (every 6 to 12 months) or "on demand" in compliant patients when a pain relapse occurs. This can be done on an ambulatory basis. At that time however, we have to choose with the patient between elective derivative surgery and repeated stent exchanges. Especially in these patients who require stenting, randomized trial agonist surgery would be ideal to define the best long life therapy (31), taking also into account the evolution of exocrine and endocrine functions. However,

the achievement of such a trial is difficult not only because of the low frequency of the disease but also because physicians refer patients to highly specialized centers specifically for endoscopic treatment and are not willing to consider random surgical decompression as a first attempt at pain relief.

Currently, its seems established that in severe CP, endoscopic MPD drainage can provide long-term pain relief with a minimal complication rate (Table 1), especially as far as major complications are considered. It could be considered as a first approach to painful severe pancreatitis and further studies will better define those patients who could benefit of elective surgery after initial endotherapy.

Endoscopic cystoenterostomy

Endoscopic cystoenterostomy must be considered as a part of the general management of severe CP (32-34) and must be associated with ductal decompression if required.

There is increasing experience with endoscopic drainage of cysts complicating CP and longer follow-up data are available. The drainage can be transmural or transpapillary if the cyst is communicating with the pancreatic duct and not clearly adjacent to the stomach or duodenum (35,36). It hab been suggested (37,38) that, when the cyst is accessible by transpapillary route, this approach has to be considered in first line. This seems reasonable except in the presence of ductal disruption occurring in the setting of severe CP (39) where both transmural drainage (to drain the residual secretion of the proximal pancreas) and transpapillary MPD decompression (to avoid relapse of the collection) are often required. It appears from these cumulative data that endoscopic approach can be considered in first line for pseudocysts adjacent to upper GI tract and/or communicating with the MPD, offering a definitive treatment in 65 to 93% of the cases. The recent availability of therapeutic endosonography has dramatically increased the possibilities for cystenterostomy in CP (40).

Conclusion

The indications of endoscopic management for CP are strictly limited to the severe types of pancreatitis where a ductal obstruction is morphologically demonstrated. This technique has gained success over the recent years and allows, with minimal complications, to avoid or postpone surgery, the indication of which might become better defined and the patient more carefully selected in the future. Endotherapy has the major advantage to be possibly repeated without an increase of morbidity. It can be proposed relatively early in the course of the disease, when pain access and morphological lesions of the MPD are evidenced. It must be considered as an iterative treatment which can be adapted to the successive problems occurring along the course of a chronic disease. It is highly probable that, with the development of non invasive techniques such as MRCP, it will become unuseful and unethical to perform ERCP just for imaging the biliary and pancreatic ducts and pancreatic endotherapy will become the single justification to gain endoscopic access to the pancreas.

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