Complications of endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy: Diagnosis, management and prevention

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ABSTRACT
Endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy are carried out for a variety of biliary-pancreatic diseases. These procedures were earlier performed at only a handful of tertiary centres in India. However, of late, they are being performed at several centres and even smaller clinics. Although, endoscopic sphincterotomy is one of the most commonly performed endoscopic procedure, there are no data on the number of procedures performed each year in India. It is estimated that in the USA alone more than 200,000 procedures are performed each year. The procedure has the dubious distinction of being considered as one of the most hazardous of all endoscopic procedures and is associated with a small but significant morbidity and mortality. The immediate complications of endoscopic sphincterotomy include pancreatitis, haemorrhage, perforation and cholangitis in addition to those associated with the use of sedation and anaesthesia. There are also reports of the long term adverse effects of the destruction of the sphincter of Oddi. There is also controversy as to what should be the minimum requirements for training and who should be allowed to perform these procedures.


INTRODUCTION
The papilla of Vater was first cannulated more than 30 years ago and it has been more than a quarter of a century since endoscopic sphincterotomy (ES) was introduced. In these 25 years, a large number of patients have benefited from its use and have been spared the morbidity and mortality (apart from the lower cost) associated with surgery. Endoscopic sphincterotomy is one of the most commonly performed endoscopic procedures. Although there are no data on the number of procedures performed each year in India, it has been estimated that in the USA alone, more than 200,000 procedures are performed each year.

MAGNITUDE OF THE PROBLEM
Despite its extensive use, ES and its modified version, ‘the pre-cut sphincterotomy’ is associated with complications. This review focuses on these complications, their management and prevention. Advances in recognizing and managing complications of ES have been facilitated by the standardized outcome-based definitions of complications proposed by Cotton and the recent report of large multicentre cohort studies using multivariate analyses. A diagnostic endoscopic retrograde cholangiopancreatography (ERCP) has complication rates of 5%–6% while therapeutic ERCP has complication rates of 4%–10%. The respective mortality rates are 0.01%–0.04% and 0.07%–0.1%. The lack of audit leads to the absence of any reliable data on the magnitude of the complications and their outcome in India. Studies from the West are mostly from established centres. Although there are several established centres in India, a large number of procedures are performed at smaller centres. Also, endoscopists in India often start performing the procedures after attending a couple of endoscopy workshops.

The short term or immediate complications of ES, such as pancreatitis, haemorrhage and perforation, occur in 10% of patients undergoing this procedure. Unfortunately, most of the studies on complications of ERCP/ES are retrospective and, therefore, have limited value. In addition, these studies, by nature of their design, cannot detect delayed complications of ERCP/ES.

In a prospective multicentre study of 17 centres in the USA and Canada, the overall complication rate of ES was 10%. The complication rate was high (22%, severe complications 4%) when ES was performed in patients with sphincter of Oddi dysfunction (SOD). In contrast, it was low (5% with no severe complications) when it was performed for removal of common bile duct stones in association with laparoscopic cholecystectomy.

Mortality from a complication of ES usually occurs from aggravation of the underlying disease. In the study by Freeman et al., the overall 30-day mortality, mostly due to progression of the underlying disease, was 2.3%. Deaths attributable to the procedure occurred in 0.4% of patients. The most common cause of mortality attributable to the procedure was cardiopulmonary complication due to sedation or anaesthesia.

PANCREATITIS
Post-ERCP and post-ES pancreatitis occur in 0%–39.5% of patients. The wide variation is because of the design of the studies (prospective or retrospective) and different definitions of pancreatitis. However, most prospective studies have observed pancreatitis in 5%–7.6% of patients. The definition of post-ES pancreatitis has been varied. The commonly used definition is post-procedure new or worsened abdominal pain with an amylase level three times the normal value more than 24 hours after the procedure, requiring more than one night’s stay in the hospital. The severity is graded by the length of hospital stay and the need
for radiological or surgical intervention. Most post-ES pancreatitis is mild in nature, but severe pancreatitis also occurs and may result in serious morbidity and mortality.

Risk factors
Several mechanisms have been proposed for the occurrence of post-ERCPIES pancreatitis. These include mechanical, chemical, enzymatic, hydrostatic, microbiological and thermal injuries to the pancreas. In the study by Freeman et al., five risk factors were identified: two linked to patients (SOD and younger age) and three linked to the endoscopic technique (difficult cannulation, higher number of injections of contrast medium into the pancreatic duct and the use of ‘pre-cutting’ technique). However, SOD was the strongest independent risk factor. Of interest was the observation that the endoscopist’s technical skill and experience was not associated with a lower incidence of pancreatitis (5.5% v. 5.3%).

Elderly patients are less likely to develop pancreatitis due to a decline in the pancreatic exocrine function with ageing; a 30-year-old patient is twice more likely to develop pancreatitis following ERCPIES compared to a 70-year-old patient.

Hydrostatic injury due to over-injection of contrast medium is considered an important risk factor. Pancreatitis is more likely if there is acinarization of the pancreas. Appearance of contrast in the parenchyma has been considered a risk factor. However, Freeman et al. did not observe this to be a risk factor. Repeated contrast injection into the pancreas is usually associated with difficult cannulation which is by itself an important independent risk factor for the development of pancreatitis. Non-ionic contrast materials have not been found to lower the incidence of pancreatitis.

Bile duct diameter has also been used as a predictor of pancreatitis. However, most studies which have noted a smaller bile duct diameter to be associated with pancreatitis had a relatively higher proportion of patients with SOD. The diameter of the duct is, therefore, not a predictor of pancreatitis when ES is performed for other indications.

Pre-cut sphincterotomy and pancreatitis
It is not clear whether or not pre-cutting the sphincter increases the risk of pancreatitis or merely reflects the problem of difficult cannulation. Several series from leading centres did not observe an increased risk. However, in the study by Freeman et al. on multivariate analysis, the use of the pre-cut technique independently increased the risk of pancreatitis by a factor of four. When the pre-cut technique was used in patients with SOD, pancreatitis occurred in 35% of patients, with 24% developing severe complications resulting in one death. Placement of a pancreatic stent before, but not after, pre-cut sphincterotomy reduces the risk of pancreatitis.

SPHINCTER OF ODDI DYSFUNCTION
Sphincter of Oddi dysfunction is an independent risk factor for the development of pancreatitis, which is independent of the technical difficulties encountered during the procedure. Severe pancreatitis may ensue even after cholangiography without filling of the pancreatic duct. Manometry for SOD was considered a risk factor for the development of pancreatitis. However, newer manometry catheters have an aspirating port through which the perfused material is aspirated resulting in a lower rise in the pancreatic ductal pressure. Biliary manometry alone seldom results in inadvertent perfusion of the pancreas, and appears to contribute little to the risk of pancreatitis. Similar observations were made more recently, where it was observed that the rate of pancreatitis was similar in patients who underwent ES empirically compared to those who underwent the procedure after manometry. Tarnasky et al. have shown that the basic fault lies in a hypertensive pancreatic sphincter. Patients with SOD and pancreatic sphincter hypertension were 10 times more likely to develop post-ERCPIES pancreatitis compared to those on whom manometry was normal. They also observed that those with a smaller distal bile duct diameter were three times more likely to develop pancreatitis compared to those with larger ducts.

Thermal injury
There is little, if any, additional risk of pancreatitis in patients undergoing an ES in addition to ERCP. However, the use of a pure cutting current (as opposed to the use of a blended current), reduces the likelihood of hyperamylasaemia and clinical pancreatitis. The use of a bipolar current for sphincterotomy has also been shown to provide this benefit.

Prevention of post-ERCPIES pancreatitis
Post-ERCPIES hyperamylasaemia occurs in up to 70% of patients. Some of these patients also develop clinical pancreatitis. Several antisecretory and antiprotease agents have been used to prevent this complication. Aprotinin, calcitonin, glucagon, nifedipine, corticosteroids, somatostatin and octreotide have shown some promise in lowering the incidence of hyperamylasaemia but have not shown any definite benefit in preventing clinical pancreatitis. Gabexate mesilate, a synthetic low-molecular weight protease inhibitor with no antigenicity reduces post-ERCPIES pancreatic enzyme levels. In a multicentre study, an intravenous (i.v.) infusion of the drug given 30–90 minutes before ERCP/ES and continued for an hour afterwards, significantly reduced the rise in pancreatic enzymes and pancreatic pain. The incidence of pancreatitis was 7.6% in the placebo group as compared to 2.4% in the group that received the drug. The drug also reduced the severity of pancreatitis.

To prevent pancreatitis, attention to technical details is helpful. The cannulation of the bile duct should be achieved as quickly as possible with minimal or no trauma to the sphincter. If biliary cannulation is difficult or unsuccessful after three attempts, it should be abandoned and attempted on another day, as persistent attempts at cannulation would result in more trauma and increase the likelihood of pancreatitis. The pre-cut technique should be used with caution and probably only by those experienced in the technique, especially if SOD is suspected. In patients with a high risk of pancreatitis, pancreatic stenting and gabexate mesilate may be tried in an attempt to reduce this complication.

Management of post-ERCPIES pancreatitis
The management of post-ERCPIES pancreatitis is no different from acute pancreatitis due to any other cause. Mild episodes may be managed by stopping oral intake and giving i.v. fluids. These usually resolve in a few days. Severe attacks need prolonged hospitalization with total parenteral nutrition and may require surgical intervention. If the patient is sick after an ES, a CT scan should be performed to differentiate pancreatitis from perforation, which can also occur along with pancreatitis.

HAEMORRHAGE
Bleeding is one of the common and feared complications of ES. The reported rate of haemorrhage varies considerably. A small amount of bleeding is commonly seen after an ES but requires no
intervention. If blood loss is so severe that blood transfusion is required, other interventions and hospitalization may be needed. Bleeding is seen in 10%–13% of patients undergoing ES. Clinically significant bleeding is defined as malaena or haematemesis with a fall in the haemoglobin level by at least 2 g/dl, or bleeding requiring secondary intervention such as blood transfusion or endoscopic therapy. It may manifest between 1 and 10 days after ES. Delayed bleeding accounts for nearly half of all post-ES haemorrhage. Fortunately, haemorrhage appears to be less common in recent reports compared to the earlier ones.

**Risk factors**
In the study by Leung et al., the risk factors for immediate bleeding after ES were an impacted stone at the ampulla, periampullary diverticulum and extension of a previous sphincterotomy. In the study by Freeman et al., the independent risk factors for haemorrhage included any degree of bleeding during ES, presence of coagulopathy or thrombocytopenia, initiation of anticoagulation therapy within 3 days of ES and low case-volume of the endoscopist (not more than one ES per week). Bleeding was noted primarily in patients with stones and was more common in those with large dilated bile ducts. However, bleeding was not related to the length of the ES or enlarging of a previous sphincterotomy.

**Prevention**
Prophylactic epinephrine injection into the apex and wall of the ES incision prevents post-ES haemorrhage. Even in patients with coagulopathy, a safe ES can be performed by prophylactic injection of the papilla with epinephrine or a sclerosing agent. Bleeding can also be prevented to a large extent by careful preparation of the patient, including obtaining a history of bleeding disorders, detection and correction of coagulopathies, withholding anticoagulant medication for at least 3 days after ES and most importantly, by cutting the sphincter slowly in a step-wise manner. In this regard the ENDO CUT (ERBE Elektromedizin GmbH, Tubingen, Germany) is a development whose more frequent use should lead to safer ES. Attempts have also been made to identify vascular abnormalities in the papilla using a Doppler ultrasonic probe.

**Management of post-ES bleeding**
Despite all the above-mentioned techniques and precautions post-ES haemorrhage does occur. A large number of bleeds stop spontaneously. However, if serious bleeding occurs, it is important to keep the endoscopic view of the papilla clean by flushing with water and performing suction, so that endoscopic interventions are possible. The sphincterotomy should be kept in place and in such a situation the long-nosed sphincterotomes and the wire-guided ones are more useful. If the bleeding appears to be venous in origin, monopolar coagulation may be applied to the apex of the incision using the sphincterotome. However, if the bleeding is arterial, cutting a few more millimeters may allow an incompletely severed artery to be severed completely, thus allowing its ends to retract and stop the bleeding. It is also useful to keep access to the bile duct open by either keeping the wire-guided sphincterotome or a guidewire in the bile duct. This will help in cannulation of the bile duct after the bleeding has been controlled, allowing introduction of a stent or nasobiliary catheter. If access is not maintained it may be very difficult to get into the bile duct after bleeding has been controlled due to oedema and swelling of the papillary area and the presence of fresh fibrin clots. If haemostasis is not achieved by these means, it is wise to quickly resort to injection therapy.

Injection therapy for arresting post-ES haemorrhage is similar to that used for the control of non-variceal upper gastrointestinal bleeding. Several substances have been used including epinephrine, polidocanol and their combination. However, it appears that, as in upper gastrointestinal non-variceal bleeding, it is the tamponade effect that is important in arresting the bleeding. Injection therapy eventually stops the bleeding in virtually all patients, without any major complication. If this therapy is required to arrest haemorrhage, it is prudent to achieve biliary drainage by inserting a nasobiliary catheter to prevent occurrence of cholangitis because of oedema, swelling and presence of blood clots in the bile duct. Definitive endoscopic therapy such as removal of bile duct calculi should be postponed and performed 48 hours later. If injection therapy fails to arrest the bleeding, and the expertise is available, angiographic treatment may be tried. More recently, haemoclips have been placed to check post-ES bleeding. However, one must be careful that the clips do not block the opening of the pancreatic duct and result in acute pancreatitis. Finally, if the bleeding persists, the patient should be operated.

**PERFORATION**
Perforations during ES are usually retroperitoneal in location; intraperitoneal perforations are rare. These result from an extension of the incision beyond the intramural bile duct or the pancreatic duct. It is seen in <1% of procedures and was observed in only 0.3% of patients by Freeman et al. It can be recognized during the procedure when there is a spillage of contrast, or air is seen beyond the confines of the bile duct and duodenum. A CT scan may be required to differentiate acute pancreatitis from a perforation.

**Risk factors**
Due to the low incidence of perforation, the risk factors for perforation are not well defined. The risk appears to be increased in patients with SOD, those with a Billroth II anastomosis and when a needle–knife sphincterotome is used. The incision in these three situations is not well controlled and therefore the chances of perforation are higher. It is also likely to occur if the incision is made beyond the 2 o'clock position.

**Management**
Management depends on the degree of perforation. Asymptomatic perforations are common and may not be detected unless a routine CT scan is performed. Minor perforations can be managed by keeping the patient fasting, passing a nasogastric or nasoduodenal tube, giving i.v. fluids and antibiotics. However, a surgical colleague should always be involved in the decision-making from the very beginning. If there is no clinical improvement or there is deterioration, the patient should be operated.

**SEPSIS, CHOLANGITIS AND CHOLECYSTITIS**
Biliary sepsis is a feared complication of ERCP/ES. Although it occurs in only 0.54%–0.8% of patients, it is associated with a high mortality rate of 8%–20%.

Cholangitis and cholecystitis are known complications of ERCP/ES, which are sometimes difficult to differentiate from each other. Cholangitis occurs primarily because of failed or incomplete biliary drainage and the use of combined percutaneous
and endoscopic procedures. Sepsis can occur in the pancreas if a pseudopancreatic cyst is filled with contrast medium and is not drained. The patient develops high fever with chills and hypotension may also ensue. Elderly patients may develop mental obtundation and hypotension.44

Cholecystitis can also occur after ERCP/ES. Both early and late cholecystitis occur more often if the gallbladder is not removed after ES.54 Cholecystitis and recurrent stones are common if the intact gallbladder has calculi. In a multicentre study, early cholecystitis occurred in 1% of patients with an intact gallbladder undergoing ES for bile duct stones.6 Cholecystitis can rarely occur after placement of a biliary endoprosthesis, when the gallbladder is filled with contrast and the stent blocks the opening of the cystic duct. The exact mechanism of post-ES cholecystitis is not clear. However, contamination of the gallbladder by contrast material, duodenobiliary reflux and bactobilia may be responsible.

Prevention
It is important that a diagnostic ERCP be performed for established indications. If biliary drainage cannot be achieved or is doubtful, in an obstructed biliary system, ERCP should not be performed. In such a situation, magnetic resonance cholangiopancreatography (MRCP) may be used, if available. It is also wise to aspirate the bile before injection of the contrast medium so that the intrabiliary pressure does not rise too much.

The role of prophylactic antibiotics in the prevention of cholangitis is not clear. While several studies have reported a reduction in bacteraemia following the use of prophylactic antibiotics, only a few have observed a reduction in the incidence of clinical sepsis.46,47 However, the European Society of Gastrointestinal Endoscopy and the American Society for Gastrointestinal Endoscopy recommend antibiotic prophylaxis in patients undergoing ERCP for known or suspected biliary obstruction.

COMPLICATIONS OF PRE-CUT SPHINCTEROTOMY
Pre-cut sphincterotomy is a controversial area. Some experts advocate that it is a dangerous technique29 while others feel that it is safe.49 Therefore, the technique should be used by an experienced endoscopist.

The reported complication rates of pre-cut sphincterotomy vary from 5%25 to 20%—30%.5,30 These occur much more often in patients with SOD. In the study by Freeman et al.,4 when performed by experienced endoscopists, ductal access was achieved in a higher number of patients and there were fewer serious complications compared to endoscopists with lesser experience.

LONG TERM COMPLICATIONS
Apart from the above-mentioned short term complications, it is now evident that patients undergoing ES may return after months or years with symptoms. In recent years, the long term complications and sequelae of ES have been described. These occur due to a permanent destruction of the sphincter. After a follow up of 6—11 years, Hawes et al. observed that 13% of their patients who had undergone ES, developed biliary complications such as stenosis, new stones and cholangitis.51 However, Prat et al. observed symptoms attributable to sphincterotomy in only 6% of their patients.52 In another study, 24% of patients developed new bile duct stones.53 Recurrent pancreatitis (because of stenosis of the pancreatic duct opening) has also been described as a long term complication of ES.54

The presence of gallstones in an in situ gallbladder has been observed to make matters worse in the long run. Wojtun et al. found that 44% of their patients, with in situ stone-bearing gallbladders required surgery within 5 years of undergoing ES.55

In a recent study, a bile duct diameter >15 mm and an in situ gallbladder have been recognized as pre-ES conditions associated with recurrence of biliary symptoms on long term follow up. Large duct diameter and periamputral diverticulae were also associated with stone formation.56 In another study, on an average follow up of 122 months, recurrent bile duct stones were observed in 12.3% of patients. Seven of the 32 patients with stones in the gallbladder developed cholecystitis (one patient developed new stones). Of importance was the finding that cholecystitis did not occur in any of the 88 patients who did not have stones in the gallbladder.57 It appears that patients undergoing ES should have their gallbladder removed at the earliest. This would at least prevent cholecystitis. However, a recent study did not find any benefit of cholecystectomy as far as recurrent biliary symptoms were concerned.58

To decrease or eliminate the long term complications of ES, endoscopic papillary balloon dilatation has been proposed as an alternative method for removing bile duct stones. The results have been good59 but have been questioned.60 We have used balloon dilatation of the sphincter for removal of common bile duct stones as well as Ascaris lumbricoides; the latter in the hope that re-invasion will be prevented if the sphincter is not cut.61 However, the procedure is cumbersome and time-consuming. A multicentre study from the USA, comparing ES and balloon sphincteroplasty for removal of bile duct stones did not advocate balloon dilatation because of its complications.62 The long term complications of balloon dilatation have not been studied and, in our opinion, till a few well conducted studies show a clear benefit of balloon dilatation over ES, it should not be adopted as the procedure of choice for removal of bile duct stones.63

WHO SHOULD PERFORM AN ERCP/ES?
This is an important issue as complications are more frequent in the hands of endoscopists who perform ERCP occasionally compared to those who perform the procedure more frequently. In the study by Freeman et al.,60 complication rates were lower in a private practice set-up compared to those in specialized centres, probably reflecting the fact that these centres carry out more complicated procedures. However, the experience of the endoscopist is most important. On multivariate analysis, a lower volume of ES was one of the factors leading to a higher complication rate. Jowell et al. have suggested that trainees require 180—200 procedures to achieve a 70% success rate for deep bile duct cannulation.64 Similar data from India are not available. The results would be optimal if fewer endoscopists performed more ERCPs.65

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