World Journal of Gastrointestinal Pathophysiology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4291/wjgp.v5.i1.1

World J Gastrointest Pathophysiol 2014 February 15; 5(1): 1-10
ISSN 2150-5330 (online)

TOPIC HIGHLIGHT

WJGP 5th Anniversary Special Issues (3): Pancreatitis

Prevention of post-ERCP pancreatitis

Lin-Lee Wong, Her-Hsin Tsai

Lin-Lee Wong, Her-Hsin Tsai, Department of Gastroenterology, Castle Hill Hospital, HEY NHS Trust and Hull York Medical School, Cottingham HU165JQ, United Kingdom
Author contributions: Wong LL performed the searches and prepared the original draft; Tsai HH edited and supplemented the manuscript.
Correspondence to: Dr. Her-Hsin Tsai, Department of Gastroenterology, Castle Hill Hospital, HEY NHS Trust and Hull York Medical School, Hull Royal Infirmary, Anlaby Road., Hull, East Riding of Yorkshire, Cottingham HU165JQ, United Kingdom. hhtsai@doctors.org.uk
Telephone: +44-1482-875875 Fax: +44-1482-622159
Received: October 31, 2013 Revised: November 21, 2013
Accepted: December 12, 2013
Published online: February 15, 2014

Abstract

Post-procedure pancreatitis is the most common complication of endoscopic retrograde cholangio pancreatography (ERCP) and carries a high morbidity and mortality occurring in at least 3%-5% of all procedures. We reviewed the available literature searching for "ERCP" and "pancreatitis" and "post-ERCP pancreatitis". in PubMed and Medline. This review looks at the diagnosis, risk factors, causes and methods of preventing post-procedure pancreatitis. These include the evidence for patient selection, endoscopic techniques and pharmacological prophylaxis of ERCP induced pancreatitis. Selecting the right patient for the procedure by a risk benefits assessment is the best way of avoiding unnecessary ERCPs. Risk is particularly high in young women with sphincter of Oddi dysfunction (SOD). Many of the trials reviewed have rather few numbers of subjects and hence difficult to appraise. Meta-analyses have helped screen for promising modalities of prophylaxis. At present, evidence is emerging that pancreatic stenting of patients with SOD and rectally administered non-steroidal anti-inflammatory drugs in a large unselected trial reduce the risk of post-procedure pancreatitis. A recent meta-analysis have demonstrated that rectally administered indomethecin, just before or after ERCP is associated with significantly lower rate of pancreatitis compared with placebo [OR = 0.49 (0.34-0.71); *P* = 0.0002]. Number needed to treat was 20. It is likely that one of these prophylactic measures will begin to be increasingly practised in high risk groups.

Key words: Acute pancreatitis; Endoscopic retrograde cholangio pancreatography

Core tip: Select patients carefully, and give high risk patients rectal indomethacin.

Wong LL, Tsai HH. Prevention of post-ERCP pancreatitis. *World J Gastrointest Pathophysiol* 2014; 5(1): 1-10 Available from: URL: http://www.wjgnet.com/2150-5330/full/v5/i1/1.htm DOI: http://dx.doi.org/10.4291/wjgp.v5.i1.1

INTRODUCTION

Pancreatitis is the most common complication of endoscopic retrograde cholangio pancreatography (ERCP) and carries a high morbidity and mortality[1,2]. There is a 3%-5% incidence of this complication occurring, as shown in various large clinical studies[2-4]. A systematic survey of 21 studies involving 16855 patients (1987-2003) found a 3.5% occurrence of post-ERCP pancreatitis. 0.4% of patients had severe pancreatitis with 0.11% deaths[5].

Predicting pancreatitis after ERCP can be very difficult but there have been numerous studies that have identified factors that increase the risk for post-ERCP pancreatitis. These can have a cumulative effect when multiple factors are present. There are multiple procedures and pharmacological interventions that have been studied to prevent post-ERCP pancreatitis. This article describes these some of these interventions and includes the latest studies.

Table 1 Consensus definition of post-endoscopic retrograde cholangio pancreatography pancreatitis

Severity of pancreatitis	Definition
Mild	Clinical pancreatitis, amylase at least 3 × normal > 24 h after procedure, requiring unplanned admission or prolongation of planned admission to 2-3 d
Moderate	Hospitalisation of 4-10 d
Severe	Hospitalisation of > 10 d, haemorrhagic pancreatitis, pancreatic necrosis or pseudocyst, or need for intervention (percutaneous drainage or surgery)

DIAGNOSIS OF POST-ERCP PANCREATITIS

Post-ERCP pancreatitis is defined as acute pancreatitis occurring following an ERCP procedure. This consists of the development of new pancreatic-type abdominal pain associated with hyperamylasemia of three times the upper-limit of normal, occurring 24 h after an ERCP requiring hospital admission. Severity of post-ERCP pancreatitis is graded based on length of hospital admission and need for intervention. It can be divided into mild, moderate and severe (Table 1), based on a consensus definition[6].

Freeman *et al*[1] studied the complication rate that occurred in 2347 patients undergoing endoscopic biliary sphincterotomy. Acute pancreatitis occurred in 127 patients (5.4%). Mild post-ERCP pancreatitis occurred in 53 (2.3%), moderate in 65 (2.8%) and severe in 9 (0.4%). Of the latter, one died of retroperitoneal perforation, one required percutaneous drainage of a pseudocyst and three required surgical drainage.

RISK FACTORS FOR POST-ERCP PANCREATITIS

Many studies have looked into factors that increase the risk of post-ERCP pancreatitis. These can be divided into patient-related risk factors, endoscopist-related risk factors and procedure-related risk factors. Table 2 summarises the general consensus of risk factors for post-ERCP pancreatitis[3,7,8]. These factors should alert the endoscopist to take special precautions in preventing post-ERCP pancreatitis[9]. In addition, there is a cumulative effect for patients with multiple risk factors. For example, a young woman with suspected sphincter of Oddi dysfunction, normal bilirubin, difficult cannulation and absence of bile duct stones has an associated increased risk of pancreatitis of 40%[10,11].

There are other factors that have been identified which require further studies. One retrospective study identified taking pancreato-toxic drugs (oestrogen, azathioprine, valproic acid, mesalazine, morphine derivatives and prednisone) increased the occurrence of post-ERCP pancreatitis (OR = 3.7)[12].

Another retrospective study of 506 patients identified angiotensin receptor blockers and smoking as independent risk factors for post-ERCP pancreatitis[13] whereas a recent case-control study of 6505 patients identified smoking and chronic liver disease as factors that reduced the risk of post-ERCP pancreatitis[14].

Table 2 Risk factors for post-endoscopic retrograde cholangio pancreatography pancreatitis

Risk factors for post ERCP pancreatitis	
Patient-related factors	Younger age
	Female sex
	Normal serum bilirubin
	Recurrent pancreatitis
	Prior ERCP-induced pancreatitis
	Sphincter of Oddi dysfunction
Endoscopist-related factors	Difficult cannulation
	Pancreatic duct injection
	Sphincter of Oddi manometry
	Precut sphincterotomy
	Pancreatic sphincterotomy
	Minor papilla sphincterotomy
Procedure-related factors	Trainee involvement in procedure

ERCP: Endoscopic retrograde cholangio pancreatography.

Testoni *et al*[7] conducted a large prospective multicentre trial (total of 3635 ERCP procedures) and showed that the rate of post-ERCP pancreatitis did not differ between high- and low-volume centres (3.9% *vs* 3.1%). However, the high-volume centres treated a larger proportion of patients at high-risk of pancreatitis and did a significantly greater number of difficult procedures. In another large multicentre prospective trial (2347 patients), case volume did not affect incidence of pancreatitis although the multivariate model indicated low case volume was independently associated with higher overall rate of complications[1].

Operator experience has been difficult to demonstrate as a risk factor for post-ERCP pancreatitis due to the heterogeneity of studies with variable case volume and case mix. One French study showed no risk associated with operator inexperience[14].

In the multivariate analysis of a randomised controlled multicentre study by Cheng *et al*[8], trainee involvement in the procedure was found to be a risk factor (OR = 1.5) for development of post-ERCP pancreatitis.

Biliary stenting was found to be an independent risk factor for pancreatitis in a single-centre prospective study by Wilcox *et al*[15]. The commonest indication for stent placement was pancreaticobiliary malignancy (37% of patients). Another retrospective study on patients undergoing ERCP for malignant biliary obstruction found the frequency of post-ERCP pancreatitis was significantly higher with placement of self-expanding metal stents compared with a plastic stent[16].

MECHANISM OF POST-ERCP PANCREATITIS

There are various mechanisms proposed in the pathogenesis of post-ERCP pancreatitis[17,18]. These include: (1)

mechanical injury from instrumentation of papilla and pancreatic duct; (2) thermal injury following application of electrosurgical current during biliary or pancreatic sphincterotomy; (3) hydrostatic injury - following injection of contrast medium into the pancreatic duct of from infusion of water or saline solution during sphincter manometry; (4) chemical or allergic injury following injection of contrast medium into the pancreatic duct; (5) enzymatic injury with intraluminal activation of proteolytic enzymes; and (6) infection from contaminated endoscope and accessories.

Preventive measures are aimed at interrupting the cascade of events resulting in the premature activation of proteolytic enzymes, autodigestion and impaired acinar secretion with subsequent clinical manifestations of local and systemic effects of pancreatitis[17].

PREVENTION OF POST-ERCP PANCREATITIS

ERCP technique

Cannulation: Various methods to ease cannulation of the bile duct and reduce trauma have been studied with view of reducing the risk of post-ERCP pancreatitis.

In general, guidewire technique to facilitate bile duct cannulation has been shown to improve primary biliary duct cannulation but incidence of post-ERCP pancreatitis has not been consistently shown to be reduced by this technique.

In a meta-analysis of five randomised controlled trials (RCTs), guidewire cannulation was shown to lower post-ERCP pancreatitis (rates 0%-3%) compared to standard contrast-injection method (rates 4%-12%) and increase primary cannulation rates compared to the standard method (OR = 2.05)[19].

A Cochrane meta-analysis of 12 RCTs (3450 patients) similarly found that post-ERCP pancreatitis incidence was lower in the wire-guided cannulation (WGC) group (3.5%) compared to contrast-assisted cannulation technique (6.7%) and primary cannulation rates were higher in the WCG group (84% *vs* 77%, RR = 1.07). However, WGC may not prevent post-ERCP pancreatitis in patients with suspected Sphincter-of-Oddi dysfunction and unintentional pancreatic duct guidewire cannulation[20].

In contrast, a recent crossover multicentre randomised controlled trial involving 322 patients compared wire-guided biliary cannulation with conventional cannulation technique - the trial found that the incidence of post-ERCP pancreatitis was similar in both groups (6.1% *vs* 6.3%, $P = 0.95$). Primary biliary cannulation rate was similar for both groups as well (83% *vs* 87%)[21].

Another prospective trial involving 1249 patients did not find any significant difference in the rates of post-ERCP pancreatitis with the guidewire technique compared with sphincterotome and contrast injection method[22].

Many advanced endoscopists use a hybrid of the two techniques (wire probes with minimal contrast to outline distal duct course) which avoid dissections or passage of the guidewire out of a side branch of the pancreatic duct. This hybrid technique however has not been formally evaluated[23].

Electrocautery: Thermal injury following application of electrosurgical current during biliary or pancreatic sphincterotomy is thought to contribute to causing post-ERCP pancreatitis. A number of studies have been conducted to compare pure cut current with blended current and bipolar *vs* monopolar electrocautery. These have produced mixed results. A meta-analysis of four trials (total: 804 patients) comparing pure current to mixed current in patients who underwent sphincterotomy found no significant difference in the rates of pancreatitis. Pure current was however associated with more episodes of bleeding, primarily mild bleeding[24]. The use of sequential combination of pure cut and blended current for sphincterotomy was studied in 142 patients - this did not change the rate of post-ERCP pancreatitis but did cause less visible bleeding than pure cut alone[25].

Pancreatic stenting: Pancreatic duct obstruction or impaired pancreatic drainage from papillary oedema or spasm of the sphincter of Oddi has been postulated to cause post-ERCP pancreatitis[17]. Numerous studies have looked into the prophylactic placement of a pancreatic stent to prevent post-ERCP pancreatitis. Due to their variability in indications for stenting, interventions and outcome measures - comparisons and conclusions can be difficult. A few trials have shown that pancreatic stent insertion reduces the rate and severity of post-ERCP pancreatitis after difficult cannulation, needle-knife precut, biliary sphincterotomy for sphincter of Oddi dysfunction (SOD) and manometry, pancreatic sphincterotomy, endoscopic ampullectomy and endoscopic balloon dilation[26-33].

A recent meta-analysis of randomised controlled trials (RCTs) comparing pancreatic stent placement and the subsequent incidence of post-ERCP pancreatitis enrolled 14 studies (total: 1541 patients). This found that pancreatic stent placement was associated with significant reduction of post-ERCP pancreatitis (RR=0.39, 95%CI: 0.29-0.53, $P < 0.001$) as compared with no stent placement. Subgroup analysis demonstrated that pancreatic stent placement was effective for both high-risk and mixed case groups[34].

Another meta-analysis by Choudhary *et al*[35] analysed eight RCTs (656 patients) and this showed that prophylactic pancreatic stents decreased the odds of post-ERCP pancreatitis (OR = 0.22; 95%CI: 0.12-0.38, $P < 0.01$) with an absolute risk difference of 13%.

Pancreatic stenting comes with some limitations. It is associated with complications such as stent-related ductal injury and strictures[36]. Many endoscopists and assistants are unfamiliar with the placement of pancreatic stents. In addition, unsuccessful stent placement can itself be associated with a risk of pancreatitis. Freeman *et al*[37] conducted a prospective study of 225 high risk ERCPs.

Table 3 Pharmacological agents studied according to postulated mechanism of action

Postulated mechanism of action	Agents
Interruption of inflam matory cascade	NSAIDs, steroids, interleukin-10, allopurinol, adrenaline spray, pentoxifylline, platelet-activating factor-acetylhidrolase, semapimod, aprepitant, risperidone
Reduction of pancreatic enzyme secretion	Octreotide, somatostatin, calcitonin
Inhibition of protease activity	Gabexate mesilate, heparin, ulinastatin, nafamostat, magnesium sulphate
Reduction of Sphincter-of-Oddi pressure	Nitroglycerin, nifedipine, botulinum toxin, lidocaine, secretin, phosphodiesterase inhibitor type 5
Prevention of infection	Antibiotics
Anti-oxidants	Beta-carotene, N-acetylcysteine, sodium selenite
Anti-metabolites	5-fluorouracil

NSAIDs: Non-steroidal anti-inflammatory drugs.

Pancreatitis occurred in two out of three (66.7%) patients in whom stent insertion failed *vs* 32 of 222 (14.4%) patients with successful insertion ($P = 0.06$).

Follow-up evaluation is necessary to ensure passage or removal of stent and placement can be technically difficult. The optimal timing for stent placement and duration for stent to remain in place is unknown. There is also variability in the type of stent used[17,33]. Short 5 French stents are easier to deploy and are more likely to migrate spontaneously compared with long 3 French stents. However, they do not confer a benefit in terms of pancreatitis risk reduction. The optimal duration for stents to remain in place is unknown. Chahal *et al*[38] compared the outcomes of a short straight 5 French stent without an inner flange with an unflanged long single pigtail 3 French stent. They found a significantly higher placement failure rate in the 3 French group (8.3% *vs* 0%, $P = 0.0003$), a higher spontaneous dislodgement rate in the 5 French group (98% *vs* 88% for 3 Fr, $P = 0.0001$) and a non-significant higher pancreatitis rate (14% *vs* 9%, $P = 0.3$).

Pharmacological prophylaxis

Since the introduction of ERCP, numerous studies have been carried out in the pursuit to discover the most effective pharmacological prophylactic agent against post-ERCP pancreatitis. These were done based on the postulated mechanisms of action through which post-ERCP pancreatitis occurred (Table 3)[39,40].

Interruption of inflammatory cascade (anti-inflammatory): Non-steroidal anti-inflammatory drugs: non-steroidal anti-inflammatory drugs (NSAIDs) have been studied for their inhibitory properties on phospholipid A2 (PLA_2) and prostaglandins, which lead to interruption of the inflammatory cascade of acute pancreatitis[41]. A Finnish group, Mäkelä *et al*[42] studied the in-vitro inhibition of PLA_2 in acute pancreatitis by 17 different pharmacological agents. They found that indomethacin was the most potent of the agents in inhibiting PLA_2 activity in the serum from patients with acute pancreatitis followed by diclofenac.

Murray *et al*[43] conducted a prospective, randomised, double-blind controlled trial involving 220 patients. In the twenty-four patients (11%) who developed acute pancreatitis, 7 had received 100mg diclofenac suppository given immediately after ERCP *vs* 17 who received placebo ($P < 0.05$). They concluded that rectal diclofenac given immediately after ERCP can reduce the incidence of acute pancreatitis.

Since then, three meta-analysis have been published, analysing the effect of NSAIDs in preventing post-ERCP pancreatitis. The results of each meta-analyses are as follows: (1) Elmunzer *et al*[44]: Four RCTs (912 patients) evaluating rectal NSAIDs (indomethacin or diclofenac) administration in the peri-procedure period were analysed. This found a significant reduced incidence of pancreatitis with pooled relative risk of 0.36. The pooled number needed to treat with NSAIDs to prevent one episode of pancreatitis was 15; (2) Dai *et al*[45]: Six RCTs (1300 patients) were analysed. These included the 4 RCTs in the above-mentioned meta-analysis as well as two additional trials. Two trials used rectal diclofenac, three used rectal indomethacin and one used oral diclofenac. The risk of pancreatitis was lower in the NSAID group than in the placebo group (OR = 0.46, $P < 0.0001$)[45]; and (3) Ding *et al*[46]: Meta-analysis of ten RCTs (2269 patients) showed that NSAIDs decreased the overall incidence of post-ERCP pancreatitis (RR = 0.57, $P = 0.007$) with an absolute risk reduction of 5.9% and number needed to treat: 17. In addition, NSAIDs use decreased the incidence of moderate to severe post-ERCP pancreatitis (RR = 0.46, $P = 0.002$). This meta-analyses included studies that were heterogenous in NSAIDs-type (indomethacin, diclofenac or valdecoxib) and route of administration. Rectal administration of NSAIDs was associated with a decreased risk of post-ERCP pancreatitis in all six trials that used this route while the other routes studied in 4 studies (oral, intramuscular, intravenous and intraduodenal) were not.

Rectal administration is the most effective route for NSAIDs in post-ERCP prevention. This is postulated to be due to wider bioavailability compared to oral route (with significant first-pass metabolism) and the quicker peak plasma NSAIDs concentrations (30 min for rectal route *vs* 2 h for oral route)[47,48].

All the trials showed no adverse effects from NSAIDs administration to patients. However, limitations to the meta-analyses were differences in pharmacological manipulation (timing, route of administration and choice of drug), inconsistent use of pancreatic stenting, inclusion of both high-risk and low-risk patients and differences in ERCP procedures (*e.g.*, number of cannulations, number of pancreatic duct injections, whether sphincterotomy was performed). In addition, different definitions of pancreatitis were used [some used 4 × upper limit of normal (ULN) hyperamylasemia while some used 3 × ULN with abdominal pain][44,45]

The latest multi-centre trial by Elmunzer *et al*[49] was carried out using a randomised, placebo-controlled and double-blind method. This compared rectal indomethacin *vs* placebo immediately after ERCP. A total of 602 patients were enrolled of which 82% were high-risk (suspected sphincter of Oddi dysfunction). Rectal indomethacin was found to significantly reduce the incidence of post-ERCP pancreatitis (9.2% *vs* 16.9%, $P = 0.005$).

A recent meta-analysis have demonstrated that rectally administered indomethacin, just before or after ERCP is associated with significantly lower rate of pancreatitis compared with placebo [OR = 0.49 (0.34-0.71); $P = 0.0002$]. Number needed to treat was 20. Moreover they found that in subgroup analysis, the difference remained unchanged for average-risk population [OR = 0.49 (0.28-0.85); $P = 0.01$] or in preventing severe PEP [OR = 0.41 (0.21-0.78); $P = 0.007$][50]. The European Society of Gastrointestinal Endoscopy published guidelines in 2010 with grade A recommendation for the administration of rectal diclofenac 100 mg or indomethacin immediately before or after ERCP as post-ERCP prophylaxis[51]. The United States and United Kingdom however have not yet come to a consensus regarding this.

The available evidence suggests that prophylactic rectal administration of NSAIDs should be used in high-risk patients due to its marked reduction in incidence post-ERCP pancreatitis. This will result in substantial medical and cost benefits.

Other anti-inflammatory agents: Glucocorticoids have been evaluated as a potential prophylactic agent in a few studies (intravenous and oral). Initial promising reports have been followed by five prospective controlled trials which have demonstrated its inefficacy in preventing post-ERCP pancreatitis[52-58]. Finally, a meta-analysis of six randomised controlled trials using intravenous or oral corticosteroids (total: 2448 patients) demonstrated that prophylactic corticosteroids did not reduce the incidence of post-ERCP pancreatitis[59].

Interleukin-10 is an anti-inflammatory cytokine that has been shown to limit the severity of acute pancreatitis in animal models. One initial study (144 patients, placebo-controlled) found the incidence of pancreatitis was reduced by a single IV dose given 30 min before ERCP (8% *vs* 24% in placebo)[60]. It was also effective for high-risk patients. However, two subsequent placebo-controlled trials (total 505 patients) did not demonstrate any efficacy[61,62].

Allopurinol has been studied for its inhibitory properties on oxygen-derived free radicals. Trials studying the effect of allopurinol on post-ERCP pancreatitis prevention have revealed conflicting results. Subsequent two meta-analyses of 10 RCTs (1554 patients and 1730 patients respectively) have concluded that allopurinol does not reduce post-ERCP pancreatitis and should be not recommended as a prophylactic agent[63,64].

Other agents studied (Adrenaline spray, pentoxifylline, platelet-activating factor acetylhidrolase, semapimod, aprepitant and risperidone) have either revealed discordant results or no effect on preventing post-ERCP pancreatitis[64-73].

Reduction of pancreatic secretion: Somatostatin and its synthetic analogue, octreotide are potent inhibitors of exocrine secretion of the pancreas. Various studies have been conducted using different dosing regimes (< 6 h, ⩾ 12 h or bolus). Andriulli *et al*[73] conducted a meta-analyses (16 studies) which concluded that somatostatin was ineffective in preventing post-ERCP pancreatitis. Two further controlled trials by Lee *et al*[74] and Chan *et al*[75] revealed conflicting results. Similar mixed results were found in studies using octreotide[76-78]. Therefore, somatostatin and octreotide are currently not recommended as a prophylactic agents.

Calcitonin has been studied and not been shown to have any prophylactic effect on pancreatic enzymes or complication rate[79,80].

Inhibition of protease activity: Protease inhibitors prevent activation of trypsin which is involved in the cascade of events leading to acute pancreatitis. Gabexate mesilate, nafamostat and ulinastatin have been studied in numerous studies. However, results of the trials have been conflicting. Some trials showed a benefit in reducing post-ERCP pancreatitis while others did not show any effect, especially in high-risk patients.

Seta *et al*[81] published a meta-analysis on 18 studies (4966 patients) evaluating the efficacy of protease inhibitors. This found that protease inhibitors showed a small risk reduction in ERCP-associated pancreatitis with high number needed to treat (34.5). Overall, the analysis concluded that there was no solid evidence to support the use of protease-inhibitors to prevent ERCP-associated complications.

A more recent meta-analysis by Yuhara *et al*[82] compared the effects of protease inhibitors and NSAIDs. This included 19 studies (nafamostat mesilate, $n = 4$ studies, NSAIDs, $n = 7$ studies and gabexate mesilate, $n = 6$ studies and ulinastatin, $n = 2$ studies). This found that nafamostat mesilate and NSAIDs had solid evidence for preventing post-ERCP pancreatitis (RR = 0.41 and RR = 0.58 respectively) while gabexate and ulinastatin were not associated with decreased risk of post-ERCP pancreatitis. These findings differed from the former meta-analysis by Seta *et al*[81] which did not distinguish between gabexate mesilate, ulinastatin and nafamostat mesilate.

Heparin has been studied for its anti-inflammatory properties with discordant results. A meta-analysis of four trials (1438 patients) demonstrated no benefit for prophylactic heparin in prevention of post-ERCP pancreatitis[83].

Magnesium sulphate (intravenous) is currently being studied as a calcium-antagonist and hence, a prophylactic agent against post-ERCP pancreatitis[84].

Reduction of sphincter-of-oddi pressure: Reducing sphincter of Oddi pressure would theoretically prevent development of post-ERCP pancreatitis.

Initial trials studying the effect of GTN (transdermal

or sublingual) showed promise[85,86] but three subsequent randomised trials demonstrated no significant preventive effect on post-ERCP pancreatitis[87-89].

Numerous other drugs have been studied with disappointing or conflicting results. These include nifedipine, botulinum toxin, lidocaine and phosphodiesterase inhibitor type 5[90].

Secretin causes relaxation of the Sphincter of Oddi and increases pancreatic secretion. Studies on secretin have revealed mixed results. In a German randomised trial studying the influence of secretin and gabexate-mesilate on ERCP-related complications, secretin was shown to have no effect on ERCP-induced hyperamylasemia[91]. On the other hand, Jowell *et al*[92] conducted a single-centre randomised placebo-controlled trial (869 patients) using intravenous secretin (16 μg) administered immediately before ERCP *vs* placebo. Secretin was found to decrease the incidence of pancreatitis (8.7% *vs* 15.1% in the placebo group, $P = 0.004$). Subgroup analysis revealed that secretin was highly protective against post-ERCP pancreatitis for patients undergoing biliary sphincterotomy (6/129 *vs* 32/132, $P < 0.001$).

Prevention of infection

Antibiotics: One old controlled study has evaluated the role of antibiotics on post-ERCP pancreatitis and found no effect on its incidence[93]. Another prospective randomised controlled trial involving 315 patients demonstrated that 2 g of ceftazidime administered intravenously 30 min before ERCP significantly reduced the incidence of post-ERCP pancreatitis (2.6% *vs* 9.4% in the control group, $P = 0.009$). However, this study was deemed of low-methodological quality due to the unclear allocation concealment (the control group received "no antibiotics" in place of placebo). Further studies are required before antibiotics can be recommended as a prophylactic agent against post-ERCP pancreatitis[94,95].

Anti-oxidants: Oxidant stress may be involved in the pathogenesis of post-ERCP pancreatitis. N-acetylcysteine and sodium selenite have both been studied in randomised controlled trials and was shown to not reduce the incidence of post-ERCP pancreatitis[96]. Beta-carotene was studied in a double-blind trial and did not reduce incidence of pancreatitis between the treatment and placebo group. However, there was some postulated protective effect of treatment with beta-carotene seen as there were no patients with severe pancreatitis, as compared to the placebo group (2.22%)[97].

A recent meta-analysis looked at of 11 randomised trials (3010 patients) using N-acetylcystein, selenite, beta-carotene, allopurinol and pentoxifylline. This concluded that anti-oxidant supplementation shows no beneficial effect on the incidence and severity of post-ERCP pancreatitis[98].

CONCLUSION

Selection of patients, good technique, and good aftercare remain the primary prevention of post-ERCP pancreatitis. Currently, rectal NSAIDs are the only pharmacological agents that have been shown to reduce the incidence of post-ERCP pancreatitis in especially in high-risk patients and is gaining wider acceptance. The other agents (protease inhibitors and anti-secretory agents) require larger multi-centre randomised trials that can control for multiple variables. ERCP techniques should be adapted according to the risk-profile of the patient. Guidewire technique eases primary biliary cannulation but has not been shown to reduce incidence of post-ERCP pancreatitis. Patient selection and stratifying risk in individual patients is vital in preventing post-ERCP pancreatitis. Manipulation should be minimised in high-risk cases. In addition, pancreatic stenting should be used in high-risk patients, particularly young female patients with suspected sphincter of Oddi dysfunction, difficult cannulation or history of post-ERCP pancreatitis.

REFERENCES

1 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/NEJM199609263351301]

2 **Cheon YK**, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, Lehman GA. Frequency and severity of post-ERCP pancreatitis correlated with extent of pancreatic ductal opacification. *Gastrointest Endosc* 2007; **65**: 385-393 [PMID: 17321236 DOI: 10.1016/j.gie.2006.10.021]

3 **Cotton PB**, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009; **70**: 80-88 [PMID: 19286178 DOI: 10.1016/j.gie.2008.10.039]

4 **Glomsaker T**, Hoff G, Kvaløy JT, Søreide K, Aabakken L, Søreide JA. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography. *Br J Surg* 2013; **100**: 373-380 [PMID: 23225493 DOI: 10.1002/bjs.8992]

5 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/j.1572-0241.2007.01279.x]

6 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]

7 **Testoni PA**, Mariani A, Giussani A, Vailati C, Masci E, Macarri G, Ghezzo L, Familiari L, Giardullo N, Mutignani M, Lombardi G, Talamini G, Spadaccini A, Briglia R, Piazzi L. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. *Am J Gastroenterol* 2010; **105**: 1753-1761 [PMID: 20372116 DOI: 10.1038/ajg.2010.136]

8 **Cheng CL**, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Lazzell-Pannell L, Rashdan A, Temkit M, Lehman GA. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006; **101**: 139-147 [PMID: 16405547 DOI: 10.1111/j.1572-0241.2006.00380.x]

9 **Kozarek RA**. ERCP economics. *Gastrointest Endosc* 1999; **49**: 660-662 [PMID: 10228274 DOI: 10.1016/

S0016-5107(99)70404-9]
10 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434 [PMID: 11577302 DOI: 10.1067/mge.2001.117550]
11 **Perney P**, Berthier E, Pageaux GP, Hillaire-Buys D, Roques V, Fabbro-Peray P, Melki M, Hanslik B, Bauret P, Larrey D, Blayac JP, Blanc F. Are drugs a risk factor of post-ERCP pancreatitis? *Gastrointest Endosc* 2003; **58**: 696-700 [PMID: 14595303 DOI: 10.1016/S0016-5107(03)02019-4]
12 **Li N**, Tieng A, Novak S, Fernandes A, Jalal PK, Akerman M, Sideridis K, Bank S. Effects of medications on post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreatology* 2010; **10**: 238-242 [PMID: 20484961 DOI: 10.1159/000279306]
13 **DiMagno MJ**, Spaete JP, Ballard DD, Wamsteker EJ, Saini SD. Risk models for post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP): smoking and chronic liver disease are predictors of protection against PEP. *Pancreas* 2013; **42**: 996-1003 [PMID: 23532001 DOI: 10.1097/MPA.0b013e31827e95e9]
14 **Vitte RL**, Morfoisse JJ. Evaluation of endoscopic retrograde cholangiopancreatography procedures performed in general hospitals in France. *Gastroenterol Clin Biol* 2007; **31**: 740-749 [PMID: 17925778 DOI: 10.1016/S0399-8320(07)91936-3]
15 **Wilcox CM**, Phadnis M, Varadarajulu S. Biliary stent placement is associated with post-ERCP pancreatitis. *Gastrointest Endosc* 2010; **72**: 546-550 [PMID: 20633882 DOI: 10.1016/j.gie.2010.05.001]
16 **Coté GA**, Kumar N, Ansstas M, Edmundowicz SA, Jonnalagadda S, Mullady DK, Azar RR. Risk of post-ERCP pancreatitis with placement of self-expandable metallic stents. *Gastrointest Endosc* 2010; **72**: 748-754 [PMID: 20630513 DOI: 10.1016/j.gie.2010.05.023]
17 **Donnellan F**, Byrne MF. Prevention of Post-ERCP Pancreatitis. *Gastroenterol Res Pract* 2012; **2012**: 796751 [PMID: 21845187]
18 **Freeman ML**, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59**: 845-864 [PMID: 15173799 DOI: 10.1016/S0016-5107(04)00353-0]
19 **Cennamo V**, Fuccio L, Zagari RM, Eusebi LH, Ceroni L, Laterza L, Fabbri C, Bazzoli F. Can a wire-guided cannulation technique increase bile duct cannulation rate and prevent post-ERCP pancreatitis?: A meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2009; **104**: 2343-2350 [PMID: 19532133 DOI: 10.1038/ajg.2009.269]
20 **Tse F**, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. *Cochrane Database Syst Rev* 2012; **12**: CD009662 [PMID: 23235679]
21 **Kobayashi G**, Fujita N, Imaizumi K, Irisawa A, Suzuki M, Murakami A, Oana S, Makino N, Komatsuda T, Yoneyama K. Wire-guided biliary cannulation technique does not reduce the risk of post-ERCP pancreatitis: multicenter randomized controlled trial. *Dig Endosc* 2013; **25**: 295-302 [PMID: 23368891]
22 **Mariani A**, Giussani A, Di Leo M, Testoni S, Testoni PA. Guidewire biliary cannulation does not reduce post-ERCP pancreatitis compared with the contrast injection technique in low-risk and high-risk patients. *Gastrointest Endosc* 2012; **75**: 339-346 [PMID: 22075192 DOI: 10.1016/j.gie.2011.09.002]
23 **Kahaleh M**, Freeman M. Prevention and management of post-endoscopic retrograde cholangiopancreatography complications. *Clin Endosc* 2012; **45**: 305-312 [PMID: 22977824]
24 **Verma D**, Kapadia A, Adler DG. Pure versus mixed electrosurgical current for endoscopic biliary sphincterotomy: a meta-analysis of adverse outcomes. *Gastrointest Endosc* 2007; **66**: 283-290 [PMID: 17643701 DOI: 10.1016/j.gie.2007.01.018]
25 **Gorelick A**, Cannon M, Barnett J, Chey W, Scheiman J, Elta G. First cut, then blend: an electrocautery technique affecting bleeding at sphincterotomy. *Endoscopy* 2001; **33**: 976-980 [PMID: 11668407 DOI: 10.1055/s-2001-17918]
26 **Smithline A**, Silverman W, Rogers D, Nisi R, Wiersema M, Jamidar P, Hawes R, Lehman G. Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in high-risk patients. *Gastrointest Endosc* 1993; **39**: 652-657 [PMID: 8224687 DOI: 10.1016/S0016-5107(93)70217-5]
27 **Fazel A**, Quadri A, Catalano MF, Meyerson SM, Geenen JE. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. *Gastrointest Endosc* 2003; **57**: 291-294 [PMID: 12612504 DOI: 10.1067/mge.2003.124]
28 **Tarnasky PR**, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology* 1998; **115**: 1518-1524 [PMID: 9834280 DOI: 10.1016/S0016-5085(98)70031-9]
29 **Harewood GC**, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. *Gastrointest Endosc* 2005; **62**: 367-370 [PMID: 16111953 DOI: 10.1016/j.gie.2005.04.020]
30 **Sofuni A**, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, Toyota M, Fujii T, Harada Y, Takada T. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. *Clin Gastroenterol Hepatol* 2007; **5**: 1339-1346 [PMID: 17981247 DOI: 10.1016/j.cgh.2007.07.008]
31 **Aizawa T**, Ueno N. Stent placement in the pancreatic duct prevents pancreatitis after endoscopic sphincter dilation for removal of bile duct stones. *Gastrointest Endosc* 2001; **54**: 209-213 [PMID: 11474392]
32 **Tsuchiya T**, Itoi T, Sofuni A, Itokawa F, Kurihara T, Ishii K, Tsuji S, Kawai T, Moriyasu F. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial. *J Hepatobiliary Pancreat Surg* 2007; **14**: 302-307 [PMID: 17520207 DOI: 10.1007/s00534-006-1147-8]
33 **Freeman ML**. Pancreatic stents for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol* 2007; **5**: 1354-1365 [PMID: 17981248 DOI: 10.1016/j.cgh.2007.09.007]
34 **Mazaki T**, Mado K, Masuda H, Shiono M. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. *J Gastroenterol* 2013 Apr 24; Epub ahead of print [PMID: 23612857 DOI: 10.1007/s00535-013-0806-1]
35 **Choudhary A**, Bechtold ML, Arif M, Szary NM, Puli SR, Othman MO, Pais WP, Antillon MR, Roy PK. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. *Gastrointest Endosc* 2011; **73**: 275-282 [PMID: 21295641 DOI: 10.1016/j.gie.2010.10.039]
36 **Bakman YG**, Safdar K, Freeman ML. Significant clinical implications of prophylactic pancreatic stent placement in previously normal pancreatic ducts. *Endoscopy* 2009; **41**: 1095-1098 [PMID: 19904701 DOI: 10.1055/s-0029-1215317]
37 **Freeman ML**, Overby C, Qi D. Pancreatic stent insertion: consequences of failure and results of a modified technique to maximize success. *Gastrointest Endosc* 2004; **59**: 8-14 [PMID: 14722540 DOI: 10.1016/S0016-5107(03)02530-6]
38 **Chahal P**, Tarnasky PR, Petersen BT, Topazian MD, Levy MJ, Gostout CJ, Baron TH. Short 5Fr vs long 3Fr pancreatic stents in patients at risk for post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol* 2009; **7**: 834-839 [PMID: 19447196 DOI: 10.1016/j.cgh.2009.05.002]

39 **Testoni PA**. Pharmacological prevention of post-ERCP pancreatitis: the facts and the fiction. *JOP* 2004; **5**: 171-178 [PMID: 15254345]

40 **Mariani A**. Pharmacological prevention of post-ERCP pancreatitis: which therapy is best? *JOP* 2003; **4**: 68-74 [PMID: 12555018]

41 **Viedma JA**, Pérez-Mateo M, Agulló J, Domínguez JE, Carballo F. Inflammatory response in the early prediction of severity in human acute pancreatitis. *Gut* 1994; **35**: 822-827 [PMID: 7517379 DOI: 10.1136/gut.35.6.822]

42 **Mäkelä A**, Kuusi T, Schröder T. Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. *Scand J Clin Lab Invest* 1997; **57**: 401-407 [PMID: 9279965 DOI: 10.3109/00365519709084587]

43 **Murray B**, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2003; **124**: 1786-1791 [PMID: 12806612 DOI: 10.1016/S0016-5085(03)00384-6]

44 **Elmunzer BJ**, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. *Gut* 2008; **57**: 1262-1267 [PMID: 18375470]

45 **Dai HF**, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 2009; **8**: 11-16 [PMID: 19208508]

46 **Ding X**, Chen M, Huang S, Zhang S, Zou X. Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis. *Gastrointest Endosc* 2012; **76**: 1152-1159 [PMID: 23164513 DOI: 10.1016/j.gie.2012.08.021]

47 **Cheon YK**, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, Schmidt S, Lazzell-Pannell L, Lehman GA. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. *Gastrointest Endosc* 2007; **66**: 1126-1132 [PMID: 18061712 DOI: 10.1016/j.gie.2007.04.012]

48 **Davies NM**, Anderson KE. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. *Clin Pharmacokinet* 1997; **33**: 184-213 [PMID: 9314611 DOI: 10.2165/00003088-199733030-00003]

49 **Elmunzer BJ**, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SM, Nicholson S, Fogel EL. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012; **366**: 1414-1422 [PMID: 22494121 DOI: 10.1056/NEJMoa1111103]

50 **Yaghoobi M**, Rolland S, Waschke KA, McNabb-Baltar J, Martel M, Bijarchi R, Szego P, Barkun AN. Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. *Aliment Pharmacol Ther* 2013; **38**: 995-1001 [PMID: 24099466]

51 **Dumonceau JM**, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH, Testoni PA. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy* 2010; **42**: 503-515 [PMID: 20506068 DOI: 10.1055/s-0029-1244208]

52 **Weiner GR**, Geenen JE, Hogan WJ, Catalano MF. Use of corticosteroids in the prevention of post-ERCP pancreatitis. *Gastrointest Endosc* 1995; **42**: 579-583 [PMID: 8674931 DOI: 10.1016/S0016-5107(95)70014-5]

53 **Manolakopoulos S**, Avgerinos A, Vlachogiannakos J, Armonis A, Viazis N, Papadimitriou N, Mathou N, Stefanidis G, Rekoumis G, Vienna E, Tzourmakliotis D, Raptis SA. Octreotide versus hydrocortisone versus placebo in the prevention of post-ERCP pancreatitis: a multicenter randomized controlled trial. *Gastrointest Endosc* 2002; **55**: 470-475 [PMID: 11923756 DOI: 10.1067/mge.2002.122614]

54 **Dumot JA**, Conwell DL, O'Connor JB, Ferguson DR, Vargo JJ, Barnes DS, Shay SS, Sterling MJ, Horth KS, Issa K, Ponsky JL, Zuccaro G. Pretreatment with methylprednisolone to prevent ERCP-induced pancreatitis: a randomized, multicenter, placebo-controlled clinical trial. *Am J Gastroenterol* 1998; **93**: 61-65 [PMID: 9448176 DOI: 10.1111/j.1572-0241.1998.061_c.x]

55 **De Palma GD**, Catanzano C. Use of corticosteriods in the prevention of post-ERCP pancreatitis: results of a controlled prospective study. *Am J Gastroenterol* 1999; **94**: 982-985 [PMID: 10201469 DOI: 10.1111/j.1572-0241.1999.999_u.x]

56 **Budzyńska A**, Marek T, Nowak A, Kaczor R, Nowakowska-Dulawa E. A prospective, randomized, placebo-controlled trial of prednisone and allopurinol in the prevention of ERCP-induced pancreatitis. *Endoscopy* 2001; **33**: 766-772 [PMID: 11558030 DOI: 10.1055/s-2001-16520]

57 **Sherman S**, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Earle D, Temkit M, Lehman GA. Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. *Gastrointest Endosc* 2003; **58**: 23-29 [PMID: 12838216 DOI: 10.1067/mge.2003.307]

58 **Bai Y**, Gao J, Shi X, Zou D, Li Z. Prophylactic corticosteroids do not prevent post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. *Pancreatology* 2008; **8**: 504-509 [PMID: 18765955 DOI: 10.1159/000151999]

59 **Devière J**, Le Moine O, Van Laethem JL, Eisendrath P, Ghilain A, Severs N, Cohard M. Interleukin 10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2001; **120**: 498-505 [PMID: 11159890 DOI: 10.1053/gast.2001.21172]

60 **Dumot JA**, Conwell DL, Zuccaro G, Vargo JJ, Shay SS, Easley KA, Ponsky JL. A randomized, double blind study of interleukin 10 for the prevention of ERCP-induced pancreatitis. *Am J Gastroenterol* 2001; **96**: 2098-2102 [PMID: 11467638 DOI: 10.1111/j.1572-0241.2001.04092.x]

61 **Sherman S**, Cheng CL, Costamagna G, Binmoeller KF, Puespoek A, Aithal GP, Kozarek RA, Chen YK, Van Steenbergen W, Tenner S, Freeman M, Monroe P, Geffner M, Deviere J. Efficacy of recombinant human interleukin-10 in prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in subjects with increased risk. *Pancreas* 2009; **38**: 267-274 [PMID: 19214137 DOI: 10.1097/MPA.0b013e31819777d5]

62 **Zheng M**, Chen Y, Bai J, Xin Y, Pan X, Zhao L. Meta-analysis of prophylactic allopurinol use in post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreas* 2008; **37**: 247-253 [PMID: 18815544 DOI: 10.1097/MPA.0b013e31816857e3]

63 **Bai Y**, Gao J, Zhang W, Zou D, Li Z. Meta-analysis: allopurinol in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis. *Aliment Pharmacol Ther* 2008; **28**: 557-564 [PMID: 18714440 DOI: 10.1111/j.1365-2036.2008.03756.x]

64 **Nakaji K**, Suzumura S, Nakae Y, Kojima K, Kumamoto M, Kozu T. Effects in the control of edema of the papilla of Vater by epinephrine saline irrigation after endoscopic retrograde cholangiopancreatography in an endoscopy center in Japan, 2003 to 2007: exploratory retrospective analysis to evaluate the characteristics of eligible patients with a focus on serum amylase levels. *Intern Med* 2009; **48**: 945-952 [PMID: 19525579 DOI: 10.2169/internalmedicine.48.1705]

65 **Matsushita M**, Takakuwa H, Shimeno N, Uchida K, Nishio A, Okazaki K. Epinephrine sprayed on the papilla for prevention of post-ERCP pancreatitis. *J Gastroenterol* 2009; **44**: 71-75 [PMID: 19159075 DOI: 10.1007/s00535-008-2272-8]

66 **Xu LH**, Qian JB, Gu LG, Qiu JW, Ge ZM, Lu F, Wang YM, Li YM, Lu HS. Prevention of post-endoscopic retrograde chol-

angiopancreatography pancreatitis by epinephrine sprayed on the papilla. *J Gastroenterol Hepatol* 2011; **26**: 1139-1144 [PMID: 21392105]

67 **Ohashi A**, Tamada K, Tomiyama T, Wada S, Higashizawa T, Gotoh Y, Satoh Y, Miyata T, Tano S, Ido K, Sugano K. Epinephrine irrigation for the prevention of pancreatic damage after endoscopic balloon sphincteroplasty. *J Gastroenterol Hepatol* 2001; **16**: 568-571 [PMID: 11350556 DOI: 10.1046/j.1440-1746.2001.02483.x]

68 **Kapetanos D**, Kokozidis G, Christodoulou D, Mistakidis K, Sigounas D, Dimakopoulos K, Kitis G, Tsianos EV. A randomized controlled trial of pentoxifylline for the prevention of post-ERCP pancreatitis. *Gastrointest Endosc* 2007; **66**: 513-518 [PMID: 17725940 DOI: 10.1016/j.gie.2007.03.1045]

69 **Sherman S**, Alazmi WM, Lehman GA, Geenen JE, Chuttani R, Kozarek RA, Welch WD, Souza S, Pribble J. Evaluation of recombinant platelet-activating factor acetylhydrolase for reducing the incidence and severity of post-ERCP acute pancreatitis. *Gastrointest Endosc* 2009; **69**: 462-472 [PMID: 19231487 DOI: 10.1016/j.gie.2008.07.040]

70 **van Westerloo DJ**, Rauws EA, Hommes D, de Vos AF, van der Poll T, Powers BL, Fockens P, Dijkgraaf MG, Bruno MJ. Pre-ERCP infusion of semapimod, a mitogen-activated protein kinases inhibitor, lowers post-ERCP hyperamylasemia but not pancreatitis incidence. *Gastrointest Endosc* 2008; **68**: 246-254 [PMID: 18455169 DOI: 10.1016/j.gie.2008.01.034]

71 **Shah TU**, Liddle R, Branch MS, Jowell P, Obando J, Poleski M. Pilot study of aprepitant for prevention of post-ERCP pancreatitis in high risk patients: a phase II randomized, double-blind placebo controlled trial. *JOP* 2012; **13**: 514-518 [PMID: 22964958]

72 **Tsujino T**, Isayama H, Nakai Y, Ito Y, Togawa O, Toda N, Arizumi T, Kogure H, Yamamoto K, Mizuno S, Yashima Y, Yagioka H, Sasaki T, Matsubara S, Yamamoto N, Hirano K, Sasahira N, Tada M, Koike K. The results of the Tokyo trial of prevention of post-ERCP pancreatitis with risperidone (Tokyo P3R): a multicenter, randomized, phase II, non-placebo-controlled trial. *J Gastroenterol* 2013; **48**: 982-988 [PMID: 23090004]

73 **Andriulli A**, Leandro G, Federici T, Ippolito A, Forlano R, Iacobellis A, Annese V. Prophylactic administration of somatostatin or gabexate does not prevent pancreatitis after ERCP: an updated meta-analysis. *Gastrointest Endosc* 2007; **65**: 624-632 [PMID: 17383459 DOI: 10.1016/j.gie.2006.10.030]

74 **Lee KT**, Lee DH, Yoo BM. The prophylactic effect of somatostatin on post-therapeutic endoscopic retrograde cholangiopancreatography pancreatitis: a randomized, multicenter controlled trial. *Pancreas* 2008; **37**: 445-448 [PMID: 18953260 DOI: 10.1097/MPA.0b013e3181733721]

75 **Chan HH**, Lai KH, Lin CK, Tsai WL, Lo GH, Hsu PI, Wei MC, Wang EM. Effect of somatostatin in the prevention of pancreatic complications after endoscopic retrograde cholangiopancreatography. *J Chin Med Assoc* 2008; **71**: 605-609 [PMID: 19114324 DOI: 10.1016/S1726-4901(09)70002-4]

76 **Bai Y**, Gao J, Zou DW, Li ZS. Prophylactic octreotide administration does not prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. *Pancreas* 2008; **37**: 241-246 [PMID: 18815543 DOI: 10.1097/MPA.0b013e31816c90a1]

77 **Zhang Y**, Chen QB, Gao ZY, Xie WF. Meta-analysis: octreotide prevents post-ERCP pancreatitis, but only at sufficient doses. *Aliment Pharmacol Ther* 2009; **29**: 1155-1164 [PMID: 19302265 DOI: 10.1111/j.1365-2036.2009.03991.x]

78 **Omata F**, Deshpande G, Tokuda Y, Takahashi O, Ohde S, Carr-Locke DL, Jacobs JL, Mine T, Fukui T. Meta-analysis: somatostatin or its long-acting analogue, octreotide, for prophylaxis against post-ERCP pancreatitis. *J Gastroenterol* 2010; **45**: 885-895 [PMID: 20373114 DOI: 10.1007/s00535-010-0234-4]

79 **Odes HS**, Novis BN, Barbezat GO, Bank S. Effect of calcitonin on the serum amylase levels after endoscopic retrograde cholangiopancreatography. *Digestion* 1977; **16**: 180-184 [PMID: 355022 DOI: 10.1159/000198070]

80 **Ohnhaus EE**, Witzel L, Halter F, Stauffacher W. [The effect of salmon calcitonin on pancreatic enzymes and hormones before and after retrograde cholangiopancreatography]. *Schweiz Med Wochenschr* 1981; **111**: 750-754 [PMID: 6166982]

81 **Seta T**, Noguchi Y. Protease inhibitors for preventing complications associated with ERCP: an updated meta-analysis. *Gastrointest Endosc* 2011; **73**: 700-706.e1-2 [PMID: 21145053 DOI: 10.1016/j.gie.2010.09.022]

82 **Yuhara H**, Ogawa M, Kawaguchi Y, Igarashi M, Shimosegawa T, Mine T. Pharmacologic prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: protease inhibitors and NSAIDs in a meta-analysis. *J Gastroenterol* 2013 May 30; Epub ahead of print [PMID: 23720090]

83 **Li S**, Cao G, Chen X, Wu T. Low-dose heparin in the prevention of post endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2012; **24**: 477-481 [PMID: 22293331 DOI: 10.1097/MEG.0b013e328351097f]

84 **Fluhr G**, Mayerle J, Weber E, Aghdassi A, Simon P, Gress T, Seufferlein T, Mössner J, Stallmach A, Rösch T, Müller M, Siegmund B, Büchner-Steudel P, Zuber-Jerger I, Kantowski M, Hoffmeister A, Rosendahl J, Linhart T, Maul J, Czakó L, Hegyi P, Kraft M, Engel G, Kohlmann T, Glitsch A, Pickartz T, Budde C, Nitsche C, Storck K, Lerch MM. Pre-study protocol MagPEP: a multicentre randomized controlled trial of magnesium sulphate in the prevention of post-ERCP pancreatitis. *BMC Gastroenterol* 2013; **13**: 11 [PMID: 23320650 DOI: 10.1186/1471-230X-13-11]

85 **Moretó M**, Zaballa M, Casado I, Merino O, Rueda M, Ramírez K, Urcelay R, Baranda A. Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: A randomized double-blind trial. *Gastrointest Endosc* 2003; **57**: 1-7 [PMID: 12518122 DOI: 10.1067/mge.2003.29]

86 **Sudhindran S**, Bromwich E, Edwards PR. Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopancreatography-induced pancreatitis. *Br J Surg* 2001; **88**: 1178-1182 [PMID: 11531863 DOI: 10.1046/j.0007-1323.2001.01842.x]

87 **Kaffes AJ**, Bourke MJ, Ding S, Alrubaie A, Kwan V, Williams SJ. A prospective, randomized, placebo-controlled trial of transdermal glyceryl trinitrate in ERCP: effects on technical success and post-ERCP pancreatitis. *Gastrointest Endosc* 2006; **64**: 351-357 [PMID: 16923481 DOI: 10.1016/j.gie.2005.11.060]

88 **Beauchant M**, Ingrand P, Favriel JM, Dupuychaffray JP, Capony P, Moindrot H, Barthet M, Escourrou J, Plane C, Barrioz T, Lacoste L, Ingrand I. Intravenous nitroglycerin for prevention of pancreatitis after therapeutic endoscopic retrograde cholangiography: a randomized, double-blind, placebo-controlled multicenter trial. *Endoscopy* 2008; **40**: 631-636 [PMID: 18680075 DOI: 10.1055/s-2008-1077362]

89 **Nøjgaard C**, Hornum M, Elkjaer M, Hjalmarsson C, Heyries L, Hauge T, Bakkevold K, Andersen PK, Matzen P. Does glyceryl nitrate prevent post-ERCP pancreatitis? A prospective, randomized, double-blind, placebo-controlled multicenter trial. *Gastrointest Endosc* 2009; **69**: e31-e37 [PMID: 19410035 DOI: 10.1016/j.gie.2008.11.042]

90 **Korkmaz H**, Temel T. Incidence, Risk Factors, Recognition and Prevention of Post-ERCP Pancreatitis. *IJMMS* 2013; **1**: 4-9

91 **Tympner F**, Rösch W. Effect of secretin and gabexate-mesilate (synthetic protease inhibitor) on serum amylase level after ERCP. *Z Gastroenterol* 1982; **20**: 688-693 [PMID: 6184898]

92 **Jowell PS**, Branch MS, Fein SH, Purich ED, Kilaru R, Robuck G, d'Almada P, Baillie J. Intravenous synthetic secretin reduces the incidence of pancreatitis induced by endoscopic retrograde cholangiopancreatography. *Pancreas* 2011; **40**: 533-539 [PMID: 21499206 DOI: 10.1097/

MPA.0b013e3182152eb6]
93 **Brandes JW**, Scheffer B, Lorenz-Meyer H, Körst HA, Littmann KP. ERCP: Complications and prophylaxis a controlled study. *Endoscopy* 1981; **13**: 27-30 [PMID: 6161804 DOI: 10.1055/s-2007-1021637]
94 **Räty S**, Sand J, Pulkkinen M, Matikainen M, Nordback I. Post-ERCP pancreatitis: reduction by routine antibiotics. *J Gastrointest Surg* 2001; **5**: 339-345; discussion 345 [PMID: 11985972 DOI: 10.1016/S1091-255X(01)80059-7]
95 **Katsinelos P**, Kountouras J, Paroutoglou G, Beltsis A, Mimidis K, Zavos C. Intravenous N-acetylcysteine does not prevent post-ERCP pancreatitis. *Gastrointest Endosc* 2005; **62**: 105-111 [PMID: 15990827 DOI: 10.1016/S0016-5107(05)01574-9]
96 **Wollschläger S**, Pätzold K, Bulang T, Meissner D, Porst H. [Effect of preventive selenium administration on development of ERCP-induced acute pancreatitis]. *Med Klin* (Munich) 1999; **94** Suppl 3: 81-83 [PMID: 10554538 DOI: 10.1007/BF03042200]
97 **Lavy A**, Karban A, Suissa A, Yassin K, Hermesh I, Ben-Amotz A. Natural beta-carotene for the prevention of post-ERCP pancreatitis. *Pancreas* 2004; **29**: e45-e50 [PMID: 15257114 DOI: 10.1097/00006676-200408000-00018]
98 **Gu WJ**, Wei CY, Yin RX. Antioxidant supplementation for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a meta-analysis of randomized controlled trials. *Nutr J* 2013; **12**: 23 [PMID: 23398675 DOI: 10.1186/1475-2891-12-23]

P- Reviewers: Mathew A, Piccinni G **S- Editor**: Wen LL
L- Editor: A **E- Editor**: Wu HL

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Telephone: +852-6555-7188
Fax: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com