

Pharmacological Prevention of Post-ERCP Pancreatitis: The Facts and the Fiction

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Chemoprevention of post-ERCP pancreatitis still remains a debated question. Acute pancreatitis represents the most common complication after ERCP procedures; the reported incidence of this complication varies from less than 1% up to 40%, but rates of about 5% are reported in most prospective studies involving non-selected patients. The risk of post-ERCP pancreatitis is determined at least as much by the characteristics of the patient as by endoscopic techniques or maneuvers. Patient-related predictors found to be significant in major studies for post-ERCP pancreatitis include younger age, documented or suspected sphincter of Oddi dysfunction, history of previous pancreatitis (either recurrent or post-ERCP), and normal serum bilirubin [1]; women may have increased risk, too. Patients with multiple risk factors have a dramatically enhanced risk. Precut, pancreatic sphincterotomy, balloon papillary dilation, and multiple pancreatic duct injections have been found to be technical risk factors for post-ERCP pancreatitis [1]. Independently of the technique-related risk factors, operator experience also seems to play a potential role in the occurrence of post-ERCP complications, although few studies have addressed the question. However, the experience of the endoscopist does not seem to be able to reduce the risk of developing pancreatitis in high-risk patients [2]. Post-ERCP insertion of unflanged stents into the

pancreatic duct of small diameter significantly reduced but did not abolish the risk of pancreatitis [3]. In fact, despite technical improvements in recent years and the increased experience of endoscopists in the use of ERCP procedures, the incidence of post-ERCP pancreatitis has not yet substantially decreased and the risk remains high in selected patients. Considering the above data, attempts at preventing post-ERCP pancreatitis by some pharmacological prophylaxis appear justifiable.

Pharmacological prevention of pancreatitis after ERCP has been the topic of several investigations in recent years but still remains a debated question. The ideal pharmacological prophylaxis should be effective in patients who really risk developing post-procedure pancreatitis; it should be as cheap as possible and should not require prolonged administration in the post-procedure period. The drug must also be safe. Although a number of trials have documented the efficacy of the drug tested, initial favorable results have been followed by contradictory reports or the lack of further studies; in fact, a routine pharmacological prophylaxis has not yet been adopted in most endoscopic centers or recommended by guidelines.

The availability of effective drugs and strategy of chemoprevention are unsettled points in the pharmacological prophylaxis of post-ERCP pancreatitis.

Which Drug is Best?

In the last four years, various papers have been published with conflicting results, investigating the prophylactic efficacy of octreotide, somatostatin, steroids (three papers, respectively), interleukin-10, gabexate mesilate, heparin, glyceryl trinitrate (two papers, respectively), allopurinol, nifedipine, diclofenac, secretin, antibiotics, botulinum toxin, and lidocaine and epinephrine sprayed (one paper, respectively). Eleven studies have proven the effectiveness of the drug tested [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. Somatostatin, octreotide, gabexate mesilate and recombinant interleukin-10 have been the drugs most investigated.

Knowledge of the mechanisms involved in the early phase of onset of acute pancreatitis plays a pivotal role in the search for a pharmacological prophylaxis of this complication. In experimental models of acute pancreatitis, it has been suggested that digestive enzyme activation might occur within acinar cells, and it has been shown that, in the early stages of acute pancreatitis, there is a co-localization of digestive enzymes and lysosomal hydrolases within large cytoplasm vacuoles. This co-localization mechanism might result in activation of the digestive enzymes, mainly trypsin. Cell injury induced by pre-mature intra-acinar trypsinogen activation to trypsin leads to oxidative stress, the subsequent production of chemo- and pro-inflammatory cytokines, and contact system activation. This system has important inflammatory activity through the release of the vasoactive peptide bradykinin. All these events take place within a very short period of time and a delay of only a few hours exists between the pancreatic injury induced by ERCP and the onset of the pancreatitis. Drugs must therefore be able to prevent the trypsinogen activation to trypsin or modulate the severity of pancreatitis within a short "therapeutic window".

Pharmacological prevention has therefore been mainly addressed to: a) reducing the amount of intrapancreatic enzymes; b) preventing co-localization of enzymes and

lysosomal hydrolases; c) blocking some steps of the enzyme-activated inflammatory cascade; d) reducing sphincter of Oddi (either biliary or pancreatic segment) post-procedure hypertension.

a) Reducing the Amount of Intrapaneatic Enzymes

This may be obtained by inhibiting exocrine pancreatic secretion at the time of ERCP. Secretin stimulation of exocrine pancreatic secretion prior to ERCP also may decrease the amount of intra-acinar enzymes.

Somatostatin, and its synthetic analogue octreotide, affect the exocrine function both directly, by reducing the secretion of digestive enzymes, and indirectly, by inhibiting secretin and cholecystokinin production. In addition to their antisecretory effects, somatostatin and octreotide have been demonstrated to modulate the cytokine cascade and may also have a cytoprotective effect on pancreatic cells. Experimental investigation has shown that both somatostatin and octreotide have protective effects on experimental acute pancreatitis; thus, the use of these drugs for the prevention of post-ERCP pancreatitis has a reasonable basis. Between 1988 and 2003, 14 randomized clinical trials were published on the prophylactic effect of somatostatin in preventing post-ERCP pancreatitis. A meta-analysis by Andriulli *et al.* [15] comparing the clinical trials published before the year 2000 which dealt with the use of prophylactic somatostatin in the prevention of post-ERCP pancreatitis indicated that somatostatin reduces the risk of post-ERCP pancreatitis in non-selected patients. However, in a multicenter trial on high-risk patients, the same Author reported that a two-hour infusion of somatostatin did not reduce the incidence of post-ERCP pancreatitis as compared to the placebo group [16]. Similarly, negative results were found more recently both by the same group in a multicenter prospective study [17] in which somatostatin was infused over a six-hour period after ERCP and by Lung [18] in a recent meta-analysis including 11

randomized, controlled trials accepted as abstracts for Digestive Disease Week for the years 2000, 2001 and 2002, enrolling a total of 2,770 patients. However, the meta-analysis showed a protective effect of the prophylactic use of somatostatin in the subgroup of patients undergoing sphincterotomy. Despite these unsatisfactory results, in the last two years, somatostatin was found to be effective in preventing post-ERCP in two published papers [10, 13].

Octreotide has the advantage of simple administration by subcutaneous injection; therefore prophylactic treatment with octreotide is cheaper than with somatostatin. Unfortunately, from 1991 up to now, 13 randomized clinical trials have been published with generally disappointing results [15]. Lung in his recent meta-analysis confirmed the inability of octreotide to prevent post-ERCP pancreatitis [18].

The overall evidence in the literature suggests that somatostatin is likely to be effective in reducing the frequency of post-ERCP pancreatitis but further evaluation is needed. Octreotide, however, has been shown not to be effective in reducing the frequency of post-ERCP pancreatitis. Whether the difference is related to the different effects of the two agents on the motor function of sphincter of Oddi or other reasons is unclear; unlike somatostatin, octreotide may stimulate and increase the pressure of the sphincter of Oddi. Secretin gives a secretory peak approximately 4 min after the stimulus and strongly stimulates pancreatic exocrine secretion with subsequent rapid depletion of intra-acinar enzyme content; a recent, prospective, randomized trial on 1,101 patients showed that synthetic secretin i.v. injection immediately prior to ERCP was effective in reducing the incidence of post-ERCP pancreatitis [11]. However, the criteria used in this study to define post-ERCP pancreatitis differed from the standard criteria adopted in most other studies, so further investigation is needed to confirm the efficacy of secretin.

b) Preventing Co-Localization of Enzymes and Lysosomal Hydrolases

Prevention of intra-acinar trypsinogen activation to trypsin and the subsequent inflammatory cascade may be achieved mainly by using antiprotease agents.

In 1995, we published a study [19] on the first attempt at using C1-inhibitor (C1-INH) plasma concentrate. The blockage of ongoing complement and contact system activation by high doses of C1-INH has been reported to improve the outcome of acute pancreatitis in experimental models.

Gabexate has effects on trypsin, kallikrein and plasmin, thrombin, phospholipase A2 and C1 esterase. Studies in experimental animals and humans, carried out mainly in Japan, have demonstrated that the prophylactic administration of gabexate prevented acute pancreatitis. In addition, in both animals and humans, gabexate has an inhibitory action on the sphincter of Oddi. In 1996, gabexate was shown to be effective in preventing post-ERCP pancreatitis in a prospective, multicenter, controlled trial involving 276 patients [20]; the incidence of pancreatitis was reduced four fold in the treatment group as compared to the placebo group (2% vs. 8%). A disadvantage of the gabexate prophylaxis was the need for a 12-hour infusion; this renders the prophylaxis expensive and not feasible in an outpatient setting. However, a recent multicenter equivalence study by the same group has demonstrated that a 6.5-hour infusion was as effective as a 12-hour infusion [10]. Although a meta-analysis study evaluating six clinical trials published between 1978 and 1996 showed that gabexate mesilate was effective in preventing post-ERCP pancreatitis [15]; however, in more recent studies, the same Author did not find any beneficial effect of the drug administered in high-risk patients over a two-hour period [16] and in both standard- and high-risk patients over a six-hour period [17].

c) Blocking Some Steps of the Enzyme-Activated Inflammatory Cascade

Attempts to block the inflammatory cascade have been carried out by using either anti-inflammatory cytokine, recombinant Interleukin (IL)-10, steroids, diclofenac - a potent nonsteroidal anti-inflammatory drug (NSAID) - or heparin.

In 2001, a single-center, double blind, placebo-controlled trial by Deviere *et al.* [5] compared a single injection of recombinant human IL-10 (at 2 different doses: 4 and 20 µg/kg, respectively), given 30 minutes before the ERCP procedure, to a placebo; not only was the treatment able to significantly decrease the incidence of post-ERCP pancreatitis, but it was also proven effective in high risk cases. Another double-blind placebo-controlled study was published in 2001 but was not conclusive [21], probably because it focused on standard-risk patients, including those undergoing diagnostic ERCP. Pooling all patients enrolled in the four available studies, the incidence of post-ERCP pancreatitis was 7.1% in the IL-10 groups, and 13.9% in the placebo groups. A potential additional advantage of the use of recombinant IL-10 could be its efficacy even if administered "on demand" in the post-procedure period. Unfortunately, a subsequent large, multicenter trial on high-risk patients was interrupted due to the lack of efficacy of IL-10.

Steroids also were investigated in three prospective trials done in 2001 [22], 2002 [23], and 2003 [24], but the results were disappointing in all the studies.

Heparin was shown to be effective in preventing post-ERCP pancreatitis in non-selected patients in a previous study [6] but such efficacy was not confirmed in a recent study done in high-risk patients [25].

More recently, rectal 100 mg diclofenac, a potent inhibitor of phospholipase A2 activity, administered immediately after the procedure, was proven effective in preventing post-ERCP pancreatitis in a single center study [8]. Advantages of this prophylaxis are the low cost and the possible "on demand" treatment

in selected cases; however, to date, no further studies aiming at confirming such encouraging results have been published.

d) Reducing Sphincter of Oddi Post-Procedure Hypertension

In recent years, attempts have been made to lower the risk of pancreatitis by reducing post-procedure hypertension of the sphincter of Oddi. Persistent sphincter contraction is believed to induce an intraductal hypertension within the pancreatic ductal system which may in turn induce trypsinogen activation. Nifedipine, glyceryl trinitrate, topical administration of either epinephrine or lidocaine, and botulinum toxin injection were used with conflicting results [6, 8, 14, 26, 27, 28].

Glyceryl trinitrate (nitroglycerin) is a rapid and short acting organic nitrite used extensively for cardiovascular diseases. The drug has a powerful relaxant effect on the smooth muscles within two minutes up to 30 minutes after administration; the reduction in the basal tone of the sphincter of Oddi lasts for approximately 15 minutes. Glyceryl trinitrate, administered either transdermally or sublingually, has been the most promising among the drugs capable of reducing the sphincter of Oddi basal pressure, since it was proven effective in reducing the frequency of post-procedure pancreatitis in all studies [6, 8].

Topical administration of lidocaine was used with the aim of both blocking intramural neural reflexes at the level of sphincter of Oddi and anesthetizing the muscarinic cholinergic receptors located in the small bowel mucosa. The supposed consequences of topical lidocaine are the reduction of post-procedure papillary edema or spasm and the inhibition of cholecystikinin (CCK) release, with the consequent reduction of pancreatic juice secretion. Although such mechanisms were documented as being effective in preventing pancreatitis in animal models, clinical results were however disappointing [28].

Botulinum toxin injection was proven effective in reducing the incidence of post-sphincterotomy pancreatitis in patients with sphincter of Oddi dysfunction, by reducing residual pancreatic sphincter hypertension; the technique appeared safe and easy to perform [14].

Nifedipine, a calcium channel antagonist given three times daily during the day of ERCP procedure, did not show any beneficial effect [27].

On the basis of the few and conflicting published results, pharmacological inhibition of sphincter of Oddi pressure represents to date only a niche for selected studies; if proven effective in larger trials, the major advantages of this prophylaxis are single dose administration and very low cost.

Which Medical Therapy?

Based on their mechanisms of action, both anti-secretory and anti-protease agents may be beneficial only when administered before the procedure but do not seem to be able to prevent the inflammatory cascade once activated and, therefore, are likely to be ineffective if used "on demand" when technique-related high-risk conditions have occurred. Moreover, available data show that these drugs are ineffective in high-risk subjects, the very subjects in whom there is a need for some pharmacological prophylaxis. On the other hand, anti-inflammatory agents, such as IL-10 and diclofenac, may be effective even if administered "on demand" at the end of the endoscopic procedure; however, studies are preliminary and positive results need to be further confirmed in high-risk patients.

Which Prevention Strategy is Best?

A focal point in the pharmacological prevention of post-procedure pancreatitis is its cost-effectiveness: should the prophylaxis be given to all patients undergoing ERCP procedures or only to those at high-risk? Since a number of conditions at high risk for developing post-procedure pancreatitis are not

predictable before the procedure but reveal themselves only during the procedure, a drug able to prevent pancreatic reaction even if administered after the procedure "on demand" would be welcome.

Although the mean incidence of post-procedure pancreatitis after diagnostic and therapeutic ERCP has been reported to be 5.2% and 4.1% respectively [29], in two recent, large Italian prospective studies in non-selected patients, the incidence was 1.3% [30] and 1.9% [31], respectively. The case-mix of the different series very likely influences the rates of post-procedure pancreatitis, which may depend more on the percentage of patients or procedures with some risk factors than on different definitions of pancreatitis, expertise or data collection methods. In fact, in the four prospective studies giving separate figures for standard- and high-risk patients, the reported incidence of pancreatitis was 7.8% and 1.6% [32], 29.2% and 3.4% [33], 19.1% and 3.6% [34], and 18.8% and 0.4% [31], in patients with and without sphincter of Oddi dysfunction, respectively.

With an incidence of post-ERCP pancreatitis lower than 5% as reported in most non-selected patients, a routine prophylactic approach in all patients does not seem useful in most cases and is costly; on the other hand, with a higher incidence of post-ERCP pancreatitis, as reported in patients with risk factors (8-29%), a prophylactic approach may not only be justified, but would also be cost-effective. A theoretical analysis of cost-effectiveness and cost-benefit ratios of gabexate in post-ERCP pancreatitis [35] confirmed that, with an average 2% post-procedure pancreatitis rate as reported for non-selected patients in recent studies, and an estimated 50% efficacy of the drug, routine prophylaxis appears too expensive. However, in a recent equivalence study, gabexate was found to be effective in preventing post-procedure pancreatitis in non-selected cases also with a dosing regimen of a 6.5-hour infusion of 0.5 g of drug [11]; halving the gabexate dosing regimen could also be economically advantageous for routine

prophylaxis with an average rate of pancreatitis of 5% or less.

Based on the above data, a strong argument can be made for pharmacological prophylaxis in high-risk groups, such as young patients and those with suspected sphincter of Oddi dysfunction, non-dilated biliary ducts, or a history of pancreatitis. To date, few trials have specifically addressed the question by using somatostatin, gabexate, recombinant interleukin-10 or diclofenac and most of them have been disappointing. Both somatostatin and gabexate were proven not to be effective by Andriulli *et al.* [16, 17]; IL-10 in a multicenter study which failed to confirm the promising results previously reported in a pilot study by Deviere *et al.* [5]. Further studies are therefore needed.

Conclusions

In conclusion, specific therapy for the prevention of post-ERCP pancreatitis has eluded endoscopists for decades. Although at present there are no drugs in widespread use, among those drugs most investigated, somatostatin, gabexate, recombinant interleukin-10, and glyceryl trinitrate, but not octreotide, have been found to be effective in reducing the frequency and severity of post-ERCP pancreatitis in non-selected cases in some studies.

A strategy of routine chemoprevention in all patients, with a risk of developing post-ERCP pancreatitis lower than 5%, is not likely to be cost-effective. However, gabexate six-hour infusion and diclofenac or glyceryl trinitrate single administration, if confirmed effective, may probably be cost-effective, even for an incidence of post-ERCP pancreatitis lower than 5%.

A strategy of chemoprevention only in high-risk cases is cost-effective, but up to now no drug has been definitely proven effective.

The "on demand" post-procedure treatment should also be of paramount importance, since it can be used even in standard-risk patients when technique-related risks occur, but no data on the potential efficacy of some drugs are available at present. A recent study

has shown that diclofenac could be effective and cheap, but further confirmation is needed.

Keywords Acute Disease; Botulinum Toxins; Chemicals and Drugs Category; Cytokines; Gabexate; Pancreatitis; Primary Prevention; Protease Inhibitors; Serine Proteinase Inhibitors

Abbreviations C1-INH: C1-inhibitor

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References

1. Freeman ML. Post-ERCP pancreatitis: patient- and technique-related risk factors. JOP. J Pancreas (Online) 2002; 3:169-76. [PMID 12432183]
2. Rabenstein T, Hahn EG. Post-ERCP pancreatitis: is the endoscopist's experience the major risk factor? JOP. J Pancreas (Online) 2002; 3:177-87. [PMID 12432184]
3. Rashdan A, Fogel EL, McHenry L Jr, Sherman S, Temkit M, Lehman GA. Improved stent characteristics for prophylaxis of post-ERCP pancreatitis. Clin Gastroenterol Hepatol 2004; 2:322-9. [PMID 15067627]
4. Raty S, Sand J, Pulkkinen M, Matikainen M, Nordback I. Post-ERCP pancreatitis: reduction by routine antibiotics. J Gastrointest Surg 2001; 5:339-45. [PMID 11985972]
5. Deviere 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]
6. 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; 88:1178-82. [PMID 11531863]

7. Rabenstein T, Roggenbuck S, Framke B, Martus P, Fischer B, Nusko G, et al. Complications of endoscopic sphincterotomy: can heparin prevent acute pancreatitis after ERCP? *Gastrointest Endosc* 2002; 55:476-83. [PMID 11923757]

8. Moreto M, Zaballa M, Casado I, Merino O, Rueda M, Ramirez K, et al. Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: a randomized double-blind trial. *Gastrointest Endosc* 2003; 57:1-7. [PMID 12518122]

9. Murray B, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2003; 124:1786-91. [PMID 12806612]

10. Poon RT, Yeung C, Liu CL, Lam CM, Yuen WK, Lo CM, et al. Intravenous bolus somatostatin after diagnostic cholangiopancreatography reduces the incidence of pancreatitis associated with therapeutic endoscopic retrograde cholangiopancreatography procedures: a randomized controlled trial. *Gut* 2003; 52:1768-73. [PMID 14633959]

11. Masci E, Cavallini G, Mariani A, Frulloni L, Testoni PA, Curioni S, et al. Comparison of two dosing regimens of gabexate in the prophylaxis of post-ERCP pancreatitis. *Am J Gastroenterol* 2003; 98:2182-6. [PMID 14572565]

12. Jowell PS, Branch S, Robuck-Mangum G, Fein S, Purich ED, et al. Synthetic Secretin administered at the start of the procedure significantly reduces the risk of post-ERCP pancreatitis: a randomized, double-blind, placebo controlled trial. [Abstract]. *Gastroenterology* 2003; 125:605.

13. Arvanitidis D, Anagnostopoulos GK, Giannopoulos D, Pantes A, Agaritsi R, Margantinis G, et al. Can somatostatin prevent post-ERCP pancreatitis? Results of a randomized controlled trial. *J Gastroenterol Hepatol* 2004; 19:278-82. [PMID 14748874]

14. Gorelick A, Barnett J, Chey W, Anderson M, Elta G. Botulinum toxin injection after biliary sphincterotomy. *Endoscopy* 2004; 36:170-3. [PMID 14765315]

15. Andriulli A, Leandro G, Niro G, Mangia A, Festa V, Gambassi G, et al. Pharmacological treatment can prevent pancreatic injury after ERCP: a meta-analysis. *Gastrointest Endosc* 2000; 51:1-7. [PMID 10625786]

16. Andriulli A, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, et al. Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-

controlled, randomized clinical trial. *Gastrointest Endosc* 2002; 56:488-95. [PMID 12297762]

17. Andriulli A, Solmi L, Loperfido S, Festa V, Belmonte A, Leo P, et al. Somatostatin (SST) and gabexate (GM) are ineffective in preventing post-ERCP complications. [Abstract]. *Gastrointest Endosc* 2004; 59:AB106.

18. Lung E. The use of somatostatin or octreotide to prevent post-ERCP pancreatitis: a meta-analysis of randomized, controlled trials. [Abstract]. *Gastrointest Endosc* 2004; 59:AB107.

19. Testoni PA, Cicardi M, Bergamaschini L, Guzzoni S, Cugno M, Buizza M, et al. Infusion of C1-inhibitor plasma concentrate prevents hyperamylasemia induced by endoscopic sphincterotomy. *Gastrointest Endosc* 1995; 42:301-5. [PMID 8536896]

20. Cavallini G, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. *N Engl J Med* 1996; 335:919-23. [PMID 8786777]

21. Dumot JA, Conwell DL, Zuccaro G Jr, 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; 96:2098-102. [PMID 11467638]

22. Budzynska 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; 33:766-72. [PMID 11558030]

23. Manolakopoulos S, Avgerinos A, Vlachogiannakos J, Armonis A, Viazis N, Papadimitriou N, et al. Octreotide versus hydrocortisone versus placebo in the prevention of post-ERCP pancreatitis: a multicenter randomized controlled trial. *Gastrointest Endosc* 2002; 55:470-5. [PMID 11923756]

24. Sherman S, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, et al. Does prophylactic administration of corticosteroids reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. *Gastrointest Endosc* 2003; 58:23-9. [PMID 12838216]

25. Rabenstein T, Fischer B, Wiessner V, Schmidt H, Radespiel-Troger M, Hochberger J, et al. Low-molecular-weight heparin does not prevent acute post-ERCP pancreatitis. *Gastrointest Endosc* 2004; 59:606-13. [PMID 15114301]

26. Ohashi A, Tamada K, Tomiyama T, Wada S, Higashizawa T, Gotoh Y, et al. Epinefrine irrigation for the prevention of pancreatic damage after endoscopic balloon sphincteroplasty. *J Gastroenterol Hepatol* 2001; 16:568-71. [PMID 11350556]

27. Prat F, Amaris J, Ducot B, Bocquentin M, Fritsch J, Choury AD, et al. Nifedipine for prevention of post-ERCP pancreatitis: a prospective, double-blind randomized study. *Gastrointest Endosc* 2002; 56:202-8. [PMID 12145597]
28. Schwartz JJ, Lew RJ, Ahmad NA, Shah JN, Ginsberg GG, Kochman ML, et al. The effect of lidocaine sprayed on the major duodenal papilla on the frequency of post-ERCP pancreatitis. *Gastrointest Endosc* 2004; 59:179-84. [PMID 14745389]
29. Gottlieb K, Sherman S. ERCP and endoscopic biliary sphincterotomy-induced pancreatitis. *Gastrointest Clin N Am* 1998; 8:87-114. [PMID 9405753]
30. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; 48:1-10. [PMID 9684657]
31. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; 96:417-23. [PMID 11232684]
32. Sherman S, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy: a prospective study with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. *Gastroenterology* 1991; 101:1068-75. [PMID 1889699]
33. Sherman S, Hawes RH, Rathgeber SW, Uzer MF, Smith MT, Khusro QE, et al. Post-ERCP pancreatitis: randomized, prospective study comparing a low- and high-osmolality contrast agent. *Gastrointest Endosc* 1994; 40:422-7. [PMID 7926531]
34. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; 335:909-18. [PMID 8782497]
35. Pasha TM, Therneau T, Petersen BT. Economic analysis of gabexate mesilate in post-ERCP pancreatitis. [Abstract]. *Gastroenterology* 1997; 112:A471.
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