Somatostatin for Prevention of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Never-ending Story?

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Although magnetic resonance cholangiopancreatography (MRCP) provides excellent anatomic detail of the biliary and pancreatic ducts and has markedly decreased the application of diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in recent years, therapeutic ERCP remains a cardinal intervention for biliary and pancreatic diseases.[1] However, ERCP is still perceived as the most worrisome procedure in the clinical setting of gastroenterology, especially when one is confronting a fatal episode of severe post-ERCP pancreatitis (PEP). In a recent systematic survey of 21 studies involving 16,855 patients, the incidences of ERCP-associated complications and mortality were 6.85% and 0.33%, respectively.[2]

Increases in serum amylase and lipase activities after ERCP are common, occurring in about 25–75% of all patients.[3] Acute pancreatitis is a major complication of ERCP. The incidence of PEP is approximately 1–10%. Although most PEP (90%) is rated as mild to moderate pancreatitis and does not require specific therapy, PEP may cause mortality in 0.11% of patients undergoing ERCP.[2] Therefore, the pharmacologic prevention of PEP has been an important issue in the past 20 years. From the literature, potential drugs for prevention of PEP include somatostatin, octreotide (a long-acting somatostatin analog), gabexate mesilate, nitroglycerin, calcium-channel blocker, N-acetylcysteine, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs; indomethacin and diclofenac), allopurinol, interleukin-10, platelet-activating factor inhibitor, tumor necrosis factor-α inhibitor, and antibiotics.[4] However, after randomized trials or meta-analyses, most of the drugs proposed for prophylaxis against PEP have not been validated.

Although the pathogenesis of acute pancreatitis has not yet been clarified, the hyperstimulation of exocrine secretion is one of the main possible causes under discussion.[5] Somatostatin has nonspecific inhibitory actions on the gut, pancreas and nervous system. Based on the potent inhibition of pancreatic exocrine secretion, somatostatin and octreotide may be useful for treatment of acute pancreatitis and prophylaxis against PEP. Animal trials have shown the beneficial effects of somatostatin and octreotide in experimental pancreatitis; however, the effects of somatostatin and octreotide for acute pancreatitis and prevention of PEP have been controversial despite extensive clinical studies.[4,6]

Several qualified, randomized and placebo-controlled trials have examined the prophylactic effects of somatostatin for PEP.[7–13] The results have hitherto been conflicting. Recently, 2 meta-analyses also showed contradictory results.[14,15] The discrepancy may be related to the heterogeneity of clinical trials with different dosages and length of somatostatin administration, and different definitions of PEP. Rudin et al analyzed 7 high-quality studies involving 3,130 patients to examine the effects of somatostatin and gabexate for PEP.[15] They divided the studies into 3 groups according to the length of somatostatin administration: (1) somatostatin infusion for 12 hours; (2) somatostatin infusion for less than 12 hours; and (3) somatostatin as a bolus. They showed that somatostatin given as an infusion for 12 hours and as a bolus yielded a significant reduction in PEP risk (7.7% and 8.2%) and rate of hyperamylasemia. They concluded that somatostatin given as a bolus seemed to be an efficacious and applicable measure for PEP prevention. In the most recent randomized, multicenter, and controlled study by Lee et al, continuous infusion of somatostatin 3 mg for 12 hours or placebo was given to 391 patients undergoing therapeutic ERCP.[7] They confirmed that somatostatin could significantly reduce the incidence of PEP

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Table 1. Summary of somatostatin trials for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP)

Ref.	Dosage	*n*	Incidence of PEP*	*p*
8	Bolus (4 μg/kg) before cannulation	160	2.5% *vs.* 10%	< 0.05
12	Bolus (250 μg) after diagnostic ERCP	270	4.4% *vs.*13.3%	0.01
13	Bolus (4 μg/kg) before cannulation	240	1.7% *vs.* 9.8%	< 0.05
9	Infusion 3 mg for 12 hr	220	3% *vs.* 10%	0.03
13	Infusion 3 mg for 12 hr	238	1.7% *vs.* 9.8%	< 0.05
7	Infusion 3 mg for 12 hr	391	3.6% *vs.* 9.6%	0.02
10	Infusion 750 μg for 2.5 hr	382	11.5% *vs.* 6.5%	NS
11	Infusion 750 μg for 6.5 hr	746	6.3% *vs.* 4.8%	NS
16	Bolus (250 μg)	89	2.5% *vs.* 4.1%	NS
16	Bolus + infusion (250 μg/hr) for 12 hr	93	6.8% *vs.* 4.1%	NS

**Somatostatin group vs. placebo group. Ref = reference; n = patient number; ERCP = endoscopic retrograde cholangiopancreatography; NS = not significant.*

(3.6% *vs.* 9.6%, $p=0.02$). Andriulli et al demonstrated that short-term administration of somatostatin (2.5 and 6.5 hours) was ineffective for the prevention of PEP.[10,11] The major data from the 7 high-quality clinical trials evaluating the prophylactic effect of somatostatin for PEP are summarized in Table 1.

In a previous issue of the *Journal of the Chinese Medical Association*, Chan et al evaluated the effect of somatostatin as a bolus-plus-continuous infusion for 12 hours and as a bolus alone for prevention of PEP.[16] They recruited 133 patients and found that there was no significant difference in the incidence of PEP between the somatostatin groups and the control group. The incidence of PEP in the somatostatin groups was 2.5% with a bolus administration and 6.8% with a bolus-plus-infusion administration as compared with 4.1% in the control group. Unfortunately, the study was terminated early due to a higher incidence of PEP (but not statistically significant) in the group who received bolus-plus-infusion of somatostatin. Interestingly, the incidences of post-procedure hyperamylasemia in the somatostatin groups with diagnostic ERCP were lower than that in the control group with diagnostic ERCP (8% and 21% *vs.* 47%). Does this indicate that somatostatin may have a beneficial effect on pancreatic injury? The limitation of Chan et al's study is that the number of patients was not sufficient to get a conclusive result.[16] Further study is required to clarify the effect of somatostatin given as a bolus plus an infusion for the prevention of PEP.

The baseline incidence of PEP (in the placebo group) is a critical factor for determining the sample size of a trial if it is to end with statistically meaningful data. The estimated sample sizes are 394 and 821 individuals with the intent to cut PEP incidence by 50% from the expected baseline incidences of 10% and 5%, respectively. It is an interesting finding that the baseline PEP incidence was around 10% in positive studies on the effect of somatostatin for prevention of PEP and was around 5% in negative studies (Table 1).[7–13,16] A large, randomized, placebo-controlled, and multicenter study recruiting around 1,000 patients to validate the effect of somatostatin may be warranted to end the story.

Multiple risk factors might contribute to the development of PEP. These include: (1) procedural factors—sphincterotomy longer than 2 cm, precut sphincterotomy, pancreatic sphincterotomy, papillary balloon dilation, sphincter of Oddi manometry, multiple injections of pancreatic duct, and difficult cannulation; (2) patient factors—young age, female sex, sphincter of Oddi dysfunction, and previous PEP; and (3) operator experience.[17] Some factors cannot be predicted before ERCP. Cost-effectiveness benefit must be considered in the routine use of prophylactic drugs for PEP. If high risk for PEP is noted before ERCP, prophylactic drugs may be administered. If high risk for PEP is noted after ERCP, pancreatic stent placement may be considered.[18]

In conclusion, pharmacologic prevention of PEP is appealing for gastroenterologists worldwide. In a review of the literature, somatostatin given as a bolus or as a continuous infusion over 12 hours appears to be effective for risk reduction of PEP. The issues regarding selection of patients at higher risk of PEP and what constitutes an effective regimen for prophylaxis against PEP still need to be elucidated by large-scale, high-quality studies.

References

1. Sahni VA, Mortele KJ. Magnetic resonance cholangiopancreatography: current use and future applications. *Clin Gastroenterol Hepatol* 2008;6:967–77.

2. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007;102:1781–8.
3. Chen CC, Wang SS, Lu RH, Lu CC, Chang FY, Lee SD. The early changes of serum proinflammatory and anti-inflammatory cytokines after endoscopic retrograde cholangiopancreatography. *Pancreas* 2003;26:375–80.
4. Lankisch PG, Lerch MM. Pharmacological prevention and treatment of acute pancreatitis: where are we now? *Dig Dis* 2006;24:148–59.
5. Steer ML, Meldolesi J. Pathogenesis of acute pancreatitis. *Annu Rev Med* 1988;39:95–105.
6. Chen CC, Wang SS, Tsay SH, Lee FY, Wu SL, Lu RH, Chang FY, et al. Effects of high dose octreotide on retrograde bile salt-induced pancreatitis in rats. *Peptides* 1998;19:543–7.
7. 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;37:445–8.
8. Bordas JM, Toledo-Pimentel V, Llach J, Elena M, Mondelo F, Ginès A, Terés J. Effects of bolus somatostatin in preventing pancreatitis after endoscopic pancreatography: results of a randomized study. *Gastrointest Endosc* 1998;47:230–4.
9. Poon RT, Yeung C, Lo CM, Yuen WK, Liu CL, Fan ST. Prophylactic effect of somatostatin on post-ERCP pancreatitis: a randomized controlled trial. *Gastrointest Endosc* 1999;49: 593–8.
10. Andriulli A, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, Leandro G, 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.
11. Andriulli A, Solmi L, Loperfido S, Leo P, Festa V, Belmonte A, Spirito F, et al. Prophylaxis of ERCP-related pancreatitis: a randomized, controlled trial of somatostatin and gabexate mesylate. *Clin Gastroenterol Hepatol* 2004;2:713–8.
12. Poon RTP, Yeung C, Liu CL, Lam CM, Yuen WK, Lo CM, Tang A, et al. Intravenous bolus somatostatin after diagnostic cholangiopancreatography reduces the incidence of pancreatitis associated with therapeutic endoscopic retrograde cholangiopancreatography procedures: a randomised controlled trial. *Gut* 2003;52:1768–73.
13. Arvanitidis D, Anagnostopoulos GK, Giannopoulos D, Pantes A, Agaritsi R, Margantinis G, Tsiakos S, et al. Can somatostatin prevent post-ERCP pancreatitis? Results of a randomized controlled trial. *J Gastroenterol Hepatol* 2004;19:278–82.
14. 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;65:624–32.
15. Rudin D, Kiss A, Wetz RV, Sottile VM. Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials. *J Gastroenterol Hepatol* 2007;22: 977–83.
16. Chan HH, Lai KH, Lin CK, Tsai WL, Lo GH, Hsu PI, Wei MC, et al. Effects of somatostatin in the prevention of pancreatic complications after endoscopic retrograde cholangiopancreatography. *J Chin Med Assoc* 2008;71:605–9.
17. Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006;101: 139–47.
18. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004;59:845–64.