Effect of Somatostatin in the Prevention of Pancreatic Complications After Endoscopic Retrograde Cholangiopancreatography

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Background: The unique clinical role of endoscopic retrograde cholangiopancreatography (ERCP) in diagnosing and treating biliary tree diseases cannot be completely replaced by other modern imaging modalities such as magnetic resonance cholangiopancreatography. However, post-ERCP pancreatitis is one of the most common and life-threatening complications. Prophylactic medication in the prevention of pancreatitis during ERCP is still controversial. The objective of the present study was to investigate the role of different regimens of somatostatin in the prevention of acute pancreatitis after ERCP and analyze the risk factors contributing to post-ERCP complications.

Methods: From July 1999 to September 2000, 133 patients with benign biliary disease who received ERCP for diagnosis or treatment were enrolled. Group A patients received a bolus of somatostatin infusion before ERCP, followed by continuous infusion for 12 hours. Group B patients received a bolus of somatostatin before ERCP only, and group C patients were the controls who did not receive somatostatin treatment. Serum amylase levels before and 24 hours after ERCP, and abdominal pain were recorded.

Results: There were no significant differences in bile duct and pancreatic duct visualization, ratio of diagnostic and therapeutic ERCP, procedure time, post-procedural hyperamylasemia and pancreatitis among the 3 groups. For patients with visualization of the pancreatic duct, the incidences of hyperamylasemia (serum amylase ≥ 220 U/L) were higher than in patients without visualization of the pancreatic duct ($p < 0.001$). All 6 patients with post-ERCP pancreatitis had pancreatic duct visualization, and recovered after conservative treatment.

Conclusion: Continuous infusion of somatostatin after ERCP does not seem to be helpful in the prevention of pancreatic complications after ERCP. Pancreatic duct visualization is a risk factor for pancreatic complications. [*J Chin Med Assoc* 2008;71(12):605–609]

Key Words: ERCP, pancreatitis, somatostatin

Introduction

Although magnetic resonance cholangiopancreatography provides similar images as endoscopic retrograde cholangiopancreatography (ERCP) for the diagnosis of pancreatobiliary diseases,[1,2] it still cannot completely replace ERCP in those patients who also require tissue sampling and therapeutic interventions. However, manipulation of the ampulla of Vater is associated with serum pancreatic enzyme elevations in up to 70% of patients, and clinically acute pancreatitis may develop in 1–6% of patients.[3–5] For those patients with severe post-procedural pancreatitis, the mortality rate was about 13%.[6,7]

Several drugs have been used to prevent post-ERCP pancreatitis, but their results are controversial. The drugs included in recently published randomized controlled studies were somatostatin[8] and its analog—octreotide,[9] steroids,[9,10] nifedipine,[11] interleukin-10,[12] allopurinol,[10] and gabexate.[13] Somatostatin and gabexate showed

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some positive effect in preventing post-ERCP pancreatitis. However, a recent meta-analysis of the randomized control trials claimed that gabexate mesilate cannot prevent pancreatic injury after ERCP.[14] In Bordas et al's study,[15] somatostatin injection at a dose of 250 μg before cannulation was reported to be effective in reducing the rate of post-procedural pancreatitis from 10% to 2.5%. The difference in frequency of pancreatitis was more significant (18% *vs.* 0%) in the subgroup undergoing endoscopic sphincterotomy. However, hyperamylasemia may occur after several hours for ERCP; whether continuous infusion of somatostatin in this setting has additional effect or not remains uncertain. The aim of this study was, therefore, to investigate the role of somatostatin (bolus with/without subsequent continuous infusion for 12 hours) for the prevention of complications after ERCP.

Methods

From July 1999 to September 2000, 133 patients with benign biliary disease who received ERCP for diagnosis or treatment were enrolled in our study. Patients with malignant disease, other severe systemic illness, and history of gastrectomy with Billroth's II anastomosis were excluded.

After enrolment, patients were randomly put into 3 groups. Group A patients received somatostatin 250 μg infusion before ERCP, followed by continuous infusion with somatostatin 250 μg/hour for 12 hours. Group B patients received somatostatin 250 μg before ERCP only, with no subsequent infusion. Group C patients did not receive any somatostatin before or after ERCP. Local anesthesia of the pharynx with 8% xylocaine and intramuscular injection with hyoscine-N-butylbromide 40 mg were given as premedication. Forty-five patients received a diagnostic ERCP only, 83 patients received endoscopic sphincterotomy (EST) for the treatment of common bile duct stones, 3 patients received EST plus plastic stent placement due to incomplete stone extraction, and 2 patients received nasobiliary drainage for obstructive jaundice and cholangitis.

Post-ERCP pancreatitis was defined as abdominal pain associated with serum amylase level at least 3 times the normal value at 24 hours or more after ERCP, requiring admission or prolongation of planned admission.[16] Post-procedural hyperamylasemia was defined as serum amylase level equal to or more than 2 times the normal value (110 U/L) or higher than the baseline serum amylase value in patients with hyperamylasemia before ERCP.

Random number tables were used to randomize the patients into the 3 groups. Continuous variables were expressed as mean ± standard deviation. Student's *t* test or 1-way ANOVA was used to analyze continuous variables, while the χ^2 or Fisher's exact test was used for categorical variables. A p value of less than 0.05 was considered to be significant.

The Department of Education and Research of Kaohsiung Veterans General Hospital approved this study, and informed consent was obtained from each patient.

Results

A total of 133 patients (group A, 44; group B, 40; group C, 49) were enrolled in our study. The sex, age, incidences of juxtapapillary diverticulum, intact gallbladder, and hyperamylasemia before ERCP were similar in the 3 groups (Table 1).

There were no significant differences in bile duct and pancreatic duct visualization, the ratio of diagnostic and therapeutic ERCP, the procedure time, post-procedural hyperamylasemia and pancreatitis among the 3 groups (Table 2). The incidence of post-procedural pancreatitis in group A was higher than in groups B and C (6.8%, 2.5% and 4.1% respectively), but there was no statistically significant difference. However, due to the more than expected number of patients (3/44, 6.8%) who

Table 1. Characteristics of the 3 groups of patients*

Characteristics	Group A (n = 44)	Group B (n = 40)	Group C (n = 49)	p
Sex (M/F)	26/18	20/20	26/23	0.69
Age (yr)	59.7 ± 15.5	62.9 ± 14.5	65.4 ± 13.7	0.18
Juxtapapillary diverticulum	15 (34)	15 (38)	13 (27)	0.52
Intact gallbladder	34	29	39	0.38
With stone	18	15	13	
Hyperamylasemia before ERCP	8 (18)	6 (15)	11 (22)	0.67

**Data presented as n or mean ± standard deviation or n (%). ERCP = endoscopic retrograde cholangiopancreatography.*

Table 2. Results of endoscopic retrograde cholangiopancreatography in the 3 groups*

	Group A ($n=44$)	Group B ($n=40$)	Group C ($n=49$)	p
Visualization of bile duct	44 (34)	38 (30)	47 (36)	0.35
Visualization of pancreatic duct	26 (59)	18 (45)	26 (53)	0.43
Diagnostic/therapeutic	12/32	14/26	19/30	0.50
Duration of procedure (min)	32.1 ± 22.3	31.7 ± 16.4	32.8 ± 17.7	0.96
Post-procedural hyperamylasemia†	13 (29.5)	13 (32.5)	20 (40.8)	0.49
Diagnostic	1 (8)	3 (21)	9 (47)	0.05
Therapeutic	12 (38)	10 (38)	11 (37)	0.99
Pancreatitis	3 (6.8)	1 (2.5)	2 (4.1)	0.63
Diagnostic	1	0	1	0.57
Therapeutic	2	1	1	0.84

**Data presented as n (%) or n or mean ± standard deviation; †serum amylase ≥ 220 U/L.*

Table 3. Post-procedural hyperamylasemia and pancreatitis in patients with and without visualization of the pancreatic duct

	Pancreatic duct		p
	Visualization	Non-visualization	
Hyperamylasemia			
Group A	11/26	2/18	0.03
Group B	7/18	6/22	0.44
Group C	16/26	4/23	0.002
Total	34/70	12/63	< 0.001
Pancreatitis			
Group A	3/26	0/18	0.14
Group B	1/18	0/22	0.26
Group C	2/26	0/23	0.17
Total	6/70	0/63	0.02

suffered from post-ERCP pancreatitis in group A (bolus + continuous infusion of somatostatin), the study was terminated early in order to prevent morbidity among the patients.

Furthermore, there was no difference in post-procedural hyperamylasemia between diagnostic and therapeutic ERCP within the same group.

For patients with visualization of pancreatic duct, the incidences of post-procedural hyperamylasemia were higher than in those without visualization of pancreatic duct in all 3 groups; it was statistically significant in groups A and C ($p=0.03$ and 0.002, respectively) (Table 3).

Six patients met the criteria for post-ERCP pancreatitis; all of them belonged to the group of pancreatic duct visualization ($p=0.02$). Fortunately, they all recovered after conservative treatment. In addition, 25 patients received ERCP for suspected gallstone pancreatitis; EST was performed in 13 of them, and the procedures were smooth. Twelve patients had normal cholangiogram, probably due to stone pass-out, and received no treatment. One patient developed acute pancreatitis again after ERCP, which was resolved by conservative treatment.

Discussion

It is generally believed that acute pancreatitis is one of the most frequent and serious complications of ERCP and EST. The risk of pancreatitis cannot be eliminated, and the search for suitable drugs to prevent this complication remains of considerable importance. The possible reasons for why somatostatin can prevent acute pancreatitis are related to the effects of inhibiting pancreatic exocrine secretion by suppressing the release of secretin and cholecystokinin[17] and reducing the pressure in the intrapancreatic ducts by inhibiting the motility of the sphincter of Oddi.[18] In our previous study, somatostatin reduced the basal pressure of the sphincter of Oddi significantly in more than 93% of patients with acute non-biliary pancreatitis.[19]

According to the results of Testoni et al's study,[20] serum amylase could attain peak level at 8 hours after the ERCP procedures. However, 46.9% (192/409) of patients still had post-procedural hyperamylasemia (>220 U/L) after 24 hours. Among them, 6.3% had more than 5 times the upper limit of normal, and 73% of these patients were considered to have some degree of pancreatic reaction, although typical pictures of pancreatitis on computed tomography were documented in only 7 patients (36.8%), which was equal to 1.7% of all patients under investigation. The reason for recording the 24-hour amylase level in our study was based on the more significant clinical value of it. The reduction of post-ERCP complications seemed more consistent for somatostatin given by bolus injection in the recent meta-analysis studies, while controversy exists regarding the effect of long duration of infusion of the drug. Andriulli et al claimed that short- or long-term infusion of somatostatin was ineffective in reducing post-ERCP pancreatitis, although bolus injection of it could have a beneficial effect on post-procedural hyperamylasemia.[21] On the other hand, Rudin et al believed that somatostatin administrated as a bolus is the optimal choice for the prophylaxis of post-ERCP complications with regard to the efficacy, ease of administration and applicability to daily practice.[22] In our study, however, there was no significant difference among the groups who received bolus injection with or without continuous infusion of somatostatin and the control, with respect to the reduction of post-procedural hyperamylasemia and pancreatitis. The higher post-procedural hyperamylasemia in group C was probably due to some effect of somatostatin in the treatment groups. Also, the incidence of post-ERCP pancreatitis was only 4% in the control group.

There are possible method-related risk factors for the occurrence of post-ERCP acute pancreatitis: repeat instrumentation of the pancreatic duct due to difficulty in selective cannulation of the bile duct, hydrostatic injury from over-injection, acinarization of the gland, high osmolality of conventional ionic contrast media, biliary obstruction, infection, and normal instead of diseased pancreas.[16,23] In our study, patients with visualization of the pancreatic duct had higher incidence of hyperamylasemia and post-ERCP pancreatitis, so, we took several measures in order to lower the severity of the possible pancreatitis after the procedures, including: avoiding unnecessary ERCP examinations, diluting the contrast medium, avoiding over-injection of contrast and acinarization by means of changing the patients' posture to obtain the opacification of the pancreatic tail, doing EST and draining the bile duct for cases with signs of biliary obstruction. As a result, even though we had a similar rate of hyperamylasemia in our cases compared to the other reports, our patients showed relatively minor symptoms.

Acute pancreatitis was once a contraindication for ERCP. However, carefully selected patients with gallstone pancreatitis have been treated successfully using ERCP procedures. Of 25 patients diagnosed as having gallstone pancreatitis before the procedure, 24 did not have deterioration of pancreatitis after ERCP. It clearly demonstrated the safety of ERCP for this group of patients.

On the other hand, all patients who suffered from post-ERCP pancreatitis also had pancreatic duct visualization during the procedure. This implies that the best way to avoid post-ERCP pancreatitis is to selectively cannulate the bile duct in simple biliary disease and avoid repeated cannulation and excessive contrast injection in cases of strong indications for visualization of the pancreatic duct.

The drawback of this study is the possible β-error resulting from the small number in the study group. However, the incidence of post-ERCP pancreatitis was low and mild in our patients, and the incidence of acute pancreatitis in the group with continuous infusion was higher than in the other groups (6.8% *vs.* 2.5% and 4.1%, respectively).

In conclusion, continuous infusion of somatostatin after ERCP does not seem to be helpful in the prevention of pancreatic complications after ERCP. Pancreatic duct visualization is the risk factor for pancreatic complications.

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References

1. Adamek HE, Albert J, Weitz M, Breer H, Schilling D, Riemann JF. A prospective evaluation of magnetic resonance cholangiopancreatography in patients with suspected bile duct obstruction. *Gut* 1998;43:680–3.
2. Lomanto D, Pavone P, Laghi A, Panebianco V, Mazzocchi P, Fiocca F, Lezoche E, et al. Magnetic resonance cholangiopancreatography in the diagnosis of biliopancreatic diseases. *Am J Surg* 1997;174:33–8.
3. Bibao MK, Dotter CT, Lee TG, Katon RM. Complications of endoscopic retrograde cholangiopancreatography: a study of 10000 cases. *Gastroenterology* 1976;70:314–20.

4. Stanten R, Frey CF. Pancreatitis after endoscopic retrograde cholangiopancreatography: an underreported disease whose severity is often unappreciated. *Arch Surg* 1990;125:1032–5.
5. Rolny P, Anderberg B, Ihse I, Lindstrom E, Olaison G, Arvill A. Pancreatitis after sphincter of Oddi manometry. *Gut* 1990; 31:821–4.
6. Trap R, Adamsen S, Hart-Hansen O, Henriksen M. Severe and fatal complications after diagnostic and therapeutic ERCP: a prospective series of claims to insurance covering public hospitals. *Endoscopy* 1999;31:125–30.
7. Male R, Lehman G, Sherman S. Severe and fatal complications from diagnostic and therapeutic ERCPs. *Gastrointest Endosc* 1994;40:A29.
8. 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.
9. Manolakopoulos S, Avgerinos A, Vlachogiannakos J, Armonis A, Viazis N, Papadimitriou N, Mathouet 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.
10. 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.
11. Prat F, Amaris J, Ducot B, Bocquentin M, Fritsch J, Choury AD, Pelletier G, et al. Nifedipine for prevention of post-ERCP pancreatitis: a prospective, double-blind randomized study. *Gastrointest Endosc* 2002;56:202–8.
12. 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.
13. Cavallini G, Tittobello A, Frulloni L, Masci E, Mariani A, Francesco VD. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. *N Engl J Med* 1996;335:919–23.
14. Zheng M, Chen Y, Yang X, Li J, Zhang Y, Zeng Q. Gabexate in the prophylaxis of post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. *BMC Gastroenterol* 2007;7:6.
15. Bordas JM, Toledo-Pimentel V, Liach J, Elena M, Mondelo F, Gines A, Teres J. Effects of bolus somatostatin in preventing pancreatitis after endoscopic pancreatography: results of a randomized study. *Gastrointest Endosc* 1998;47:230–4.
16. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991;37:383–93.
17. Baxter JN, Jenkins SA, Day DW, Shields R. Effects of somatostatin and a long-acting somatostatin analogue on the prevention and treatment of experimentally induced acute pancreatitis in the rat. *Br J Surg* 1985;72:382–5.
18. Ahrendt SA, McGuire GE, Lillemoe KD, Trias M, Kaloo A, Pitt HA. Somatostatin inhibits sphincter of Oddi motility. *Gastroenterology* 1990;98:242A.
19. Lai KH, Lo GH, Cheng JS, Fu MT, Wang EM, Chan HH, Wang YY, et al. Effect of somatostatin on the sphincter of Oddi in patients with acute non-biliary pancreatitis. *Gut* 2001;49: 843–6.
20. Testoni PA, Caporuscio S, Bagnolo F, Lella F. Twenty-four hour serum amylase predicting pancreatic reaction after endoscopic sphincterotomy. *Endoscopy* 1999;31:131–6.
21. 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.
22. 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.
23. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996;335:909–18.