

BRIEF ARTICLES

## Prophylactic effect of glyceryl trinitrate on post-endoscopic retrograde cholangiopancreatography pancreatitis: A randomized placebo-controlled trial

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Received: September 12, 2008 Revised: December 12, 2008

Accepted: December 19, 2008

Published online: January 21, 2009

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Hao JY, Wu DF, Wang YZ, Gao YX, Lang HP, Zhou WZ. Prophylactic effect of glyceryl trinitrate on post-endoscopic retrograde cholangiopancreatography pancreatitis: A randomized placebo-controlled trial. *World J Gastroenterol* 2009; 15(3): 366-368 Available from: URL: <http://www.wjgnet.com/1007-9327/15/366.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.366>

### Abstract

**AIM:** To examine the prophylactic effect of glyceryl trinitrate on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and hyperamylasemia.

**METHODS:** Patients scheduled for ERCP were randomly divided into study group and placebo group. Patients in study group and placebo group were treated with 5 mg glyceryl trinitrate and 100 mg vitamin C, respectively, 5 min before endoscopic maneuvers.

**RESULTS:** A total of 74 patients were enrolled in the final analysis. Post-ERCP pancreatitis occurred in 3 patients (7.9%) of the study group and 9 patients (25%) in the placebo group ( $P = 0.012$ ). Hyperamylasemia occurred in 8 patients of the study group (21.1%) and 13 patients (36.1%) of the placebo group ( $P = 0.037$ ).

**CONCLUSION:** Glyceryl trinitrate before ERCP can effectively prevent post-ERCP and hyperamylasemia.

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**Key words:** Glyceryl trinitrate; Cholangiopancreatography; Endoscopic retrograde; Pancreatitis

**Peer reviewer:** Zvi Fireman, MD, Associate Professor of

### INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely applied method in the diagnosis and treatment of pancreatobiliary disease. Post-ERCP pancreatitis is the most common postoperative complication of ERCP. Although most cases of post-ERCP pancreatitis are mild, some may be severe and lethal. The incidence of post-ERCP pancreatitis is 1%-40%<sup>[1-3]</sup> and how to prevent it becomes an urgent clinical challenge. Some studies on drugs for preventing post-ERCP pancreatitis are available<sup>[4,5]</sup>, but their results remain debatable. Therefore, most endoscopy centers do not give patients a conventional preventive drug therapy. Glyceryl trinitrate, a strong smooth muscle relaxant, is widely used in treatment of cardiovascular diseases. Glyceryl trinitrate could lower the basal pressure in the sphincter of Oddi and depress the resistance of bile outflow. Moretó *et al*<sup>[6]</sup> demonstrated that glyceryl trinitrate can reduce the incidence of post-ERCP pancreatitis. This prospective placebo-controlled double-blind randomized trial enrolled 74 patients scheduled for ERCP and observed the preventive effect of glyceryl trinitrate on post-ERCP pancreatitis.

### MATERIALS AND METHODS

#### Study population

Seventy-four eligible patients at the age of 18 years and over were included in this study. ERCP was performed for them by the same experienced endoscopist.

Patients with acute or active chronic pancreatitis,

and a nitrate allergic history, and those undergone sphincterotomy, were excluded.

### Research regimen

All the enrolled patients were randomly divided into study group and placebo group. Patients in study group took 5 mg sublingual glyceryl trinitrate 5 min before the procedure, while patients in placebo group took 100 mg sublingual vitamin C. Patients could receive antibiotics, analgesics or ataractics as needed, but somatostatin or octreotide was forbidden. Patients, operators or result observers were blinded to their grouping.

### Observing targets

Serum amylase concentration in each patient was measured before and 4 and 24 h after endoscopy. Abdominal pain, fever, vomiting or other symptoms or signs were observed, and their laboratory or specifically evaluated results were recorded. Meanwhile, details of therapeutic endoscopic procedure, including expansion of bile duct, operating time (hours) and treatment, were also recorded.

### Diagnostic criteria

According to the postoperative complications of ERCP<sup>[7,8]</sup>, post-ERCP pancreatitis could be defined as a disease with sustained pancreatitis symptoms (such as abdominal pain) and high-amylase value over the normal value after ERCP. Hyperlipidemia was defined as the higher serum amylase concentration without or only with mild abdominal pain.

### Statistical analysis

Data were analyzed using SPSS11.5 for statistics. Statistical analysis was performed by Student's *t*-test and  $\chi^2$ -test.

## RESULTS

### General results

A total of 74 patients were randomly divided into study group ( $n = 36$ ) and placebo group ( $n = 36$ ). Of these patients, 6 were eliminated because of intubation failure, 1 had a BillrothII gastroectomy history, 2 did not allow endoscopy because of obstruction at duodenal descending part, and 3 failed to intubate the papilla. All the patients completed the trial. No significant difference was found in baseline characteristics between the two groups, such as gender, age, etiology, duct expansion, ERCP operating time, or treatment (Table 1).

### Incidence of pancreatitis after ERCP

Post-ERCP pancreatitis occurred in 3 patients of the study group (7.9%), in 9 patients of the placebo group (25%), showing a significant difference between the two groups ( $P = 0.012$ ). The condition of patients who developed post-ERCP pancreatitis was significantly improved after conservative treatment (Table 2).

Table 1 Baseline characteristics of study and placebo groups

	Study group	Placebo group	<i>P</i>
Demographic characteristics			
Number	38	36	
Sex ratio (M/F)	15/23	16/20	0.665
Mean age (yr)	64.29 ± 13.40	63.36 ± 15.13	0.781
Etiology			0.972
Cholelithiasis (cases)	33	31	
Others(cases)	5	5	
Cholangiectasis (cases)	26	20	0.254
Treatment			0.841
Cholelithostomy	26	26	
Stent intervention	6	6	
Sphincterotomy and drainage	6	4	
ERCP operating time (min)	36.89 ± 20.51	40.00 ± 24.73	0.558

Table 2 Complications occurred in study and placebo groups

Group	PEP	Hyperamylasemia	Normal
Study	3	8	27
Placebo	9	13	14
<i>P</i>	0.012	0.037	

### Incidence of hyperamylasemia after ERCP

Hyperamylasemia occurred in 13 patients of the placebo group (36.1%) and 8 patients of the study group (21.1%). There was a significant difference between the two groups ( $P = 0.037$ , Table 2).

## DISCUSSION

ERCP is an indispensable method for diagnosis and treatment of hepatic and pancreatobiliary disease. Pancreatitis is the most common postoperative complication of it. The nosogenesis may include<sup>[9]</sup>: (1) papilla edema due to reiterative intubation at duodenal papilla leading to pancreatic outflow obstruction, (2) pancreatic secretion caused by contrast agent over filling pancreatic duct or excessive contrast agent or bubbles entering the pancreas, (3) mechanical injury of pancreatic ducts and acini, (4) bacteria brought by imaging equipment or liquid infection in pancreatic duct or triggering original inflammation, (5) edema around pancreatic duct openings due to excessive coagulation in duodenal EST (EST) and impeding outflow of pancreatic secretion. Theoretically, post-ERCP pancreatitis could be reduced by mitigating papilla edema, keeping pancreatic and bile ducts open, controlling pancreatic secretion, avoiding contact of pancreatic tissue with active enzymes. Glyceryl trinitrate can relax smooth muscles not only in vascular wall but also in gastrointestinal tract, especially in the sphincter of Oddi. Sublingual glyceryl trinitrate shows its effect in 1-2 min and maintains its effect for 30 min. It also relaxes the sphincter of pancreatic and bile ducts when ERCP is performed, thus helping intubation and reducing spasm of sphincter of Oddi, keeping ducts open for contrast agent and pancreatin drainage, and reducing post-ERCP pancreatitis.

Sudhindran *et al*<sup>[10]</sup> suggested that sublingual glyceryl trinitrate (2 mg) before ERCP could relax sphincters, induce intubation and reduce 10% postoperative pancreatitis. Our study revealed that sublingual glyceryl trinitrate (5 mg) before ERCP could reduce pancreatitis and hyperamylasemia. Kaffes *et al*<sup>[11]</sup> showed that transdermal GTN could not improve the success rate of ERCP cannulation or prevent post-ERCP pancreatitis in either average or high-risk patient groups.

There was a significant difference between the study and placebo groups. Compared with other drugs, glyceryl trinitrate is inexpensive, convenient and has less side-effects, and can be used as a prospective drug for preventing post-ERCP pancreatitis.

## COMMENTS

### Background

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely applied method for the diagnosis and treatment of pancreatobiliary disease. Post-ERCP pancreatitis is the most common postoperative complication of ERCP and how to prevent it has become an urgent clinical challenge.

### Research frontiers

ERCP is an indispensable method for the diagnosis and treatment of hepatic and pancreatobiliary disease, and pancreatitis is the most common postoperative complication of it. There are some studies on drugs for preventing post-ERCP pancreatitis, but their results remain debatable. Therefore, most endoscopy centers do not give patients a conventional preventive drug therapy.

### Innovations and breakthroughs

This trial revealed that sublingual glyceryl trinitrate (5 mg) before ERCP could reduce pancreatitis and hyperamylasemia.

### Applications

Sublingual glyceryl trinitrate (5 mg) 5 min before the ERCP can prevent post-ERCP pancreatitis. Compared with other drugs, glyceryl trinitrate is inexpensive, convenient and has less side-effects, and can be as a prospective drug for preventing post-ERCP pancreatitis.

### Terminology

Post-ERCP pancreatitis stands for post-endoscopic retrograde cholangiopancreatography pancreatitis; ERCP stands for endoscopic retrograde cholangiopancreatography.

### Peer review

Pancreatitis is the most common postoperative complication of ERCP. This study showed that glyceryl trinitrate could relax the sphincter of pancreatic and bile ducts when ERCP was performed, thus helping intubation and reducing the spasm of sphincter of Oddi, keeping ducts open for contrast agent and pancreatic drainage, and reducing post-ERCP pancreatitis. Glyceryl trini-

trate is inexpensive, convenient and has less side-effect, and can be used a prospective drug for preventing post-ERCP pancreatitis.

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S- Editor Li LF L- Editor Wang XL E- Editor Zheng XM