Does glyceryl nitrate prevent post-ERCP pancreatitis? A prospective, randomized, double-blind, placebo-controlled multicenter trial

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Objective: Acute pancreatitis is the most dreaded complication of ERCP. Two studies have shown a significant effect of glyceryl nitrate (GN) in preventing post-ERCP pancreatitis (PEP). We wanted to evaluate this promising effect in a larger study with a realistically precalculated incidence of PEP.

Design/Patients: A randomized, double-blind, placebo-controlled multicenter study including patients from 14 European centers was performed. A total of 820 patients were entered; 806 were randomized.

Intervention: The active drug was transdermal GN (Discotrine/Minitran, 3M Pharma) 15 mg/24 hours; placebo (PL) was an identical-looking patch applied before ERCP. A total of 401 patients received GN; 405 received PL.

Results: Forty-seven patients had PEP (5.8%), 18 (4.5%) in the GN group and 29 (7.1%) in the PL group. The relative risk reduction of PEP in the GN group of 36% (95% CI, 11%-65%) compared with the PL group was not statistically significant ($P = .11$). Thirteen had mild pancreatitis (4 in the GN group, 9 in the PL group), 26 had moderate pancreatitis (9 in the GN group, 17 in the PL group), and 8 had severe pancreatitis (5 in the GN group, 3 in the PL group). Headache ($P < .001$) and hypotension ($P = .006$) were more common in the GN group. Significant variables predictive of PEP were not having biliary stones extracted; hypotension after ERCP; morphine, propofol, glucagon, and general anesthesia during the procedure; or no sufentanil during the procedure.

Conclusions: The trial showed no statistically significant preventive effect of GN on PEP. Because of a considerable risk of a type II error, an effect of GN may have been overlooked. (ClinicalTrials.gov ID: NCT00121901.) (Gastrointest Endosc 2009;69:e31-e37.)

Acute pancreatitis is a common and serious complication of ERCP. The incidence ranges from 1% to 40%, with a median of about 5%.[1] Although most episodes of post-ERCP pancreatitis (PEP) are mild (90%), some patients have severe necrotic pancreatitis, resulting in prolonged hospitalization, intensive care, and procedure-related death or sequelae. Therefore, attempts to prevent PEP have been tried by changing the technique, cautious patient selection, and pharmacologic measures.

Abbreviations: GN, glyceryl nitrate; PEP, post-ERCP pancreatitis; PL, placebo.

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Several drugs have been investigated, but few have been tested in controlled trials; somatostatin,[2,3] octreotide,[4] gabexate mesylate,[5] diclofenac,[6,7] and recombinant interleukin-10[8,9] are the drugs most investigated. In accordance with the theory of acute pancreatitis caused by sphincter hypertension, drugs relaxing the sphincter of Oddi have been tested. Nifedipine, a calcium-channel blocker, failed to reduce the rate of PEP,[10] but treatment with transdermal or sublingual glyceryl nitrate (GN) has been reported to be effective in 2 trials.[11,12] Moretó et al[11] and Sudhindran et al[12] showed a promising (ie, statistically significant) preventive effect, but their sample sizes were relatively small and the reported incidences of PEP were relatively high, probably because of rather liberal definitions of PEP.

The aim of this study was to answer the following clinical question: does GN prevent PEP compared with placebo (PL)?

PATIENTS

Inclusion and exclusion criteria are shown in Table 1. Patients were entered from October 2004 to April 2007; 820 were enrolled, and 14 were secondarily excluded (Fig. 1), which left 806. Center 1, Hvidovre, Denmark, included 105; center 2, Glostrup, Denmark, included 37; center 3, Gentofte, Denmark, included 77; center 4, Rigshospitalet, Denmark, included 33; center 5, Odense, Denmark, included 89; center 6, Stavanger, Norway, included 79; center 7, Malmö, Sweden, included 28; center 8, Fredrikstad, Norway, included 81; center 9, Haugesund, Norway, included 110; center 10, this center never started; center 11, Halmstad, Sweden, included 26; center 12, Marseille, France, included 23; center 13, Marseille, France, included 29; center 14, Oslo, Norway, included 50; and center 15, Køge, Denmark, included 39.

The study was stopped in accordance with the protocol because it had run for more than 2 years after the first patient was entered.

Capsule Summary

What is already known on this topic

- Acute pancreatitis as a complication of ERCP occurs at a median rate of 5% and has the potential to develop into severe necrotic pancreatitis, making prophylaxis against it highly desirable.

What this study adds to our knowledge

- In a randomized double-blind placebo-controlled trial of 806 patients, glyceryl nitrate had no effect in preventing post-ERCP pancreatitis.

METHODS

Randomization

The study was a randomized, double-blind, placebo-controlled parallel-group comparison. The patients were randomized to receive either a GN patch or a PL patch. The GN patch (Discotrine/Minitran, 3M Pharma, Denmark, Sweden, Norway, France) releases 15 mg of GN over 24 hours.[13] It was applied to the precordial area 30 to 45 minutes before the ERCP procedure. Patients in the control group had a similar-looking PL patch applied. Because the GN and PL patches looked slightly different, both kinds were covered with an opaque patch. The patch was removed 24 hours later by the patient. The time for removal was written on the cover patch.

A computer-generated randomization code in blocks of 10 stratified by center was prepared by an independent statistician (Johan Bring, Sweden). Each consecutive patient was given the next randomization number, and eligible patients were assigned in a 1:1 ratio to receive GN or PL. Opaque, closed, numbered envelopes contained a randomization number and information about whether the patient should have a GN or a PL patch. Envelopes were opened and patches placed by an endoscopy assistant who was not involved in the endoscopic procedure or in the observation of the patients afterward.

ERCP procedure

ERCP procedures were done according to local practice. Patients were monitored by pulse oximetry, and supplemental oxygen was administered. Contrast medium was injected manually under fluoroscopic guidance. Selective cannulation of the bile or pancreatic duct was done according to the ERCP indication. To inhibit excessive duodenal peristalsis, hyoscine butylbromide (Buscopan) or glucagon was administered intravenously at the discretion of the endoscopist. The use of current medication and premedication was registered in the case record form, which was filled in before and after the ERCP procedure (Table 2). Indications for ERCP and therapeutic procedures are shown in Table 3. Many of the procedures had more than 1 indication, and often more than 1 therapeutic procedure was performed.

Primary outcome measure

Acute pancreatitis within 7 days of the ERCP procedure was the primary outcome. A blind independent committee at each center judged retrospectively whether suspected patients had had PEP in respect to a specific definition.[14,15] The independent committee consisted of specialists who had no other personal involvement in the trial.

Secondary outcome measures

Secondary outcome measures were mild, moderate, and severe pancreatitis, as defined by Cotton et al[15]; PEP-related death; and side effects (headaches, vomiting/nausea, hypotension, skin rash, premature removal of the patch, other side effects).

Follow-up

Primary and secondary outcome measures were followed up by a letter concerning self-reporting of illness (specifically concerning pain, fever, hospitalization, and contact with general practitioner) after the ERCP procedure. If the letter was not received within 14 days of the procedure, patients were contacted by phone. If there was any suspicion of PEP, data from the patient file were collected. Patients with PEP were followed up until recovery, death, or the steady state had been reached. If the steady state had not been reached before the end of the trial, the patient was to be removed. This was not necessary in any patient.

Stopping rules and safety

When 800 patients had been enrolled, a blind interim analysis by an independent statistician was planned. If a significant difference in mortality rates between the 2 groups was seen, the study must stop. The study should