Efficacy of intramuscular diclofenac and fluid replacement in prevention of post-ERCP pancreatitis

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Abstract

AIM: To assess the efficacy of intramuscular diclofenac and fluid replacement for prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

METHODS: A prospective, placebo-controlled study was conducted in 80 patients who underwent ERCP. Patients were randomized to receive parenteral diclofenac at a loading dose of 75 mg followed by the infusion of 5-10 mL/kg per hour isotonic saline over 4 h after the procedure, or the infusion of 500 mL isotonic saline as placebo. Patients were evaluated clinically, and serum amylase levels were measured 4, 8 and 24 h after the procedure.

RESULTS: The two groups were matched for age, sex, underlying disease, ERCP findings, and type of treatment. The overall incidence of pancreatitis was 7.5% in the diclofenac group and 17.5% in the placebo group (12.5% in total). There were no significant differences in the incidence of pancreatitis and other variables between the two groups. In the subgroup analysis, the frequency of pancreatitis in the patients without sphincter of Oddi dysfunction (SOD) was significantly lower in the diclofenac group than in the control group ($P = 0.047$).

CONCLUSION: Intramuscular diclofenac and fluid replacement lowered the rate of pancreatitis in patients without SOD.

INTRODUCTION

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), with a reported incidence of 1%-10% in most prospective studies[1-9]. The generally accepted criteria for the diagnosis of post-ERCP pancreatitis were proposed in 1991 during a consensus workshop. These criteria include new onset of pancreatic-type abdominal pain associated with at least a threefold increase in serum amylase or lipase occurring within 24 h after ERCP, and the pain symptoms need to be sufficiently severe to require admission to the hospital or to extend the length of stay of patients who are already hospitalized[1,10].

There have been numerous theories about the mechanisms of pancreatitis. The most widely accepted theory is that mechanical trauma to the papilla or pancreatic sphincter, caused during instrumentation, creates transient obstruction of outflow of pancreatic juice[1]. Another theory suggests that the increased hydrostatic pressures in the pancreatic duct caused by injection of contrast or saline could cause injury to the pancreatic duct or parenchyma[1].

Risk factors reported for ERCP-induced pancreatitis include a history of pancreatitis[11], difficult cannulation[2], repeated injection of the pancreatic duct[11], pancreatic acinar opacification[12], sphincter of Oddi dysfunction (SOD)[3,13] and precut or needle-knife endoscopic sphincterotomy[9,13,14].

Cellular events that lead to pancreatitis involve an inflammatory process with premature activation of trypsin in acinar cells[15,16]. Phospholipase A_2 is believed to play a critical role in the initial inflammatory cascade of acute pancreatitis by regulating a number of pro-inflammatory mediators, including arachidonic acid products and platelet-activating factors[17]. Prevention or interruption of this cascade may prevent development of pancreatitis and its consequences. Although drug development has been impressive, the availability of effective drugs in the prevention and management of pancreatitis remains limited[15].

Chemoprevention of pancreatitis still remains a debated question. Pharmacological prevention of pancreatitis after ERCP has been the topic of several investigations in recent years.

Diclofenac, a potent inhibitor of phospholipase A_2 activity, administered immediately after the procedure, is effective at preventing pancreatitis[9,18]. Advantages of this prophylaxis are the low cost and the possibility of "on-demand" treatment. Addition of non-steroidal anti-inflammatory drugs (NSAIDs) has also been shown to have beneficial effects in experimental acute pancreatitis[19].

The aim of this study was to evaluate the efficacy of intramuscular (IM) diclofenac and fluid replacement for the prevention of pancreatitis in all eligible patients who underwent ERCP at our medical center.

MATERIALS AND METHODS

The study described in this report was approved by the ethics committee of Suleyman Demirel University School of Medicine, Isparta, Turkey. Between August 2006 and April 2008, 91 patients fulfilled the inclusion criteria, 80 of whom were included in the final analysis. Patients were excluded from study participation if they had a contraindication for diclofenac, including patients with recently diagnosed peptic ulcer disease, renal failure, those who had taken an NSAID during the preceding week, those who developed acute pancreatitis during the 2 wk before ERCP, those with a history of chronic pancreatitis, and those who did not agree to participate in the study. Entry to the study was restricted to patients advised to have endoscopic retrograde cholangiography with or without pancreatography for extrahepatic cholestasis and/or impaired liver function tests.

A prospective, placebo-controlled trial was conducted in 80 patients who underwent ERCP. The patients received 75 mg IM diclofenac and intravenous (IV) isotonic saline at a rate of 5-10 mL/kg per hour for 4 h or an inert placebo (500 mL IV isotonic saline) immediately after ERCP. At the end of each procedure, the researchers recorded the details of the maneuvers performed, including the total time of the procedure, the number of attempts at cannulation, the number of pancreatic duct cannulations, the final diagnosis, and whether a sphincterotomy, a needle-knife papillotomy, or stent placement were performed. We did not use pancreatic duct stenting for prevention of pancreatitis.

Patients were sedated with IV midazolam. Xylocaine spray was used as a local anesthetic.

Serum amylase was determined 4 h after ERCP. If the 4-h serum amylase level was < 3 times the upper normal limit and there was no clinical evidence of acute pancreatitis at that time, patients were allowed free oral fluids and a diet. If the 4-h serum amylase level was > 3 times the upper normal limit and the patient exhibited pain or nausea and vomiting, then the patient was kept fasting and IV crystalloid fluids with opiate analgesics were prescribed. The following 8 h and 24 h blood tests were repeated for serum amylase and the patients were interviewed and examined for clinical evidence of acute pancreatitis. Acute pancreatitis was defined as serum amylase > 3 times the upper limit of normal associated with epigastric pain, back pain, and epigastric tenderness. Patients with persistent signs and symptoms of pancreatitis after 48 h underwent contrast-enhanced computed tomography.

Pancreatitis was graded as mild, moderate, or severe. Sphincter of Oddi dysfunction (SOD) was defined according to the Milwaukee Biliary Group Classification[20].

The instruments used were cannula, sphincterotome, guidewire, and stone basket (Boston Scientific, Natick, MA, USA).

Statistical analysis

Data were summarized by descriptive statistics. The χ^2 square and Fischer's exact tests were used to compare categorical patient data. The Mann-Whitney U test and Student's t test were used to compare continuous variables. Two-tailed $P < 0.05$ were considered to indicate significance.

RESULTS

A total of 80 patients were eligible for the study. Forty patients received 75 mg diclofenac and isotonic saline replacement (diclofenac group), and 40 received inert parenteral fluid replacement (control group). No patients discontinued the study medication because of adverse effects. Overall, the baseline characteristics were consistent across all treatment groups (Table 1). The mean ages of patients in the diclofenac and control groups were 60.3 ± 16.1 years and 59.3 ± 14.4 years, respectively. There were 15 women in the diclofenac group and 22 in the control group. Similarly, there were no statistically significant differences between the groups considering the procedures, and factors that might increase the risk of pancreatitis, including single or repeated pancreatic duct injection, SOD, younger age, female sex and precut endoscopic sphincterotomy (Table 2). Although the frequency of pancreatitis in the patients with SOD did not differ between the diclofenac and control groups, it was statistically significant between groups when the patients with SOD was excluded ($P = 0.047$). The most frequent indication for ERCP was bile duct stone in the diclofenac (57.5%) and control (27.5%) group. Post-endoscopic bleeding

Table 1 Characteristics of patients in the diclofenac and control groups[1]

Variables	Diclofenac group (n = 40)	Control group (n = 40)	P
Age (yr)[2]	60.3 ± 16.1	59.3 ± 14.5	0.766
Female sex	15 (37.5)	22 (55.0)	0.116
Bile duct canulation time (min)[3]	5.0 (3.0-5.0)	5.0 (3.0-10.0)	0.601
Operation time (min)[3]	15 (15-20)	15 (10-25)	0.904
Sphincterotomy			
Precut	10 (25)	12 (30)	0.617
Pancreatic duct injection	19 (47.5)	18 (45.0)	0.823
Pancreatic duct cannulation, twice or more	8 (20.5)	6 (15.0)	0.556
Post-ERCP pancreatitis	3 (7.5)	7 (17.5)	0.176
Final diagnosis			
BD stone	23 (57.5)	11 (27.5)	
SOD	3 (7.5)	10 (25.0)	0.082
Biliopancreatic tumors	5 (12.5)	9 (22.5)	
Others[4]	9 (22.5)	10 (25.0)	

[1]All data were presented as [*n* (%)] and comparisons were made with χ^2 or Fisher's exact test unless otherwise stated. [2]Data was presented as (mean ± SD) and comparison was made with Student's *t* test. [3]Data were presented as [median (interquartile range)] and comparisons were made with Mann-Whitney *U* test. [4]Primary sclerosing cholangitis, hydatid cysts communicating with the bile ducts, Mirizzi sendrome, and postoperative complications. Post-ERCP: Post-endoscopic retrograde cholangiopancreatography; SOD: Sphincter of Oddi dysfunction.

Table 2 Incidence of post-ERCP pacreatitis in different subgroups[1]

Variables	Diclofenac group (n = 40)	Control group (n = 40)	P
Age group (yr)			
> 60	2/23	4/20	0.300
≤ 60	1/17	3/20	0.420
Sex			
Male	0/25	2/18	0.850
Female	3/15	5/22	0.092
Pre-cut sphincterotomy			
Yes	1/10	4/12	0.210
No	2/30	3/28	0.590
Pancreatic duct injection			
Yes	2/19	4/18	0.350
No	1/21	3/22	0.330
Pancreatic duct cannulation, twice or more	2/8	1/6	0.730
SOD			
Yes	2/3	2/10	0.150
No	1/37	5/30	0.047[1]

[1]All data were comparisons with the χ^2 test. There were no statistically significant differences except in the patients without SOD.

Table 3 Serum amylase level (mean ± SE, IU/L) following ERCP in diclofenac and control groups

Group	Amylase 4 h	Amylase 8 h	Amylase 24 h
Diclofenac	223.95 ± 33.45	218.39 ± 35.44	161.82 ± 31.03
Control	283.15 ± 82.74	308.34 ± 96	231.56 ± 57.73

There were no statistically significant differences.

because of sphincterotomy was observed in three of 75 sphincterotomy patients (3.75%). All the bleeding was seen during the procedure. No case of delayed bleeding occured. Two of three bleeding episodes in the control group and one in the diclofenac group were self-limited and stopped during endoscopy without intervention.

Pancreatitis occurred in 10/80 patients (12.5%), three of whom (7.5%) belonged to the diclofenac group and seven (17.5%) belonged to the control group (Table 1). Four and eight hours after endoscopy, the mean ± SE serum amylase level was 283.15 ± 82.74 IU/L and 308.34 ± 96 IU/L in the control group and 223.95 ± 35.45 IU/L and 218.39 ± 35.44 IU/L in the diclofenac group. Twenty-four hours after endoscopy, the mean ± SE serum amylase level was 231.56 ± 57.73 IU/L in the control group and 161.82 ± 31.03 IU/L in the diclofenac group (Table 3). In the diclofenac group, the mean values of amylase were low but the statistical difference was not significant ($P > 0.01$).

DISCUSSION

The number of ERCP procedures performed annually worldwide has increased dramatically over the past 25 years. Pancreatitis occurs in 1%-10% of patients but may approach ≥ 25% depending on the presence of other risk factors[15].

Several mechanical and pharmacological interventions have been evaluated in the prevention of pancreatitis. The availability of effective drugs and strategy of chemoprevention are unresolved issues in the pharmacological prophylaxis of pancreatitis. Previous studies on reducing the incidence of pancreatitis have targeted reduction of pancreatic secretion, prevention of intra-acinar trypsinogen activation, interruption of the inflammatory cascades, relaxation of the sphincter of Oddi, and prevention of infection[21].

An ideal agent is highly effective in reducing pancreatitis, is safe for the patient, well tolerated, relatively affordable, and does not have a prolonged administration time[1]. Various pharmacological agents (such as nifedipine, glucagon, calcitonin, lidocaine, nitroglycerine, antibiotics, steroids, allopurinol, interleukin-10, and heparin) have been tried, but have met with disappointing results in preventing pancreatitis in randomized controlled trials[1,22-34].

Only two agents seem to offer any clinical benefit: the protease inhibitor gabexate mesilate[35-37] and the antisecretory agent somatostatin may be efficacious in preventing pancreatitis when given by continuous IV infusion[34,38,39]. Since these agents require continuous and prolonged IV infusion, they are not suited for same-day outpatient ERCP[34].

Several prospective randomized studies have shown that pancreatic stents have a beneficial role for prevention of pancreatitis in high-risk patients, including biliary and pancreatic sphincterotomy for SOD[40-42], biliary balloon dilation for stone[43] and precut biliary sphincterotomy[21]. Although pancreatic stenting is

often beneficial, the down sides include the difficulty of stent insertion in patients with small or tortous ducts and the follow-up required for stent removal. A simple prophylactic medication would be highly desirable[21].

NSAIDs may prevent pancreatitis by inhibiting prostaglandin synthesis and interrupting the inflammatory cascade of pancreatitis[34].

In the report by Sotoudehmanesh et al[15], eligible patients undergoing ERCP (n = 490) were randomized to receive a 100-mg indomethacin rectal suppository (n = 245) or placebo (n = 245) just prior to ERCP, and rates of post-procedure pancreatitis were assessed. Pancreatitis occurred in 7/221 (3.2%) patients in the indomethacin group and in 15/221 (6.8%) of those receiving placebo (P = 0.06), with an overall pancreatitis rate of 5% (22/442).

Montaño Loza et al[45] have reported a randomized prospective clinical trial that compared indomethacin with placebo in the prevention of pancreatitis. They enrolled patients undergoing ERCP for suspected bile duct obstruction rather than selecting for a high-risk cohort. Rectal indomethacin (100 mg) or placebo was administered prior to ERCP. Seventy-five patients were randomized to each group, a sample size that was calculated a priori to detect a 15% reduction in pancreatitis. The overall incidence of pancreatitis was 10.7%. The incidence of pancreatitis was 16% (12/75) in the placebo group and 5.3% (4/75) in the indomethacin group. This difference was statistically significant, with a P value of 0.034. All pancreatitis cases in both groups were categorized as mild[44,45].

Diclofenac, an NSAID, inhibits phospholipase A_2, which is thought to play a critical role in the early inflammatory cascade. In addition, it strongly inhibits neutrophil/endothelial attachment, thus preventing accumulation of neutrophils at the site of tissue damage[46], and inhibits the expression of nitric oxide synthase, an enzyme associated with inflammation and cell damage[47]. It is a cheap, widely available agent with a short, easy method of administration.

Murray et al[9] have conducted a single-center, prospective, randomized, double-blind, placebo-controlled study to determine if a single dose of rectally administered 100 mg diclofenac, given after ERCP, reduced the incidence of pancreatitis. Of 220 patients, 110 received rectal diclofenac, and the others, an inert placebo. Pancreatitis occurred in 6.4% of patients in the diclofenac group and in 15.5% of those receiving placebo (P = 0.049). This difference was statistically significant. Also, the drug was not effective in the subgroup of patients with SOD, the very group at highest risk[9].

Khoshbaten et al[18] have reported a randomized controlled study that compared 100 mg rectal diclofenac with placebo in 100 patients who underwent high-risk ERCP. To select high-risk cases, only those undergoing pancreatography (with or without cholangiography) were enrolled. The study drug or placebo was administered on arrival in the recovery area. The overall incidence of pancreatitis was 15%. The incidence of pancreatitis in the placebo group was 26% (13/50), whereas the incidence of pancreatitis in the diclofenac group was 4% (2/50). This difference was statistically significant, with P < 0.01. No patients in this clinical trial developed necrotizing pancreatitis or required surgical intervention[18,44].

We showed that, in the diclofenac group, pancreatitis was seen less than in the control group, but this was not statistically significant. The absence of the statistical difference may have been caused by the small number of patients.

A number of risk factors for post-ERCP pancreatitis have been identified by a multitude of studies that have different study designs, have examined different candidate predictor variables, and have taken place in a variety of settings[15]. The impact of some of these associations has been supported by large, multicenter prospective trials, while others have been suggested in smaller series and by clinical experience. Risk factors that have been recognized as independent predictors in more than one study include: younger age, female sex, pancreas divisum, SOD, prior ERCP-induced pancreatitis, difficulty of cannulation, and pancreatic duct injection[15]. None of the patients in our study had pancreas divisium or prior ERCP-induced pancreatitis. Also, there was no significant difference in the incidence of pancreatitis when comparing diclofenac with placebo, in patients with younger age, female sex, SOD, pre-cut sphincterotomy and twice or more pancreatic duct cannulation (P > 0.01). In our study, subgroup analysis showed that diclofenac significantly decreased the frequency of pancreatitis only in the patients without SOD. All the cases of pancreatitis were mild and the patients were discharged from the hospital within several days without any complication.

Acute pancreatitis is an unstable disease that causes intravascular fluid loss because of local and systemic inflammation. Clinical improvement can be achieved by fluid infusion. Fluid resuscitation is the most important treatment during the first 72 h after onset of acute pancreatitis. Therefore, the two goals of early phase fluid resuscitation are amelioration of tissue hypoxia and prevention of complications[48].

In our study, IV isotonic saline was given to the diclofenac group in the initial 4 h (5-10 mL/kg per hour) after ERCP. Five hundred milliliters isotonic saline was given to the control group to keep the IV line open. Although the importance of fluid management in acute pancreatitis is known, there have not been so many studies about the prophylactic effects of this approach.

In conclusion, our study showed that parenteral diclofenac and hydratation tended to prevent post-ERCP pancreatitis, but the finding was not statistically significant. In the whole group, diclofenac did not prevent the occurrence of pancreatitis but, according to the subgroup analysis, in patients without SOD, it significantly prevented pancreatitis. For this reason, further studies are required on the efficacy of this treatment with other doses and combinations of diclofenac and hydratation that might prevent pancreatitis.

COMMENTS

Background

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Pharmacological prevention of pancreatitis after ERCP has been the topic of several investigations in recent years.

Research frontiers

Various pharmacological agents have been tried but have met with disappointing results in preventing pancreatitis in randomized controlled trials. Non-steroidal anti-inflammatory drugs may prevent pancreatitis by inhibiting prostaglandin synthesis and interrupting the inflammatory cascade of pancreatitis. The importance of fluid management in acute pancreatitis is known, but there have not been many studies about the prophylactic effects of this approach.

Innovations and breakthroughs

The overall results of this study showed that parenteral diclofenac and fluid replacement had no beneficial effect on the prevention of pancreatitis. Although diclofenac and fluid replacement did not prevent the occurrence of post-ERCP pancreatitis, the rate of pancreatitis was lower in those patients without sphincter of Oddi dysfunction (SOD) who received diclofenac. To prevent post-ERCP pancreatitis, further studies should be carried with the other doses and combinations of diclofenac and hydratation in a larger group of patients.

Applications

This study was designed to evaluate the efficacy of prophylactic intramuscular diclofenac and fluid replacement for the prevention of post-ERCP pancreatitis.

Peer review

This study aimed to find a pharmacological way for preventing post-ERCP pancreatitis. The results show that prophylactic intramuscular diclofenac and fluid replacement has no benefit except in patients without SOD.

REFERENCES

1   **Cooper ST**, Slivka A. Incidence, risk factors, and prevention of post-ERCP pancreatitis. *Gastroenterol Clin North Am* 2007; **36**: 259-276, vii-viii

2   **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434

3   **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918

4   **Andriulli A**, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, Leandro G, Leo P, De Maio G, Perri F. 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**: 488-495

5   **Christoforidis E**, Goulimaris I, Kanellos I, Tsalis K, Demetriades C, Betsis D. Post-ERCP pancreatitis and hyperamylasemia: patient-related and operative risk factors. *Endoscopy* 2002; **34**: 286-292

6   **Masci E**, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; **96**: 417-423

7   **Vandervoort J**, Soetikno RM, Tham TC, Wong RC, Ferrari AP Jr, Montes H, Roston AD, Slivka A, Lichtenstein DR, Ruymann FW, Van Dam J, Hughes M, Carr-Locke DL. Risk factors for complications after performance of ERCP. *Gastrointest Endosc* 2002; **56**: 652-656

8   **Cheng CL**, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Lazzell-Pannell L, Rashdan A, Temkit M, Lehman GA. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006; **101**: 139-147

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**: 1786-1791

10 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393

11 **Podolsky I**, Haber GB, Kortan P, Gray R. Risk factors for pancreatitis following ERCP: A prospective study (abstract). *Am J Gastroenterol* 1987; **82**: 972A

12 **Bilbao MK**, Dotter CT, Lee TG, Katon RM. Complications of endoscopic retrograde cholangiopancreatography (ERCP). A study of 10,000 cases. *Gastroenterology* 1976; **70**: 314-320

13 **Barthet M**, Lesavre N, Desjeux A, Gasmi M, Berthezene P, Berdah S, Viviand X, Grimaud JC. Complications of endoscopic sphincterotomy: results from a single tertiary referral center. *Endoscopy* 2002; **34**: 991-997

14 **De Palma GD**, Catanzano C. Use of corticosteroids in the prevention of post-ERCP pancreatitis: results of a controlled prospective study. *Am J Gastroenterol* 1999; **94**: 982-985

15 **Sotoudehmanesh R**, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. *Am J Gastroenterol* 2007; **102**: 978-983

16 **Whitcomb DC**. Acute pancreatitis: molecular biology update. *J Gastrointest Surg* 2003; **7**: 940-942

17 **Gross V**, Leser HG, Heinisch A, Schölmerich J. Inflammatory mediators and cytokines--new aspects of the pathophysiology and assessment of severity of acute pancreatitis? *Hepatogastroenterology* 1993; **40**: 522-530

18 **Khoshbaten M**, Khorram H, Madad L, Ehsani Ardakani MJ, Farzin H, Zali MR. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. *J Gastroenterol Hepatol* 2008; **23**: e11-e16

19 **Wildenhain PM**, Melhem MF, Birsic WI, Sell HW, Rao KN. Acute hemorrhagic pancreatitis in mice: improved survival after indomethacin administration. *Digestion* 1989; **44**: 41-51

20 **Hogan WJ**, Geenen JE. Biliary dyskinesia. *Endoscopy* 1988; **20** Suppl 1: 179-183

21 **Cheon YK**, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, Schmidt S, Lazzell-Pannell L, Lehman GA. Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. *Gastrointest Endosc* 2007; **66**: 1126-1132

22 **Sherman S**, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB, Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Earle D, Temkit M, Lehman GA. Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. *Gastrointest Endosc* 2003; **58**: 23-29

23 **Katsinelos P**, Kountouras J, Chatzis J, Christodoulou K, Paroutoglou G, Mimidis K, Beltsis A, Zavos C. High-dose allopurinol for prevention of post-ERCP pancreatitis: a prospective randomized double-blind controlled trial. *Gastrointest Endosc* 2005; **61**: 407-415

24 **Dumot JA**, Conwell DL, O'Connor JB, Ferguson DR, Vargo JJ, Barnes DS, Shay SS, Sterling MJ, Horth KS, Issa K, Ponsky JL, Zuccaro G. Pretreatment with methylprednisolone to prevent ERCP-induced pancreatitis: a randomized, multicenter, placebo-controlled clinical trial. *Am J Gastroenterol* 1998; **93**: 61-65

25 **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**: 2098-2102

26 **Rabenstein T**, Fischer B, Wiessner V, Schmidt H, Radespiel-Tröger M, Hochberger J, Mühldorfer S, Nusko G, Messmann H, Schölmerich J, Schulz HJ, Schönekäs H, Hahn EG, Schneider HT. Low-molecular-weight heparin does not

prevent acute post-ERCP pancreatitis. *Gastrointest Endosc* 2004; **59**: 606-613

27   **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**: 1178-1182

28   **Moretó M**, Zaballa M, Casado I, Merino O, Rueda M, Ramírez K, Urcelay R, Baranda A. Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: A randomized double-blind trial. *Gastrointest Endosc* 2003; **57**: 1-7

29   **Sand J**, Nordback I. Prospective randomized trial of the effect of nifedipine on pancreatic irritation after endoscopic retrograde cholangiopancreatography. *Digestion* 1993; **54**: 105-111

30   **Prat F**, Amaris J, Ducot B, Bocquentin M, Fritsch J, Choury AD, Pelletier G, Buffet C. Nifedipine for prevention of post-ERCP pancreatitis: a prospective, double-blind randomized study. *Gastrointest Endosc* 2002; **56**: 202-208

31   **Silvis SE**, Vennes JA. The role of glucagon in endoscopic cholangiopancreatography. *Gastrointest Endosc* 1975; **21**: 162-163

32   **Ohnhaus EE**, Witzel L, Halter F, Stauffacher W. [The effect of salmon calcitonin on pancreatic enzymes and hormones before and after retrograde cholangiopancreatography] *Schweiz Med Wochenschr* 1981; **111**: 750-754

33   **Odes HS**, Novis BN, Barbezat GO, Bank S. Effect of calcitonin on the serum amylase levels after endoscopic retrograde cholangiopancreatography. *Digestion* 1977; **16**: 180-184

34   **Wagh MS**, Sherman S. Indomethacin for post-ERCP pancreatitis prophylaxis: another attempt at the Holy Grail. *Am J Gastroenterol* 2007; **102**: 984-986

35   **Andriulli A**, Leandro G, Niro G, Mangia A, Festa V, Gambassi G, Villani MR, Facciorusso D, Conoscitore P, Spirito F, De Maio G. Pharmacologic treatment can prevent pancreatic injury after ERCP: a meta-analysis. *Gastrointest Endosc* 2000; **51**: 1-7

36   **Andriulli A**, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, Leandro G, Leo P, De Maio G, Perri F. 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**: 488-495

37   **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. Gabexate in digestive endoscopy--Italian Group. *N Engl J Med* 1996; **335**: 919-923

38   **Arvanitidis D**, Anagnostopoulos GK, Giannopoulos D, Pantes A, Agaritsi R, Margantinis G, Tsiakos S, Sakorafas G, Kostopoulos P. Can somatostatin prevent post-ERCP pancreatitis? Results of a randomized controlled trial. *J Gastroenterol Hepatol* 2004; **19**: 278-282

39   **Thomopoulos KC**, Pagoni NA, Vagenas KA, Margaritis VG, Theocharis GI, Nikolopoulou VN. Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis. *Gastrointest Endosc* 2006; **64**: 726-731

40   **Tarnasky PR**, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology* 1998; **115**: 1518-1524

41   **Fogel EL**, Eversman D, Jamidar P, Sherman S, Lehman GA. Sphincter of Oddi dysfunction: pancreaticobiliary sphincterotomy with pancreatic stent placement has a lower rate of pancreatitis than biliary sphincterotomy alone. *Endoscopy* 2002; **34**: 280-285

42   **Patel R**, Tarnasky P, Hennessy WS, Hawes RH, Payne KM, Nelles SE, Cunningham JT, Cotton PB. Does stenting after pancreatic sphincterotomy reduce post-ERCP pancreatitis in patients with prior biliary sphincterotomy? Preliminary results of a prospective randomized trial [abstract]. *Gastrointest Endosc* 1999; **49**: AB80

43   **Aizawa T**, Ueno N. Stent placement in the pancreatic duct prevents pancreatitis after endoscopic sphincter dilation for removal of bile duct stones. *Gastrointest Endosc* 2001; **54**: 209-213

44   **Elmunzer BJ**, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. *Gut* 2008; **57**: 1262-1267

45   **Montaño Loza A**, Rodríguez Lomelí X, García Correa JE, Dávalos Cobián C, Cervantes Guevara G, Medrano Muñoz F, Fuentes Orozco C, González Ojeda A. [Effect of the administration of rectal indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes] *Rev Esp Enferm Dig* 2007; **99**: 330-336

46   **Tarnasky P**, Cunningham J, Cotton P, Hoffman B, Palesch Y, Freeman J, Curry N, Hawes R. Pancreatic sphincter hypertension increases the risk of post-ERCP pancreatitis. *Endoscopy* 1997; **29**: 252-257

47   **Ohashi A**, Tamada K, Tomiyama T, Wada S, Higashizawa T, Gotoh Y, Satoh Y, Miyata T, Tano S, Ido K, Sugano K. Epinephrine irrigation for the prevention of pancreatic damage after endoscopic balloon sphincteroplasty. *J Gastroenterol Hepatol* 2001; **16**: 568-571

48   **Mao EQ**, Tang YQ, Fei J, Qin S, Wu J, Li L, Min D, Zhang SD. Fluid therapy for severe acute pancreatitis in acute response stage. *Chin Med J* (Engl) 2009; **122**: 169-173