

SID



سرویس های ویژه



سرویس ترجمه تخصصی



کارگاه های آموزشی



بلاگ مرکز اطلاعات علمی



عضویت در خبرنامه



فیلم های آموزشی

کارگاه های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی



کارگاه آنلاین آشنایی با پایگاه های اطلاعات علمی بین المللی و ترند های جستجو



مباحث پیشرفته یادگیری عمیق؛ شبکه های توجه گرافی (Graph Attention Networks)



کارگاه آنلاین مقاله نویسی IEEE و ISI ویژه فنی و مهندسی

Original Article

Prophylactic Effect of Rectal Indomethacin Administration, with and without Intravenous Hydration, on Development of Endoscopic Retrograde Cholangiopancreatography Pancreatitis Episodes: A Randomized Clinical Trial

Mousalreza Hosseini MD¹, Payman Shalchiantabrizi MD², Khadijeh Yektaroudy MD³, Maliheh Dadgarmoghaddam MD⁴, Masoumeh Salari MD⁵

Abstract

Background: Acute Post ERCP Pancreatitis (PEP) is the most common major complication of Endoscopic retrograde cholangiopancreatography (ERCP). The aim of the current study was to assess the utility of single dose rectal indomethacin with and without intravenous perfusion of normal saline to prevent acute pancreatitis.

Methods: In this randomized clinical trial, 406 patients with choledocolithiasis underwent ERCP. Based on computer-generated numbers, the patients were allocated into 4 groups, each group receiving a different intervention prior to the ERCP procedure. The interventions included rectal indomethacin (100mg) in the first group, intravenous (IV) saline perfusion in the second, both rectal indomethacin and IV saline in the third, and the fourth (control) group receiving rectal glycerin. Serum amylase levels were measured and clinical pancreatitis episodes were quantified and classified according to APACHE II prognostic criteria. Statistical inference was performed using the chi-square or Fisher's exact test for qualitative variables, while Student's zxA-test was used for quantitative variables.

Results: A diagnosis of mild pancreatitis was present in 38 (9.4%) cases. The numbers of events in the four study groups were 11, 10, 0, and 17, respectively, corresponding to an absolute risk reduction of 5.2% , 6.2%, 16.2% (number needed to prevent one episode of PEP) and a relative risk reduction of 32%, 38% and 100% in the three study groups, respectively. The frequency of PEP was only significant in the third group ($P < 0.001$).

Conclusions: The combination of rectal indomethacin and intravenous normal saline before ERCP significantly prevents post-ERCP pancreatitis.

Keywords: Endoscopic retrograde cholangiopancreatography (ERCP), cholangiopancreatography pancreatitis (PEP)Indomethacin, post-endoscopic retrograde, saline solution

Cite this article as: Hosseini M, Shalchiantabrizi P, Yektaroudy K, Dadgarmoghaddam M, Salari M. Prophylactic Effect of Rectal Indomethacin Administration, with and without Intravenous Hydration, on Development of Endoscopic Retrograde Cholangiopancreatography Pancreatitis Episodes: A Randomized Clinical Trial. *Arch Iran Med.* 2016; **19**(8): 538 – 543.

Introduction

ERCP is a procedure used to both diagnose and treat diseases of the pancreaticobiliary tree. The figure for Iran is yet to be reported. The use of ERCP can be accompanied by perforation, bleeding and pancreatitis.¹ The frequencies of these problems for diagnostic and therapeutic ERCP have been estimated to be up to 6% and 10%, respectively.^{1,2} The extent of mortality depends on the severity of comorbidities. The most

common cause of death is cardiopulmonary failure due to sedation or anesthesia.

Acute PEP is the most common major complication of ERCP accounting for substantial morbidity, occasional death, and significant health care expenditures. Its incidence rates after diagnostic and therapeutic ERCP in average risk patients are 1.5% and 5.4%, respectively, but may approach 39% in high-risk patients.³ The exact numbers for Iranian population are unknown. The wide range for this incidence stems from patient characteristics, as well as procedure-related, and operator-related factors.^{1,4} The diagnosis of PEP is based on the presence of new or worsened abdominal pain, increase in serum amylase at least 3 times above the upper limit of normal measured 24 h after the procedure and need for more than one night of hospitalization.³ The patients, depending on the severity of pancreatitis, may be stratified into three classes of mild, moderate and severe.⁵

The patient's inflammatory response to pancreatic duct imaging or instrumentation is thought to play a critical role.^{4,6} Risk factors include female gender, younger age, difficult cannulation, unjustified persistent abdominal pain in the absence of anatomic abnormalities, history of pancreatitis, use of pre-cutting technique,

Authors' affiliations: ¹Assistant Professor of Gastroenterology and Hepatology, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ²Internist, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ³Postgraduate Student of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ⁴Assistant Professor of Community Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ⁵Assistant Professor of Internal Medicine, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Corresponding author and reprints: Masoumeh Salari MD, Assistant Professor of Internal Medicine, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985138012742; Cellphone: +989155050927; E-mail: salarim@mums.ac.ir

Accepted for publication: 15 May 2016

sphincter of Oddi dysfunction and repeated contrast perfusion.⁷ The goal of recognizing the risk factors of PEP is the development of a strategy for prevention of PEP including careful patient selection for ERCP and selection of appropriate mechanical and pharmacological preventive measures.

The risk of PEP is greater in patients who undergo simultaneous sphincterotomy. Amylase elevation can be observed in more than 70% of these patients. However, not all these patients show the clinical signs of pancreatitis.⁸ Preventative measures include paying attention to the details of the technique. Cannulation must be performed quickly and with minimum trauma.⁸

Various pharmacologic agents have been employed, before or immediately after the ERCP procedure, to minimize the incidence and severity of PEP. These pharmacologic agents include aprotinin, calcitonin, glucagon, nifedipine, glucocorticoid, N-acetyl-cysteine, protease inhibitors such as gabexate mesilate and several antibiotics.^{2,3,9-13}

Nonsteroidal antiinflammatory drugs (NSAIDs) are potent inhibitors of phospholipase A₂, cyclooxygenase, and neutrophil-endothelial interactions, all believed to play an important role in the pathogenesis of acute pancreatitis. NSAIDs are inexpensive and easily administered and have a favorable risk profile when given as a single dose, making them an attractive option in the prevention of PEP. Previous studies evaluating the protective effects of single-dose rectal indomethacin in PEP as well as experimental models of pancreatitis have been conducted and a meta-analysis suggests benefit. Despite these data, rectal NSAIDs are seldom used in clinical practice because efforts to endorse them for PEP prophylaxis have been limited by small studies with conflicting results and because previous positive meta-analyses of other agents have been disproved by further investigation.^{14,15} To this end, we conducted a randomized, controlled clinical trial to evaluate the efficacy of prophylactic rectal indomethacin with and without intravenous perfusion of normal saline for prevention of PEP in conscious patients undergoing elective ERCP. Its effect was also compared with the effect of intravenous perfusion of normal saline.

Materials and Methods

Study design

This randomized clinical trial was carried out on patients who underwent ERCP from 2014 to 2015 at the Gastroenterology Department of Ghaem Teaching and referral Hospital, Mashhad University of Medical Sciences, Iran. Sample size was estimated by specific clinical trial formula based on $\alpha = 0.05$ and $\beta = 0.2$ that was equal to 80 in each group. Considering 20% attrition, we calculated 100 samples in each of the four groups. Out of a total number of 600 candidates, 406 patients meeting the criteria underwent ERCP. We enrolled patients after approval from the Safety Monitoring and Human Studies Review Board at Ghaem Hospital. The board provided regulatory oversight by reviewing the research protocol and blinded subject data quarterly. This study is registered in the Iranian Registry Of Clinical Trials (IRCT.Number:2014082418915N1).

Patients

The patients accepted their enrollment in the study by signing an informed consent form prior to the study. Only those patients with choledocolithiasis who were candidates for elective ERCP,

as opposed to emergent, were eligible. In addition, candidates were required to have no risk factors for PEP, such as procedural/anatomical complexities or a significant medical history. A diagnosis of PEP was established if serum amylase levels were at least three times the upper limit of the normal value and the patient presented with abdominal pain, nausea and vomiting.

The patients who did not consent to the study, had unsuccessful cannulation, or were unsuited for elective ERCP due to sepsis and its complications (e.g., decreased state of consciousness, coagulaopathy, or deteriorating general conditions) were excluded from the study. These patients had received multiple medications and intravenous serum infusions and were not suitable candidates for the trial. Likewise, those with a history of the Whipple surgical procedure or cardiovascular/renal diseases including need for dialysis were excluded. Furthermore, no patients with clinically evident acute pancreatitis, chronic pancreatitis, pancreatic cancer, hyperamylasemia (≥ 150 IU/L) before the procedure, or ingestion of NSAIDs within the prior week were enrolled. Patients allergic or hypersensitive to indomethacin or water-soluble contrast solutions were also removed from the study. The eligible patients were hospitalized and put on fast from 8 hours before the procedure to 12 hours afterwards. They underwent randomization into four groups before ERCP.

Intervention

The patients were randomly allocated into 4 groups by simple randomization based on computer-generated random numbers. The subjects, investigators, and involved health care providers did not know to which group a subject would be allocated before that subject entered the study and allocation concealment was kept.

The patients were oriented about the general goals of the study. However, they did not have any information regarding the specific goals (i.e., they were not aware of what was performed routinely for ERCP or what was done based on the study requirements in addition to the routine measures), so all the patients were blinded.

An internist completed the interventional procedure independently of the gastroenterologist prior to referral of the patient to the ERCP room, thus making the gastroenterologist unaware of the group to which each patient belonged.

The first study group (100 subjects) received 100 mg of indomethacin rectally two hours before the ERCP procedure. The patients in the second group (100 subjects) received 1 liter of intravenous normal saline within 2 hours before the procedure and 2 liters within 16 hours after completion of the procedure. The patients in the third group (101 subjects) were simultaneously administered rectal indomethacin and intravenous normal saline. The patients in the control group (105 subjects) received 2 g of glycerin in suppositories. The indomethacin suppositories were commercial products with confirmed potency and content uniformity testing. All cases of ERCP were performed under midazolam sedation and by an experienced gastroenterologist from the hospital who collaborated in a prospective study. The technique and contrast medium employed were similar for all patients. During the procedure, the patients underwent cardiac monitoring and pulse oximetry. Bile duct cannulation and sphincterotomy were performed on all patients with choledocolithiasis. In cases with unsuccessful cannulation attempts, the patients were inserted with a catheter without sphincterotomy and were discharged.

Blood samples were taken from patients to determine serum amylase levels before the procedure as well as 2, 12, and 24 hours

afterwards. The cases were controlled by intravenous hydration while fasting. Pancreatitis episodes were classified into three grades of mild, moderate and severe according to APACHE II prognostic criteria. Patients with elevated serum amylase and no evidence of pancreatitis were removed from the study. These patients were contacted within 5 days to capture delayed occurrence of the primary end point and again at 30 days to assess for delayed adverse events. Details describing the endoscopic procedure and follow-up data were recorded. The patients were observed in the recovery area for at least 2 hours after the procedure. Decisions regarding evaluation of complications and inpatient care were up to the gastroenterologist who was unaware of study-group assignments. The outcome of the study was development of PEP. Any cases of PEP, other complications of the procedure, and adverse events that were potentially attributable to the intervention were reported to the local institutional review board and the data and safety monitoring board.

Statistical analysis

Results are shown as average values, percentages, and means with standard deviations. Statistical inference was performed using the Chi square or Fisher's exact test for qualitative variables, while Student's *t*-test was used for quantitative variables. To explore the behavior of risk factors, relative risks and 95% confidence intervals were estimated. All *p* values lower than 0.05 were considered statistically significant. Finally, the reduction in absolute risk (RRA) and the reduction in relative risk (RRR), were analyzed in order to prevent an episode of pancreatitis. The statistician was not aware of the type of intervention received by each group.

Results

From 2014 to 2015, out of the 600 patients initially considered for participation in the study, a total of 406 subjects were ultimately enrolled. Figure 1 shows who was included and excluded from the trial.

The data and safety monitoring board performed an interim analysis to assess the outcomes of the first 406 patients and recommended that the study be terminated early on the basis of the benefit of preventive approaches as compared with placebo. Follow-up of all patients for the end points was complete. The distribution by gender consisted of 202 men (50%) and 204 women (50%) with no significant difference ($P = 0.8$). The mean age values of males and females were 51.7 ± 13.2 and 47.71 ± 12.1 , respectively, with no significant difference ($P > .05$).

All patients had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels two to twenty times the upper limit of normal. Similarly, alkaline phosphatase (ALP) levels were four times the upper limit of normal. Total bilirubin was in the normal upper limit range. The common bile duct was dilated in all patients with stone or sludge on ultrasound exam. The demographic characteristics of patients are shown in Table 1.

All participating subjects underwent ERCP and sphincterotomy. The baseline characteristics were similar in the four study groups. The interventions included rectal indomethacin (100mg) in the first group (100 subjects), intravenous (IV) saline perfusion in the second (100 subjects), both rectal indomethacin and IV saline in the third (101 subjects), and the fourth (control) group receiving rectal glycerin (105 subjects) (Table 2).

Totally, 38 patients (9.4%) met the criteria for the outcome (PEP). The distribution by gender out of 202 males and 204 females, consisted of 18 (8.9%) and 20 (9.8%), respectively, with no statistically significant difference ($P = 0.7$). The numbers of events in the four study groups were 11, 10, 0, and 17, respectively, corresponding to an absolute risk reduction of 5.2%, 6.2%, 16.2% and a relative risk reduction of 32%, 38% and 100%, respectively.

The number of patients who received rectal glycerin and later presented with PEP was compared to the other three groups receiving intervention. Those patients who had received both intravenous normal saline and rectal indomethacin had a significant reduction in PEP events compared to the group receiving rectal

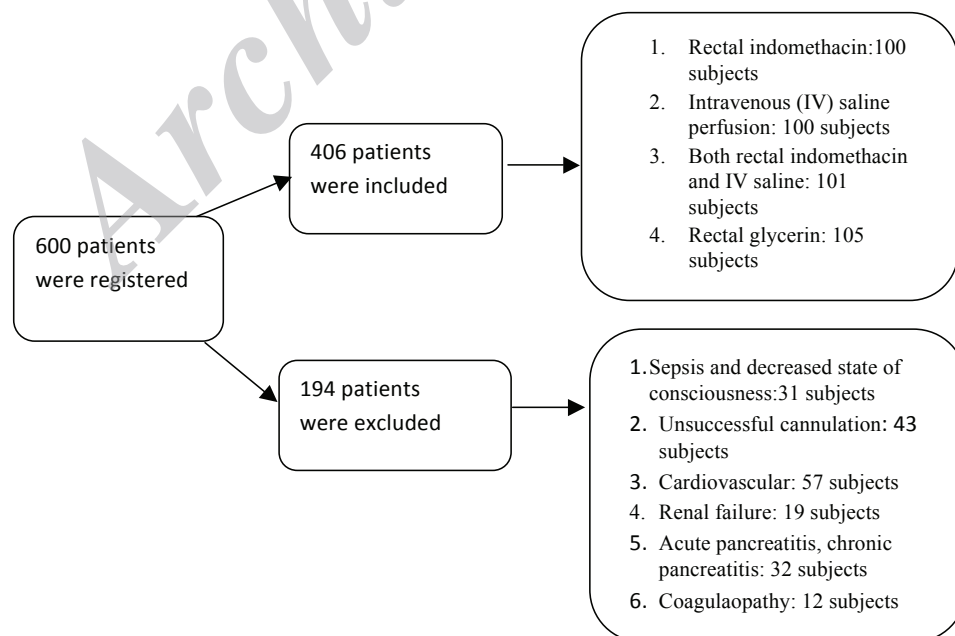


Figure 1. The characteristics of patients included in or excluded from the study.

Table 1. The demographic characteristics of 406 patients undergoing ERCP.

Variable	Mean ± SD	Confidence Interval	Median	Minimum	Maximum
Age	49.7 ± 12.79	(48.45,50.96)	50	21	90
AST	199.78 ± 173.72	(182.79,216.78)	150	15	930
ALT	250.64 ± 196.78	(231.39,269.88)	200.50	10	955
ALP	623.27 ± 298.31	(594.09,652.44)	620	91	1300
Amylase	225.72 ± 211.743	(187.77,263.67)	119.00	10	1200

Table 2. The demographic characteristic of four groups of patients undergoing ERCP.

Groups	Age		Sex		Total
	Mean ± SD	Confidence Interval	Male	Female	
Rectal indomethacin	51.20 ± 12.12	(48.78,53.62)	60 (60*)	40 (40*)	100
Intravenous saline perfusion	50.76 ± 13.32	(48.1,53.41)	47 (47)	53 (53)	100
Both intervention	47.91 ± 11.06	(45.72,50.1)	39 (38.6)	62 (61.4)	101
Rectal glycerin	49 ± 14.26	(46.23,51.77)	56(53.3)	49(46.7)	105
*N(%)					

glycerin ($P < 0.001$). However, when either rectal indomethacin or normal saline was administered, no significant difference was observed in the number of PEP cases in comparison to the glycerin group ($P = 0.2$ and $P = 0.1$, respectively).

No patient who simultaneously received both interventions before ERCP developed PEP. The chi-square test showed that this zero value was lower and significantly different compared to the patients who had received indomethacin ($P = 0.001$) or normal saline ($P = 0.001$) alone. No cases of adverse events that were potentially attributable to the study intervention (e.g., clinically significant bleeding, acute renal failure, myocardial infarctions, strokes or deaths) were observed during the 30-day follow-up. This included the use of rectal glycerin suppositories.

Discussion

There is a wealth of reports with conflicting conclusions on the effects of various pharmacological agents including NSAIDs on the frequency and intensity of PEP. To evaluate the protective effect of rectal indomethacin and hydration on PEP, we conducted a large scale randomized clinical trial and showed that the prevalence of PEP reduced significantly when both interventions were applied.

The rectal route was selected on the basis of available pilot data suggesting that only rectal NSAIDs are effective in preventing post-ERCP pancreatitis, perhaps owing to more rapid and complete bioavailability than with oral administration. Nevertheless, gastrointestinal adverse effects such as bleeding and ulceration that may occur with long-term NSAID use do not occur after 1 or 2 doses.

In the current study, PEP occurred more commonly in the female population although it was not statistically significant. This was compatible with studies conducted by Freeman and Misra.^{1,4} Our findings suggest that sex can be a risk factor for PEP.

Elmunzer and coworkers administered 100 mg of rectal indomethacin after ERCP and reported that rectal indomethacin significantly lowered the number of severe PEP.¹⁶ They also reported that prophylactic indomethacin was associated with a decreased severity of PEP, which is congruent with previous findings by Sotoudehmanesh and colleagues.¹⁷

Sotoudehmanesh *et al.*, who reported a rate of PEP of only 3.2% in patients receiving 100 mg of rectal indomethacin, administered the agent before ERCP, and the placement of pancreatic was avoided.¹⁷ This protective benefit has been confirmed by the meta-analysis studies performed by Yaghoobi.¹⁸ However, DuBernat failed to demonstrate a significant difference in the incidence of PEP when using pre-ERCP rectal indomethacin.¹⁹ This is in line with studies conducted by Part²⁰ where no clear preventive effect was observed in patients receiving oral nifedipin before and after procedure in finding by Sotoudehmanesh and colleagues.²¹ These findings compare with those of our trial in that rectal indomethacin failed to alter the results significantly. Using transdermal nitroglycerine to reduce the pressure of the Oddi sphincter, Morto reported a significant decrease in the risk of pancreatitis.²² In studies performed by Alavinejad,²³ N-acetyl-cysteine had a role in protecting against PEP. Moreover, Katsinlas reported a clear reduction in the frequency of PEP in simultaneous administration of diclofenac and somatostatin.²⁴ On the other hand, Tesogino did not observe an additive beneficial effect against PEP with oral use of risperidone when combined with alinastatin.²⁵

Ebbehoj and coworkers conducted a controlled clinical trial on patients with acute pancreatitis where 50 mg of indomethacin was administered rectally twice a day.²⁶ They reported a decrease in pain and need for opiate analgesics. The results of the clinical trial by Murray and coworkers,²⁷ where the rectal application of diclofenac after ERCP reduced the incidence of pancreatitis episodes, are a further indication of NSAID effectiveness which supports our findings. The majority of cases of PEP are mild and uncomplicated; however, severe pancreatitis can occur in up to 30% of cases. In the current study, all patients presented with mild form and no clinical evidence of severe pancreatitis was observed.

In a meta-analysis review, from 12 randomized controlled clinical trials comparing the efficacy of NSAIDs in the prevention of PEP, only 6 trials fulfilled the criteria for consideration. The study concluded that the risk of pancreatitis was significantly lower in the patients who received NSAIDs than those who received placebo. All trials demonstrated no adverse effects from one or two NSAID doses given to the patients. This was consistent with the observation of our study.²⁸

As a routine practice, patients undergoing ERCP fast before the procedure. We found that when patients are hydrated with intravenous normal saline, subsequent inflammation is reduced. However, the finding was not statistically significant. The results of the current study suggest that hydration, if not contraindicated, could be used as a simple and cost-effective method to reduce PEP. This also indicates that dehydration would have a role in PEP. Larger clinical trials are needed.

We observed that both rectal indomethacin and intravenous saline perfusion prevent PEP significantly. This is indicative of the cumulative beneficial effect of using both interventions. We also noted that the combined administration of both interventions significantly potentiated this protective effect, compared to the use of either intervention alone. Our results reflected this hypothesis that inflammatory pathways in PEP may be regulated by adequate hydration and indomethacin. Larger clinical trials should be conducted to further confirm the findings.

Our findings showed that one dose of rectal indomethacin given before ERCP and hydration reduced the incidence of PEP. Moreover, we found that prophylactic indomethacin and hydration decreased the severity of post-ERCP pancreatitis and was associated with a shorter hospital stay. In agreement with previous clinical trials assessing NSAIDs in the context of post-ERCP pancreatitis, the risk of adverse events that were potentially attributable to indomethacin in this study was similar in the intervention and control groups. Specifically, the rate of PEP in the control group of this trial was similar to that in the two previous studies of NSAID pharmacoprevention in high-risk subjects, in which the mean rates of PEP were 17% and 19%.

The validity of the conclusions of the current study is supported by the strengths of the research methodology including blinded randomized design, adequate allocation concealment, a strict clinically meaningful definition of PEP, thorough follow up, and intention-to-treat analysis. The authors should also be commended for following the patients thirty days post-procedure to evaluate for any delayed pancreatitis or adverse events. This finding is congruent with previous trials suggesting a maximal benefit from prophylactic NSAIDs in patients undergoing ERCP. The limitations of the study consist of exclusion of those patients with cholangitis, sepsis and unsuccessful cannulation which limit the generalizability of the results. Another limitation is the inability to identify all cases of dysfunctional sphincter of Oddi (SOD) or anatomical abnormalities of the pancreas by ultrasound.

In conclusion, this large randomized controlled trial further supports the use of prophylactic rectal indomethacin together with hydration in prevention of PEP and addresses several limitations of previous studies that have been met with general skepticism. It also demonstrates that the combination of rectal indomethacin and hydration can significantly decrease the incidence and severity of PEP. Since the main limitation of this study is exclusion of patients with difficult and failed cannulation and SOD (about 8% of all patients), this study is not generalizable to these patients. Additional studies are needed to optimize the dose and timing of administration of indomethacin and serum therapy and verify whether the efficacy can be generalized to all patients with elevated baseline risk of pancreatitis or restricted to particular subgroups. Several endoscopists increase the validity of the data.

In future, larger controlled trials of other anti-inflammatory agents or combinations of drugs with various inhibitory effects on inflammatory pathways would be of value.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

We acknowledge the Office of the Vice Chancellor for Research at Mashhad University of Medical Sciences for funding and supporting this study. This paper is part of the dissertation of the third author (ID=2971).

References

- Misra SP, Dwivedi M. Complications of endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy: diagnosis, management and prevention. *Natl Med J India*. 2002; 15(1): 27 – 31.
- Badalov N, Tenner S, Baillie J. The Prevention, recognition and treatment of post-ERCP pancreatitis. *JOP*. 2009; 10(2): 88 – 97.
- Arata S, Takada T, Hirata K, Yoshida M, Mayumi T, Hirota M, et al. Post-ERCP pancreatitis. *J Hepatobiliary Pancreat Sci*. 2010; 17(1): 70 – 78.
- Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc*. 2004; 59(7): 845 – 864.
- Takeda K, Yokoe M, Takada T, Kataoka K, Yoshida M, Gabata T, et al. Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading. *J Hepatobiliary Pancreat Sci*. 2010; 17(1): 37 – 44.
- 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(4): 286 – 292.
- Masci E, Mariani A, Curioni S, Testoni PA. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. *Endoscopy*. 2003; 35(10): 830 – 834.
- Bailey AA, Bourke MJ, Williams SJ, Walsh PR, Murray MA, Lee EY, et al. A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis. *Endoscopy*. 2008; 40(04): 296 – 301.
- Rätty S, Sand J, Pulkkinen M, Matikainen M, Nordback I. Post-ERCP pancreatitis: reduction by routine antibiotics. *J Gastrointest Surg*. 2001; 5(4): 339 – 345.
- 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(4): 982 – 985.
- 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(5): 593 – 598.
- Zheng M, Bai J, Yuan B, Lin F, You J, Lu M, et al. Meta-analysis of prophylactic corticosteroid use on post-ERCP pancreatitis. *BMC Gastroenterol*. 2008; 8: 6.
- 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(13): 919 – 923.
- Dai HF, Wang XW, Zhao K. Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. *Hepatobiliary Pancreat Dis Int*. 2009; 8(1): 11 – 16.
- Zheng MH, Xia HH, Chen YP. Rectal administration of NSAIDs in the prevention of post-ERCP pancreatitis: a complementary meta-analysis. *Gut*. 2008; 57(11): 1632 – 1633.
- Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med*. 2012; 366(15): 1414 – 1422.
- Sotoudehmanesh R, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraei M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. *Am J Gastroenterol*. 2007; 102(5): 978 – 983.
- Yaghoobi M, Rolland S, Waschke KA, McNabb-Baltar J, Martel M, Bijarchi R, et al. Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. *Aliment Pharmacol Ther*. 2013; 38(9): 995 – 1001.
- Döbrönte Z, Toldy E, Márk L, Sarang K, Lakner L. Effects of rectal

- indomethacin in the prevention of post-ERCP acute pancreatitis. *Orv Hetil.* 2012; 153(25): 990 – 996.
20. Prat F, Amaris J, Ducot B, Bocquentin M, Fritsch J, Choury AD, et al. Nifedipine for prevention of post-ERCP pancreatitis: a prospective, double-blind randomized study. *Gastrointest Endosc.* 2002; 56(2): 202 – 208.
 21. Sotoudehmanesh R, Eloubeidi MA, Asgari AA, Farsinejad M, Khatibian M. A Randomized Trial of Rectal Indomethacin and Sublingual Nitrates to Prevent Post-ERCP Pancreatitis. *Am J Gastroenterol.* 2014; 109(6): 903 – 909.
 22. Moretó M, Zaballa M, Casado I, Merino O, Rueda M, Ramirez K, et al. Transdermal glyceryl trinitrate for prevention of post-ERCP pancreatitis: A randomized double-blind trial. *Gastrointest Endosc.* 2003; 57(1): 1 – 7.
 23. Alavi Nejad P, Hajjani E, Hashemi J, Masjedizadeh AR, Shayesteh AA, Sebghatollahi V. Evaluation of N-acetyl Cysteine for the Prevention of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Prospective Double Blind Randomized Pilot Study. *Middle East J Dig Dis.* 2013; 5(1): 17 – 21.
 24. Katsinelos P, Fasoulas K, Paroutoglou G, Chatzimavroudis G, Beltsis A, Terzoudis S, et al. Combination of diclofenac plus somatostatin in the prevention of post-ERCP pancreatitis: a randomized, double-blind, placebo-controlled trial. *Endoscopy.* 2012; 44(01): 53 – 59.
 25. Tsujino T, Isayama H, Nakai Y, Ito Y, Togawa O, Toda N, et al. The results of the Tokyo trial of prevention of post-ERCP pancreatitis with risperidone (Tokyo P3R): a multicenter, randomized, phase II, non-placebo-controlled trial. *J Gastroenterol.* 2013; 48(8): 982 – 988.
 26. Ebbenhøj N, Friis J, Svendsen LB, Bülow S, Madsen P. Indomethacin treatment of acute pancreatitis: a controlled double-blind trial. *Scand J Gastroenterol.* 1985; 20(7): 798 – 800.
 27. 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(7): 1786 – 1791.
 28. Puig I, Calvet X, Baylina M, Isava Á, Sort P, Llaó J, Porta F, Vida F. How and when should NSAIDs be used for preventing post-ERCP pancreatitis? A systematic review and meta-analysis. *PLoS One.* 2014; 9(3): e92922.

Archive of SID

SID



سرویس های ویژه



سرویس ترجمه تخصصی



کارگاه های آموزشی



بلاگ مرکز اطلاعات علمی



عضویت در خبرنامه

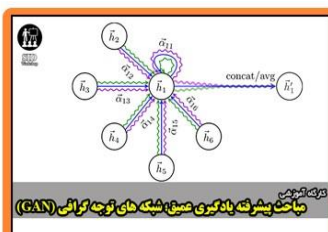


فیلم های آموزشی

کارگاه های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی



کارگاه آنلاین آشنایی با پایگاه های اطلاعات علمی بین المللی و ترند های جستجو



مباحث پیشرفته یادگیری عمیق؛ شبکه های توجه گرافی (Graph Attention Networks)



کارگاه آنلاین مقاله نویسی IEEE و ISI ویژه فنی و مهندسی