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Original Article

Naproxen, isosorbide dinitrate and co-administration cannot prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: Randomized controlled trial

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Backgrounds/Aims: Acute pancreatitis is the most widespread complication of endoscopic retrograde cholangiopancreatography. Here, we investigated the efficacy of rectal suppository naproxen, sublingual isosorbide dinitrate and their co-administration in the prevention of post-ERCP pancreatitis. **Methods:** This double-blind randomized clinical trial carried out from June 2015 to February 2016 at the Gastrointestinal and Liver Diseases Research Center in Rasht, Iran. A total of 585 patients were selected from candidates for diagnostic or therapeutic ERCP by using the simple sampling method. Patients divided into three groups. Group A received 500 mg naproxen, group B took 5 mg isosorbide dinitrate, and group C was co-administrated both agents before ERCP. The primary outcome measure was the development of pancreatitis onset of pain in the upper abdomen and increase of serum amylase activity more than 3 times over the upper normal limit (60-100 IU/L) within first the 24 h post-ERCP. **Results:** Totally, 80 patients developed PEP included 29 (4.9%), 24 (4.1%), and 27 (4.6%) patients in groups A, B, and C, respectively (p=0.845). Longer ERCP time (p=0.041), using diazepam (p=0.033), a higher number of pancreatic ducts cannulation ($p<0.001$), pancreatic duct injection (p=0.013), and using pancreatic stent (p=0.004) were the predisposing factors for PEP. **Conclusions:** Our findings indicated that prophylactic naproxen suppository or isosorbide dinitrate sublingually or co-administration had no significant difference in the prevention and severity of PEP, however, enhancing the endoscopist's skills can be effective. Departments and educational hospitals should develop their assessment and quality assurance measures for the training of fellows' not only technical training but also an understanding of the diagnostic and therapeutic roles of the procedure. **(Ann Hepatobiliary Pancreat Surg 2020;24:259-268)**

Key Words: ERCP; Pancreatitis; Naproxen; Isosorbide dinitrate

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most effective techniques in the diagnosis and treatment of biliary ducts and pancreas disorders.[1] However, this technique is accompanied by certain complications and among them, pancreatitis is the most common and serious ones. Post-ERCP pancreatitis (PEP) identified as clinical signs of acute pancreatitis after ERCP with elevated levels of pancreatic enzymes.[2] Despite significant advances in endoscopic technology, a subsidiary of ERCP and learn how to use it, the prevalence of PEP is steady during the past 30 years.[3] Incidence of PEP is varied from 0.4% to 5.4% of patients depending on the risk factors and the indication of ERCP[4] and totally 0.4-0.6% of patients showed severe PEP which needs en-

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doscopic or surgical interventions.[5] Diagnosis of PEP is based on both clinical and laboratory findings and defined and characterized mostly using Cotton criteria. Mild PEP is defined as abdominal pain that needs hospitalization or hospitalization's extension for 2-3 days and elevation of serum amylase activity more than 3 times over the upper limit of normal 24 hours after ERCP. Moderate and severe PEP are defined by the hospitalization period of 4-10 and more than 10 days, respectively. Also, severe PEP is accompanied by certain complications such as necrosis or pseudocyst and sometimes need drainage or surgery as interventions.[6]

Although several endoscopic and pharmacologic strategies have been reported for prevention or reducing the occurrence of PEP,[7-14] there are controversies about their effectiveness. In the present study, we aimed to evaluate and compare the therapeutic effects of administration of naproxen as a suppository, isosorbide dinitrate as sublingual and their combination in the prevention of PEP.

MATERIALS AND METHODS

Patients

In a double-blinded randomized clinical trial (IRCT 201409251155N22), all patients with age more than 16 years who referred for ERCP to Gastroenterology ward of Razi hospital as a referral center of the Rasht, the capital of Guilan province, from June 2015 to February 2016 were enrolled. Patients with acute pancreatitis in the recent two weeks, history of chronic pancreatitis, previous sphincterotomy, consumption of non-steroidal anti-inflammatory drugs (NSAIDs) or nitrate in the recent week, and contraindications of administration of NSAIDs or nitrate such as renal failure, peptic ulcer with recent hemorrhage, hypotension, sensitivity to one of both drugs and lack of satisfaction to precipitation in the study were excluded. The sample size of 202 patients for each group was calculated based on the previous report[15] and consideration of p=0.06, α=0.05, and β=0.1 using the following formula:

$$N = \frac{2(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 (P_2 - P_1)}{(P_1 - P_2)^2}$$

After providing informed consent, randomization was performed using a random block (https://www.sealed-envelope.*com/simple-randomiser/v1*/lists). Patients, physicians, and nurses who administered treatment were unaware of the nature of the drugs. The protocol was approved by the Ethical Committee of Guilan University of Medical Sciences (Reference number: 1930175708) and followed the Helsinki Declaration of 1975, as revised in 2000 (available at http://www.wma.net/e/policy/17-c_e.html).

Grouping and interventions

Totally, 606 patients were allocated into groups A, B, and C, respectively and received the following treatments immediately before the ERCP:

- Group A: 500 mg rectal suppository naproxen (Behvazan Co., Iran)
- Group B: 5 mg sublingual isosorbide dinitrate (UCB Pharma GmbH, Germany)
- Group C: 5 mg sublingual isosorbide dinitrate and 500 mg rectal suppository naproxen

ERCP was done using a standard therapeutic duodenoscope (EXERA CV-160, Olympus CO.) when the patient was under local anesthesia with 2% lidocaine and after premedication by intravenous administration of 0.05 mg/kg of Midazolam or in cases with a contraindication, intravenous administration of 1 mg/kg pethidine. This condition was indefeasible, except in certain cases, that needs changes. Blood pressure, heart rate, and oxygen saturation were monitored routinely. Contrast medium (Meglumine Compound 76%) was injected manually, under fluoroscopic guidance and experienced endoscopists carried out ERCPs.

In Group A, 6 patients and in Group B 15 patients failed ERCP. The reasons for technical and clinical failure of ERCP in both groups were mucosal edema, chronic duodenal ulcer disease, impacted stones, tumor infiltration due to pancreatic cancer, periampullary diverticulum, cardiac arrhythmia and poor cooperation of patient. After excluding patients who were not eligible for analysis, 196, 187 and 202 patients (totally 585 *patients*) were included in groups A, B, and C, respectively

Assessments

Pancreatitis and its severity were defined based on Cotton criteria[6] as the onset of pain in the upper abdomen and increase of serum amylase activity more than 3 times over the upper normal limit (60-100 IU/L) within first the 24 h post-ERCP. The severity of pancreatitis categorized based on the duration of treatment for PEP as mild (2-3 day), moderate (4-10 day) and severe (more than 10 days and/or necessitated surgical or intensive treatment, or contributed to death).

Demographic information includes age and gender plus risk factors, ERCP elements, and follow-up data were collected at the time of the procedure, 2 and 24 hrs after ERCP. Oral intake was allowed for patients who had normal serum amylase after 2 hrs and showed no history of abdominal pain, nausea, and vomiting. ERCP duration, the number of biliary and pancreatic cannulations, findings of the biliary and/or pancreatic duct, presence or absence of juxta-ampullary diverticulum and interventions were recorded. Finally, patients with persistent pancreatitis symptoms more than 48 hrs were evaluated for pancreatitis complications such as abscess, pseudocyst, or fluid collection by CT-scanning.

Statistical analysis

Qualitative and quantitative data were reported as frequency (percentage) and mean±SD, respectively. Data were analyzed using IBM SPSS Statistics version 23. Associations between qualitative variables were checked using the Chi-square test. One way analysis of variance (ANOVA) was used to compare quantitative data between three groups and Tukey was used as Post-hoc test. $p < 0.05$ was considered a significant difference.

RESULTS

Totally, 196 (33.5%), 187 (32%) and 202 (34.5%) patients were assessed in groups A, B, and C, respectively. The three groups were age-, sex-, and body mass index (BMI)-matched ($p > 0.05$, Table 1). The most common reason for ERCP in our patients was common bile duct stone (370 patients, 63.2%).

No significant differences were detected between three groups about amylase level before ERCP (p=0.147), after

Table 1. Comparison of mean±SD and frequency (%) of age, BMI and sex between three groups

Parameters		Group A (n=196)	Group B (n=187)	Group C (n=202)	*p*-value
Age (years) (mean ±SD)		61.36±18.23	61.05±18.18	61.90±17.04	0.892
BMI (kg/m^2) (mean ±SD)		26.50±15.38	24.48±4.79	25.04±5.91	0.165
Sex n (%)	Female	128 (65.3)	105 (56.1)	127 (62.9)	0.164
	Male	68 (34.7)	82 (43.9)	75 (37.1)	

Group A, 500 mg rectal suppository naproxen; Group B, 5 mg sublingual isosorbide dinitrate; Group C, 5 mg sublingual isosorbide dinitrate and 500 mg rectal suppository naproxen

Table 2. Comparison of frequency (percentage) of pancreatitis, severity of pancreatitis and abdominal pain between three groups

Parameters	Group A (n=196)	Group B (n=187)	Group C (n=202)	*p*-value
Pancreatitis n (%)				0.845
Yes (n=80)	29 (14.8)	24 (12.8)	27 (13.4)	
No (n=505)	167 (85.2)	163 (87.2)	175 (86.6)	
Severity of pancreatitis n (%)				0.647
Mild (n=51)	16 (55.2)	17 (70.8)	18 (66.7)	
Moderate (n=21)	10 (34.5)	4 (16.7)	7 (25.9)	
Severe (n=8)	3 (10.3)	3 (12.5)	2 (7.4)	
Abdominal pain n (%)				0.328
Yes (n=78)	26 (13.3)	30 (16.0)	22 (10.9)	
No (n=507)	170 (86.7)	157 (84.0)	180 (89.1)	

Group A, 500 mg rectal suppository naproxen; Group B, 5 mg sublingual isosorbide dinitrate; Group C, 5 mg sublingual isosorbide dinitrate and 500 mg rectal suppository naproxen

Table 3. Incidence of post-ERCP pancreatitis based on different categorized variables

Variables		Group A 196 (%)	Group B 187 (%)	Group C 202 (%)	*p*-value
n (%)	Pancreatitis: 80 (13.7)	29 (14.8)	24 (12.8)	27 (13.4)	0.845
Sex					
Female (n=360)	57	20 (35.1)	18 (31.6)	19 (33.3)	0.486
Male (n=225)	23	9 (39.1)	6 (26.1)	8 (34.8)	0.899
Age (years)					
＜40 (n=96)	19	8 (42.1)	4 (21.1)	7 (36.8)	0.502
＞40 (n=489)	61	21 (34.4)	20 (32.8)	20 (32.8)	0.929
BMI (kg/m^2)					
＜25 (n=289)	41	15 (36.6)	11 (26.8)	15 (36.6)	0.681
25-30 (n=220)	28	11 (39.3)	9 (32.1)	8 (28.6)	0.698
＞30 (n=76)	11	3 (27.2)	4 (36.4)	4 (36.4)	0.553
Sphincterotomy					
No (n=58)	8	5 (62.5)	0 (0)	3 (37.5)	0.278
Precut papillotomy (n=74)	10	3 (30)	4 (40)	3 (30)	0.856
Sphincterotomy (n=453)	62	21 (33.9)	20 (32.2)	21 (33.9)	0.841
Pancreatic duct injection					
Yes (n=28)	10	4 (40)	3 (30)	3 (30)	0.390
No (n=351)	59	25 (42.4)	10 (16.9)	24 (40.7)	＜0.001
ERCP duration (min)					
1-19 (n=82)	8	4 (50)	3 (37.5)	1 (12.5)	0.501
20-39 (n=122)	41	14 (34.2)	8 (19.5)	19 (46.3)	0.135
40-59 (n=154)	21	6 (28.6)	9 (42.8)	6 (28.6)	0.564
60-80 (n=34)	10	5 (50)	4 (40)	1 (10)	0.110
Anesthetic drug					
Midazolam & pethidine (n=188)	21	4 (19.1)	5 (23.8)	12 (57.1)	0.172
Diazepam & pethidine (n=19)	3	2 (66.7)	0 (0)	1 (33.3)	0.027
Diazepam (n=16)	5	2 (40)	1 (20)	2 (40)	0.306
Fentanyl & propofol & midazolam (n=88)	17	10 (58.8)	7 (41.2)	0 (0)	0.513
Fentanyl & propofol & lidocaine (n=9)	0	0 (0)	0 (0)	0 (0)	NC
General anesthesia (n=5)	1	0 (0)	1 (100)	0 (0)	0.171
Number of attempts to cannulate the papilla					
No (n=204)	24	21 (87.5)	1 (4.2)	2 (8.3)	0.604
1 (n=53)	7	0 (0)	3 (42.8)	4 (57.2)	0.353
2 (n=80)	7	1 (14.2)	3 (42.9)	3 (42.9)	0.733
3 (n=87)	13	1 (7.6)	6 (46.2)	6 (46.2)	0.355
4≤ (n=161)	29	6 (20.7)	11 (37.9)	12 (41.4)	＜0.001
Number of CBD cannulation					
No (n=82)	11	5 (45.5)	2 (18.2)	4 (36.3)	0.330
1 (n=123)	12	2 (16.6)	5 (41.7)	5 (41.7)	0.670
2 (n=115)	14	5 (35.7)	4 (28.6)	5 (35.7)	0.972
3 (n=150)	24	8 (33.3)	7 (29.2)	9 (37.5)	0.900
4≤ (n=115)	19	9 (47.4)	6 (31.6)	4 (21)	0.650
Number of pancreatic duct cannulation					
No (n=374)	29	8 (27.6)	9 (31)	12 (41.4)	0.990
1 (n=73)	17	7 (41.2)	4 (23.5)	6 (35.3)	0.156
2 (n=60)	12	3 (25)	4 (33.3)	5 (41.7)	0.155
3 (n=46)	11	4 (36.4)	4 (36.4)	3 (27.2)	0.995
4≤ (n=32)	11	7 (63.6)	3 (27.3)	1 (9.1)	0.127
Using pancreatic stent					
Yes (n=24)	8	0 (0)	3 (37.5)	5 (62.5)	0.183
No (n=503)	62	29 (46.7)	12 (19.4)	21 (33.9)	0.189
Juxta-ampullary diverticulum					
Yes (n=30)	5	0 (0)	3 (60)	2 (40)	0.429
No (n=507)	65	29 (44.6)	12 (18.5)	24 (36.9)	0.109

Group A, 500 mg rectal suppository naproxen; Group B, 5 mg sublingual isosorbide dinitrate; Group C, 5 mg sublingual isosorbide dinitrate and 500 mg rectal suppository naproxen; NC, not calculated

2 hrs (p=0.396) and after 24 hrs (p=0.808). Also, no significant associations between post-ERCP abdominal pain (p=0.328) and pancreatitis (p=0.845) with types of treatment were observed. Although severe pancreatitis included the lowest and mild pancreatitis included the highest percentages of patients with pancreatitis in all three groups, but this difference in the severity of pancreatitis was not statistically significant (p=0.647, Table 2). Just one patient died in the follow-up who belonged to sublingual isosorbide dinitrate. All other patients were discharged in good condition without reported side effects.

Incidence of PEP based on different categories in the three groups is presented in Table 3. Higher incidences of PEP was seen in patients of rectal suppository group (group A) who used diazepam & pethidine as anesthetic drugs (p=0.027) and had four or more attempts to cannulate the papilla ($p<0.001$).

Although no significant differences were detected in the incidence of PEP based on groups and categorized ERCP duration, patients with PEP had higher ERCP time in comparison to patients without PEP (42.25±14.88 min vs. 37.67±15.25 min respectively, p=0.013).

Totally, we found that 80 patients (13.7%) suffered from PEP. Comparisons of PEP occurrence based on different patient- and procedure-related variables are presented in Figs. 1, 2, respectively. No significant associations were detected between sex, age and BMI with the occurrence of PEP (p=0.055, p=0.056, and p=0.873, respectively). Among procedure-related variables, patients with pancreatic duct injection (p=0.013), using pancreatic stent (p=0.004), equal or more than 4 pancreatic ducts cannulation ($p<0.001$), ERCP duration of 60-80 min

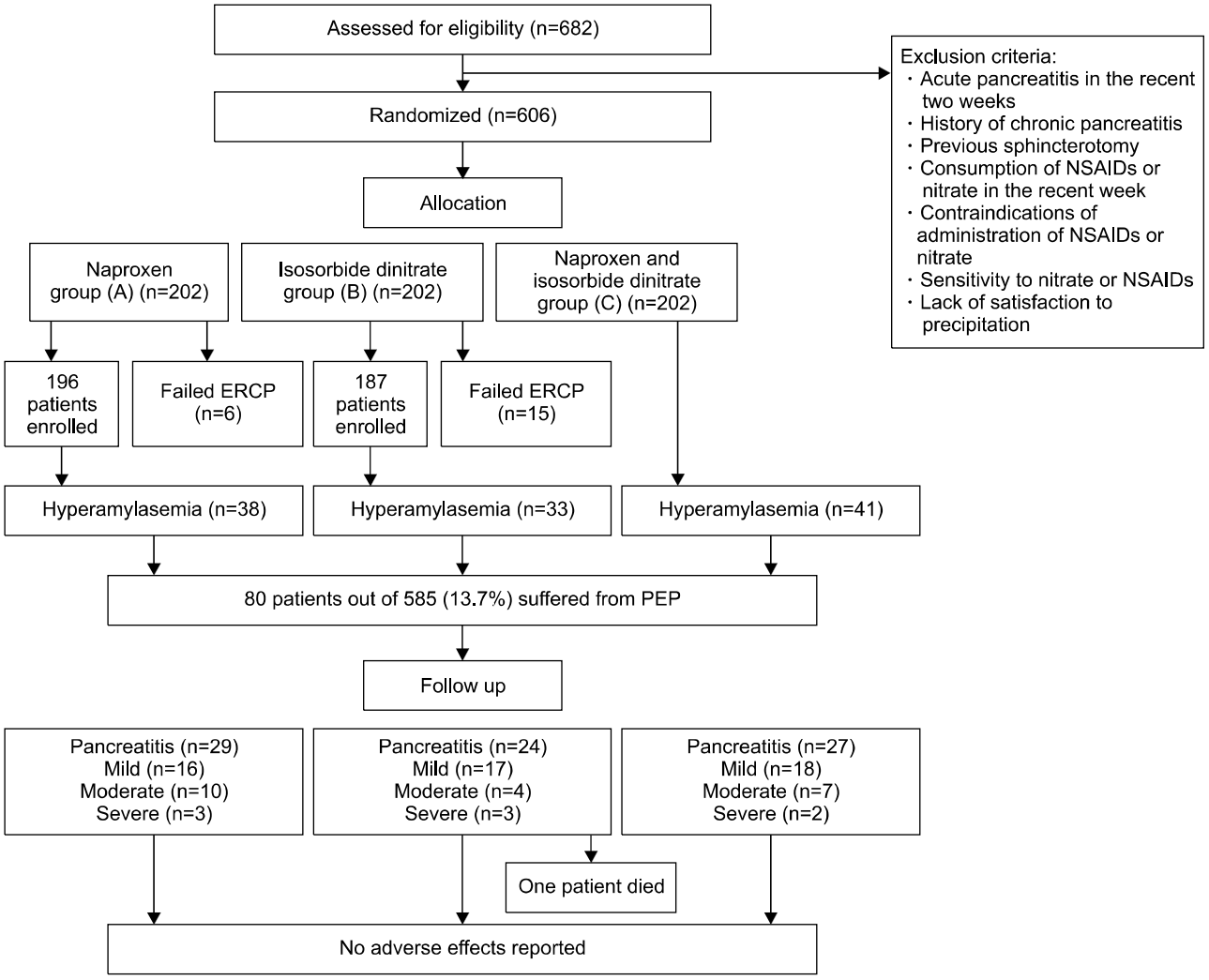

Fig. 1. Flowchart of patients registered in this study. PEP, post-ERCP pancreatitis.

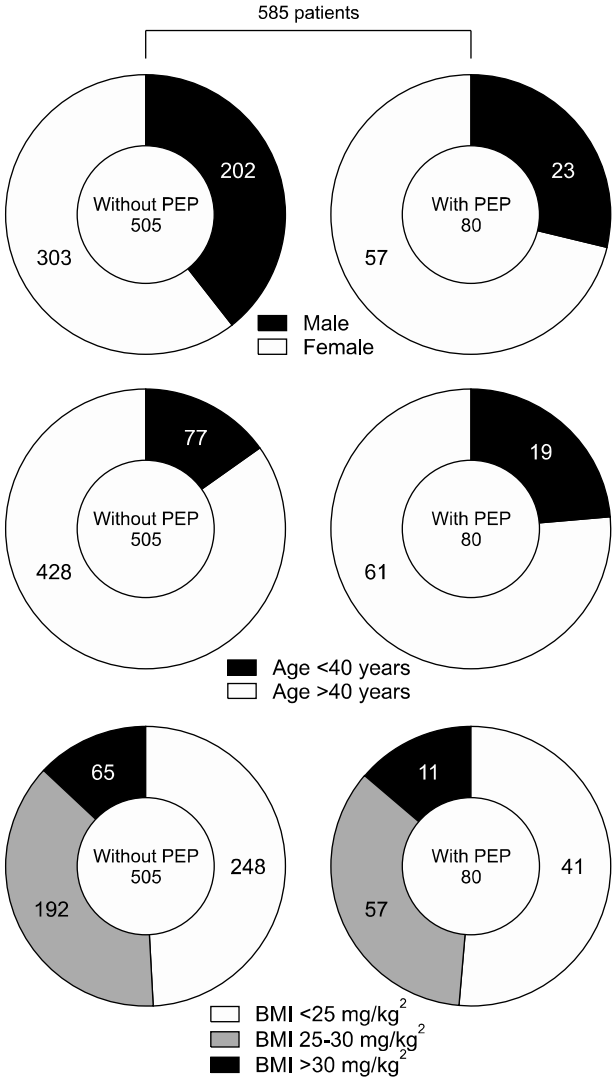

Fig. 2. Comparison of PEP occurrence based on patient-related variables.

(p=0.041), and anesthetized with diazepam (p=0.033) were mostly suffered from PEP (Fig. 3).

DISCUSSION

In the present RCT, it has been shown that howbeit totally PEP incidence was not changed in response to our administered agents, the frequency of PEP was higher in patients of rectal suppository group without pancreatic duct injection who used Diazepam & Pethidine as anesthetic drugs with four or more attempts to cannulate the papilla in comparison to other two groups. If all patients considered totally and ignored the patients' groups, pancreatic duct injection, using a pancreatic stent, equal or more than 4 pancreatic ducts cannulation, ERCP duration of 60-80 min, using other methods of sphincterotomy rather than needle-knife, precut or sphincterotomy and anesthetizing with diazepam were predisposed patients to PEP.

Pancreatitis is the most usual severe complication of ERCP.[4] Our PEP incidence (13.7%) is slightly higher in comparison to those reported in the systematic review as 3-10%. However, they reported rates can increase to 15% or more in high patient- and procedure-related at risks populations.[16] To prevent PEP some strategies must be attended. These include selecting patients carefully, training of GI man, considering of alternative methods, cannulation under the guide of wire for all patients and using pancreatic duct stent and a single dose of rectal NSAIDs such as indomethacin or diclofenac for high-risk patients.[17] For the first time, Elmunzer et al.[18] reported that using rectal indomethacin as a nonsteroidal anti-inflammatory drug (NSAID) could decrease the rate of PEP near 8% (9.2% vs. 16.9%) in comparison to placebo. Indeed, NSAIDs inhibit some of the important inflammatory enzymes like cyclooxygenase and phospholipase A2.[16] After them, several studies were performed about the effects of NSAIDs application in the prevention of PEP with supportive or opposite findings. For instance, in opposite to Elmunzer et al.,[18] Levenick et al.[19] in a double-blind randomized controlled clinical trial found that rectal indomethacin did not prevent PEP in consecutive patients. Also, the protective efficacy of rectal indomethacin against PEP just confirmed in high-risk patients,[20,21] rejected in moderate[20] and low-risk patients.[22] In a meta-analysis of 6 studies with more than 2400 patients, no significant difference was obtained between indomethacin and placebo administration before ERCP in overall, moderate to severe and mild rates of PEP (OR: 0.67, 0.66 and 0.71, respectively).[23] In another systematic review of 16 RCTs with a total number of 6458 patients that evaluated the efficacy of rectal NSAIDs with placebo or no treatment in the prevention of PEP, it has been confirmed that rectal NSAIDs decreased the overall risk of PEP.[24] Moreover, reduce the risk ratio, a number of patients needed to treat, and the decrease of risk ration of moderate to severe PEP by using indomethacin and diclofenac is confirmed by a meta-analysis of 17 trials with the total number of 4741 patients.[25] Furthermore, among the NSAIDs, diclofenac was acted better than indomethacin[24] and naproxen.[26] Howbeit some

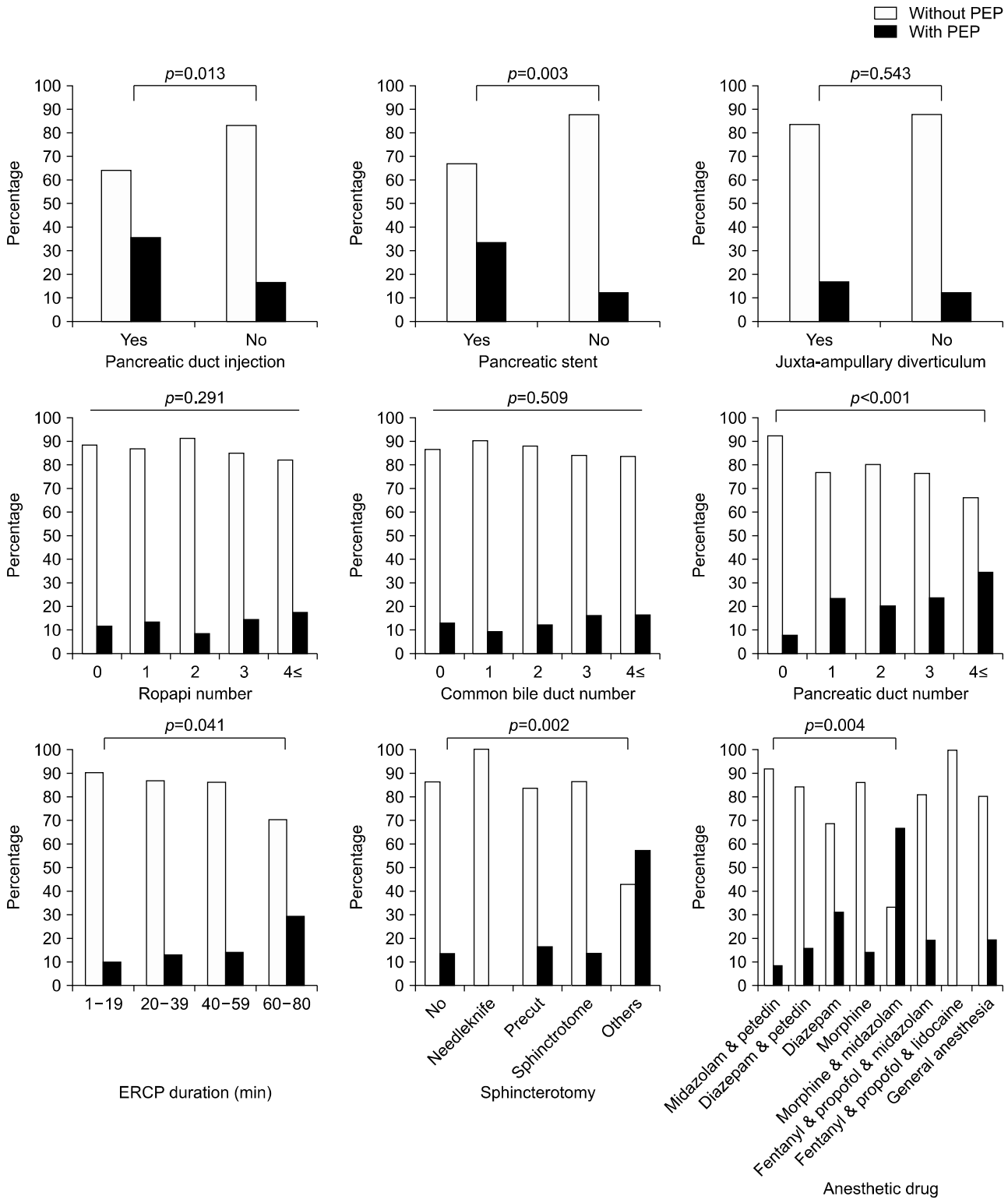

Fig. 3. Comparison of PEP occurrence based on procedure-related variables.

controversies have existed about the superiority of diclofenac against other NSAIDs.[25-27] We also previously in a double-blind RCT reported that single suppository dose of 500 mg naproxen, as another member of NSAIDs, immediately before ERCP decreased the rate of PEP.[28] Based on all of the above mentioned shreds of evidence, it seems that rectal NSAIDs are effective and safe in the prevention of PEP in all levels of risk. However, our findings

of the effectiveness of naproxen as one of the NSAIDs are mostly similar to those reported by Levenick et al.[19] which showed that using naproxen had no beneficial in comparison to other treatments and some cases with special conditions, the rate of PEP was more in the groups who received rectal suppository naproxen.

Despite NSAIDs, there are some other medications, which evaluated their efficacy in the prevention of PEP. These include nitrates,[29-31] protease inhibitors,[13,32] somatostatin,[33] heparin,[11] allopurinol,[8,34] secretin,[14] epinephrine,[10] neurokinin-1 receptor antagonist,[7] anti-tumor necrosis factor-a (TNF-a) agent,[12] β-carotene,[9] and intravenous fluid hydration.[35] One of them is nitrate which administrated through different routes and provides conflicting results ranged from a significant decline[29,30] to no specific effects[36] on the occurrence of PEP. The basic mechanism of nitrate's effectiveness is through papillary relaxation and simulate PD placement.[37] Although the use of nitrates for prevention of PEP is limited due to lack of their efficacy and having serious side effects,[29,38] one of the recent studies advised the use of nitrates in co-administration with NSAIDs to provide better results of both of them.[31] We found no significant differences in the occurrence of PEP between three groups and therefore, it can be said that using of sublingual isosorbide dinitrate is effective in the prevention of PEP as well as rectal suppository naproxen and their combination.

As another important finding, a positive association between using pancreatic stent and occurrence of PEP regardless of patients groups was detected. Although, several studies reported that pancreatic stent placement prevented PEP, but it seems that there is controversy in its effectiveness yet. Pancreatic stent placement related adverse events is reported about 4%.[39-41] Moreover, in two almost old studies, stent-induced ductal alterations were introduced as cause of chronic pancreatitis-like changes.[42,43] In light of our additional data about the significant positive relationship between stent and PEP and also based on previous reported chronic pancreatitis as stent complication, we suggested performing the updated study as systematic review and/or meta-analysis covering all newly published RCTs. This can clearly reveal whether post-ERCP pancreatic stent placement is beneficial for the prevention of PEP or not.

In conclusion, it can be said that prophylactic naproxen suppository or isosorbide dinitrate sublingually or co-administration had no significant difference in the prevention and severity of PEP, however, enhancing the endoscopist's skills can be effective. Departments and educational hospitals should develop their assessment and quality assurance measures for the training of fellows' not only technical training but also an understanding of the diagnostic and therapeutic roles of the procedure including of the indications, risks, benefits, limitations, contraindications, possible adverse events, alternatives to the procedure.

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CONFLICT OF INTEREST

There is no conflict of interests.

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AUTHOR CONTRIBUTIONS

Conceptualization: FMG, FJ. Data curation: AAK, SFA, KM. Formal analysis: FJ, MS. Funding acquisition: FMG. Methodology: MRN, SY. Project administration: FMG, FJ. Visualization: FMG. Writing - original draft: HSS. MS, SY. Writing - review & editing: FMG, FJ.

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