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Original article

PROPHYLACTIC EFFECT OF NAPROXEN AND INDOMETHACIN IN POST- ENDOSCOPIC PANCREATITIS: RANDOMIZED CONTROLLED TRIAL

Tanaj Halil[1], Kondov Goran[2], Krasniqi Shaip[3]

[1]Clinic of Abdominal Surgery – Endoscopy Service, University Clinical Centre of Kosovo, Prishtina, Republic of Kosovo
[2] University Clinic for Thoracic and Vascular Surgery, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[3] Department of Pharmacology, University of Prishtina, Prishtina, Republic of Kosovo

Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced technique in the diagnosis and treatment of biliary pathway obstruction. However, ERCP can be accompanied with complications like post-ERCP pancreatitis (PEP). In this study we aimed to examine and compare the effects of 500 mg naproxen and 100 mg indomethacin as a single dose rectal administration in prevention of PEP in patients after diagnostic or therapeutic ERCP.

This double-blind randomized prospective monocentric clinical study was implemented during the period of January-April 2022 in 60 patients referred for ERCP at the University Clinical Centre of Kosovo – Prishtina. Patients were divided into two groups with 30 patients each. Before the ERCP, group A received 500 mg naproxen and group B received 100 mg indomethacin.

The incidence of PEP was 15% (9/60), 16.67% *vs.* 13.33% in groups A and B, respectively (p=0.5000). No significant differences were found between patients with PEP in groups A/B related to age (p=0.8065), BMI (p=0.8064) and ERCP duration (p=0.6242). The comparison of amylases, lipase and CRP in patients with PEP from group A/group B (before, 4h and 24h after ERCP) showed no significant differences.

Prophylactic naproxen or indomethacin had no significant difference in prophylaxis of PEP after ERCP. Differences between PEP cases from the two groups regarding selected parameters were not significant. Taking into account the relatively small sample of patients with PEP in our study, we are aware of the need for more extensive research in this field in the Republic of Kosovo for defining an effective way in reduction of PEP after ERCP.

Keywords: naproxen, indomethacin, NSAIDs, ERCP, pancreatitis

Introduction

Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP)[1-3]. The criteria for diagnosis of PEP cover the epigastric pain with radiation to the back, with elevation of amylase and/or lipase at least 3 times higher than normal within 24 h after ERCP[4].

The incidence of PEP varies from 1 to 10% of patients undergoing this procedure, but also may reach 30% in high-risk cases[1]. However, many authors indicate that post-

endoscopic retrograde PEP is severe in 0.1 to 0.5% cases only [3,4]. Although mortality due to PEP is low (<1%), it can be morbid, with significant annual health care costs[2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are reported to be effective in PEP prophylaxis so far[5]. Rectal NSAIDs are one of the most effective, cheap, and easy-to-use agents for preventing post-ERCP pancreatitis[6]. The guidelines of the European Society of Gastrointestinal Endoscopy from 2014 recommend routine administration of 100 mg of diclofenac or indomethacin immediately before or after ERCP to prevent PEP[7].

The four main mechanisms by which NSAIDs act are: inhibition of cyclooxygenase (COX), inhibition of phospholipase A2, prevention of leukocyte adhesion and migration and inhibition of integrins[6-8]. The best-described mechanism is the inhibition of the COX-2 enzyme, which may or may not be selective. The COX-2 inhibitors drug is a subclass of nonsteroidal anti-inflammatory drugs with more benefit than NSAIDs given upper gastrointestinal safety.

Based on meta-analysis-level evidence, Pezzilli *et al*. reported that NSAIDs present considerable variations in the risk of acute pancreatitis - diclofenac posed the largest risk (OR 5.0, 95% CI: (4.2-5.9) and naproxen presented the lowest (OR 1.1, 95% CI: 0.7-1.7)[9]. Although most studies on NSAIDs for preventing or alleviating PEP were carried out with indomethacin or diclofenac [10–11], rectal naproxen may also be effective. Recently, only one documented study has reported the efficacy of 500 mg rectal naproxen for the prevention of PEP[12].

Although ERCP has been practiced in the Republic of Kosovo for two decades, till now no data has been published related to the experience of PEP prophylaxis. In this study, we aimed to examine and compare the effects of 500 mg naproxen and 100 mg indomethacin as a single dose rectal administration in prevention of PEP in patients after diagnostic or therapeutic ERCP.

Material and methods

This double-blind randomized prospective monocentric clinical study included 60 patients referred for diagnostic or therapeutic ERCP at the Endoscopy Unit in the Abdominal Surgery Ward of the University Clinical Centre of Kosovo - Prishtina during the period of January-April 2022. Patients were allocated into groups A and B with 30 patients each by using the simple sampling method. In prevention of PEP, 30 minutes before the ERCP patients received: 1) Group A - 500 mg naproxen; and 2) Group B - 100 mg indomethacin, both as single dose rectal administration. To keep participating clinicians blinded to patient allocation, rectal NSAIDs were prepared by the pharmacy of the hospital. At the time of ERCP, the pharmacy delivered one suppository labeled with patient codes depending on the allocation.

Inclusion criteria involved only patients ≥18 years, regardless of gender and other demographic characteristics. The exclusion criteria understood minimum one of the conditions such as: acute pancreatitis, active peptic ulcer disease, rectal disease, aspirin-induced asthma, nonsteroidal anti-inflammatory drug (NSAID) induced hypersensitivity, pregnancy, breast feeding, renal dysfunction or history of gastrectomy with billroth II anastomosis.

The ERCP procedure was done with Olympus duodenoscope when the patient was under total intravenous anesthesia (TIVA) with midazolam, propophol, and hyoscine butyl-bromid used as premedication after intubation of the duodenum to stabilize the papilla. The required laboratory tests for the patient to undergo ERCP procedure were: hemogram, time of bleeding, time of coagulation, INR, prothrombin time, urea, creatinine, glycose level in blood, total bilirubin, direct and indirect bilirubin, GGT, amylases level in serum, lipase in serum, HbsAg, HCV. For diagnostic purposes abdominal ultrasound, CT scan of the abdomen and

MRCP were required from each patient. The patient had to stop taking aspirin and other anticoagulants at least 5 days prior to intervention to prevent bleeding. We suggested to took fraxiparin s.c. injections instead.

The primary outcome measure was the development of pancreatitis onset of pain in the upper abdomen and elevation of the serum amylase level to >3 × the upper normal limit (60-100 IU/L) within 24 h after ERCP.

Demographic information included age and gender. BMI (kg/m²) was calculated for each patient before the intervention. Procedure-related parameters as ERCP duration, pancreatitis duct presence, shincterotomy and/or papilla in diverticulum as well as abdominal pain and fever were recorded. The levels of amylase, lipase, and CRP were measured before ERCP, 4 hours and 24 h after the procedure. The reference values were: amylase <100 U/L, lipase <60 U/L, and CRP <5 mg/L.

This study was conducted in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2000. An informed consent was obtained from all participants prior to study enrolment. The Ethics Committee of the University Clinical Centre of the Republic of Kosovo approved the implementation of the study.

Statistical analysis

The data obtained in this study were analyzed with the SPSS software package, version 22.0 for Windows. Qualitative and quantitative series were analyzed with measures of central tendency (mean, median, range), as well as by dispersion measures (standard deviation). The Shapiro-Wilk W test was used to determine the normality of frequency distribution of age, duration of ERCP procedure, BMI, amylase, lipase and CRP. Association between qualitative variables was checked using the Pearson Chi square test and Fisher exact test. Mann Whitney U test was used to compare differences between two independent groups when the dependent parameters were either ordinal or continuous, but not normally distributed. Difference test was used to compare the proportions. A two-sided analysis with a significance level of $p<0.05$ was used to determine the statistical significance.

Results

The study analyzed 60 patients with diagnostic or therapeutic ERCP assigned in groups A and B with 30 (50%) participants each. In prevention of PEP, patients in groups A and B received per-procedural single dose rectal administration of 500 mg naproxen or 100 mg indomethacin respectively. No significant association was found between the treatment group and sex (p=0.0693), age (p=0.2198), and BMI (p=0.1886). Among our patients, the most common reason for ERCP was choledocholithiasis, recorded in 44 (73.33%) (Table 1).
Of all patients included in the study, after the ERCP procedure, PEP was diagnosed in 9 (15%) patients - 4 (14.81%) males and 5 (15.15%) females. In the groups A and B separately, with PEP after ERCP were 5 (16.67%) *vs.* 4 (13.33%) of patients respectively, with no significant association between the type of the treatment and the development of PEP (p=0.5000). Post-ERCP abdominal pain (p=0.0242) and fever (p=0.0413) associated significantly with group B (Table 1).

Table 1. Comparison of demographic parameters, pancreatitis and clinical features between two groups

Parameters	**Treatment groups**		**p**
	Group A	**Group B**	
Sex - N (%)			
Male	17 (56.67%)	10 (33.33%)	X^2=3.299; df=3; p=0.0693
Female	13 (43.33%)	20 (66.67%)	
Total	30 (50%)	30 (50%)	
Age (years)			
Mean ±SD	58.90±16.40	53.97±16.41	Z=1.227; p=0.2198
Range	18/82	25/86	
Median (IQR)	63 (48.5-72)	56 (40.5-65)	
BMI			
Mean ±SD	26.65±4.40	26.57±5.13	Z=10.00; p=0.1886
Range	19/36	18/39.8	
Median (IQR)	26.8 (23-28.7)	26.9 (23.3-28.5)	
Pancreatitis - N (%)			
PEP – no	25 (83.33%)	26 (86.67%)	[1]p=0.5000
PEP – yes	5 (16.67%)	4 (13.33%)	
Abdominal pain – N (%)			
No	25 (88.33%)	17 (56.67%)	X^2=5.079; df=1; p=0.0242*
Yes	5 (16.67%)	13 (43.33%)	
Fever – N (%)			
No	24 (80%)	16 (55.17%)	X^2=4.163; df=1; p=0.0413*
Yes	6 (20%)	13 (44.83%)	

Group A – 500 mg naproxen single dose rectal administration; Group B = 100 mg indomethacin single dose rectal administration; X^2 = Pearson Chi-square test; Z=Mann-Whitney U Test; [1]Fisher exact test; *Significant for p<0.05

The average age of patients with PEP in the groups A and group B was 62.80±8.23 with 50% younger than 62 years *vs.* 56.25 ± 21.62 with 50% younger than 60 years, respectively. Elevated BMI value was registered in 3 (60%) patients with PEP in group A, and 1 (25%) in group B. No significant differences were found between patients with PEP from groups A and B related to age (p=0.8065), and BMI (p=0.8064) (Table 2).

With reference to ERCP duration, no significant differences were detected in the whole sample between patients without PEP (17.35 ± 6.39) and with PEP (20.67 ± 10.25) (p=0.3569). The average duration of the ERCP procedure among patients with PEP was 21.60 ± 10.59 minutes in group A and 19.50 ± 11.27 minutes in group B, with 75% of patients in whom the procedure was shorter than 20 *vs.* 26.5 minutes, respectively. No significant difference between the PEP patients in the two treatment groups was found related to the duration of the procedure (p=0.6242) (Table 2).

Sphincterotomy was registered in all 5 (100%) patients with PEP from group A and in 1 (25%) from group B, with significant percentage differences in favour of group A (p=0.0253). Among patients with PEP, pancreatic duct wire cannulation happened in 2 (40%) patients from group A and in none from group B. One (20%) patient with PEP in group A had papilla in diverticulum, with no such case in group B.

Table 2. Incidence of PEP based on age, sex, BMI and procedure-related parameters by treatment groups

Parameters	**Patients with post-ERCP pancreatitis**		**p**
	Group A	**Group B**	
Sex – N (%)			
Male	2 (40%)	2 (50%)	[1]p=0.6428
Female	3 (60%)	2 (50%)	
Age (years)			
Mean ±SD	62.80±8.23	56.25±21.62	Z=0.244; p=0.8065
Range	51/72	29/76	
Median (IQR)	62 (60-69)	60 (39-73.5)	
BMI			
Mean ±SD	27.80±6.12	26.65±4.11	Z=0.245; p=0.8064
Range	20.8-30.8	21.0-30.8	
Median (IQR)	28.4 (23.3-30.1)	27.4 (23.9-29.3)	
Duration of procedure (minutes)			
Mean ±SD	21.60±10.59	19.50±11.27	Z=0.489; p=0.6242
Range	14/40	8/35	
Median (IQR)	19 (15-20)	17.5 (12.5-26.5)	

Group A – 500 mg naproxen single dose rectal administration; Group B = 100 mg indomethacin single dose rectal administration; [1]Fisher exact test; *Significant for p<0.05

The comparison of amylases, lipase and CRP levels in patients with PEP from the two treatment groups - group A/ group B (before, 4h and 24h after ERCP) showed no significant differences in all three measurement times (Table 3). At 4h and 24h after ERCP we found that: a) elevated amylases level had 4 (80%) *vs*. 4 (80%) patients with PEP from group A and 3 (75%) *vs.* 4 (100%) from group B; b) elevated lipase level had 4 (80%) *vs.* 4 (80%) patients with PEP from group A and 3 (75%) *vs.* 4 (100%) from group B; and c) elevated CRP level had 3 (60%) *vs*. 4 (80%) patients with PEP from group A and 3 (75%) *vs.* 4 (100%) from group B.

Only one patient died in the follow-up period, and he belonged to group A. All other patients were discharged in good condition without reported side effects.

Table 3. Incidence of PEP based on selected clinical parameters by treatment groups

Treatment groups	**Patients with post-ERCP pancreatitis**			**p**
	Mean ±SD	**Range**	**Median (IQR)**	
Amylases levels (U/L) - before ERCP				
Group A	43.88±19.44	14/64	51 (36.3-54)	Z=-2.082; p=0.0513
Group B	80.67±23.38	54/102	83.3 (61.1-100.2)	
Amylases levels (U/L) - 4h after ERCP				
Group A	266.86±226.09	26/592	179 (140.1-397)	Z=0.001; p=0.9998
Group B	252.97±214.06	55/547	204.9 (99.9-406)	
Amylases levels (U/L)- 24h after ERCP				
Group A	525.28±186.60	351/2/810	540 (363-562)	Z=-1.225; p=0.2207
Group B	1335.75±846.99	290/2313	1370 (717-1954)	
Lipase levels (U/L) - before ERCP				
Group A	28.36±8.67	15.8/38.2	27.4 (25.8-34.6)	Z=-1.959; p=0.0501
Group B	67.47±27.95	32.7/100	68.6 (47.6-87.3)	

Lipase levels (U/L) - 4h after ERCP				
Group A	619.08±513.09	19/1330	500 (329.3-916.4)	Z=-0.4989; p=0.6242
Group B	720.27±553.79	35.5/1200	822.8 (271-1169.5)	
Lipase levels (U/L) - 24h after ERCP				
Group A	704.26±224.34	557.4/1080	579 (558.9-746)	Z=-0.979; p=0.3272
Group B	924.70±571.71	177/1464	1028.9 (486.2-1363.1)	
CRP levels (mg/L) - before ERCP				
Group A	49.60±59.02	3.3/146.2	30.6 (5.6-62.3)	Z=0.012; p=0.9963
Group B	87.66±129.23	1.4/279.8	34.7 (13.9-161.4)	
CRP levels (mg/L) - 4h after ERCP				
Group A	53.66±54.12	3.3/144.3	34.3 (29.6-56.8	Z=0.735; p=0.7348
Group B	47.91±74.36	1.2/158.3	16 (3.7-92.1)	
CRP levels (mg/L) - 24h after ERCP				
Group A	63.18±61.93	7.4/140.3	44.2 (7.5-116.4)	Z=0.011; p=0.9881
Group B	71.35±86.99	4.1/199.1	41.1 (20.7-122)	

Group A – 500 mg naproxen single dose rectal administration; Group B = 100 mg indomethacin single dose rectal administration; Z=Mann-Whitney U Test; *Significant for $p<0.05$

Discussion

Post-ERCP pancreatitis is the acute pancreatitis form that occurs following endoscopic retrograde cholangiopancreatography[13,14]. There are several underlying mechanisms for pancreatic injury during ERCP, including mechanical, thermal, chemical, hydrostatic, enzymatic, and microbiological insults [15,16]. Therefore, the indications for implemetation of ERCP should be clear, sustained and well-based on the evidence.

Drugs used to prevent PEP are commonly divided to sphincter relaxants, antisecretory agents, protease inhibitors, anti-inflammatory agents, antioxidants, etc. The rationale of NSAIDs for PEP is based on their ability to inhibit inflammatory substances in the early phase of pancreatitis, such as prostaglandins, phospholipase A2, and a neutrophil–endothelial interaction [15].

This study included 60 patients with diagnostic or therapeutic ERCP assigned in two groups with 30 (50%) participants each. In prevention of PEP, the group of patients received either per-procedural single dose rectal administration of 500 mg naproxen or 100 mg indomethacin. No significant association was found between the treatment groups and sex (p=0.0693), age (p=0.2198), and BMI (p=0.1886).

Our finding of no significant association between the gender of patients and development of PEP in naproxen or indomethacin group corresponds with the results from other similar studies [16-19]. The PEP incidence of 15% in our study was higher in comparison to 3-10% reported in a systematic review paper [17].

In our study, we found no significant differences between patients with PEP treated either with naproxen or indomethacin related to age (p=0.806), BMI (p=0.806) and duration of the procedure (p=0.624). In line with our findings are the results derived from the research of El Nakeeb *et al.* based on univariate analysis of predictors of severity such as age, sex, pancreatic duct cannulation, and time of the procedure for PEP [20].

Testoni *et al.* concluded that the level of serum amylase measured four hours after endoscopic sphincterotomy was the most reliable predictor of post-ERCP pancreatitis, as more than two-thirds of cases of pancreatitis ocurred among patients whose four-hour amylase level was higher than five times the normal upper limit [21]. The comparison of amylases, lipase and CRP levels in patients with PEP treated with naproxen or indomethacin

in our study showed no significant differences in all three measurement times (before, 4h and 24h after ERCP).

Serum lipase level was found more useful than serum amylase level for the early diagnosis of PEP after ERCP [22]. Our analysis indicated no significant differences between the PEP cases from the groups treated with naproxen or indomethacin related to lipase levels at all three measurement times. Additionally, many studies reported that the level of CRP was useful for prediction of post-endoscopic pancreatitis [23,24]. In our clinical trial, the level of CRP did not significantly differ between the PEP patients treated with naproxen or indomethacin.

Conclusion

Our findings indicated that prophylactic naproxen or indomethacin single dose rectal administration had no significant difference in prophylaxis of PEP after ERCP. We found no significant differences between patients with PEP from the two treatment groups related to age, sex, BMI, procedure-related parameters and clinical parameters (amylases, lipase and CRP in three measurement times). However, among patients with PEP from the group treated with naproxen we registered sphincterotomy in 100%, pancreatic duct wire cannulation in 40%, and papilla in diverticulum in 20%. Among patients with PEP from the indomethacin group, there were only 25% patients with sphincterotomy. Taking into account the relatively small sample of patients with PEP in our study, we are aware of the need for more extensive research in this field in the Republic of Kosovo for defining an effective way in reduction of PEP after ERCP.

Conflict of interest statement. None declared.

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