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PREDICTIVE FACTORS FOR PROPHYLAXIS EFFECT OF NAPROXEN IN POST ENDOSCOPIC PANCREATITIS

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) can be associated with complications like post-ERCP pancreatitis (PEP). We aimed to examine the possible influence of selective demographic and clinical factors on efficacy of periprocedural 500 mg Naproxen single dose rectal administration in prevention of PEP in patients after diagnostic or therapeutic ERCP.

This randomized prospective mono-centric clinical study was implemented during January-April 2022 on 30 patients referred for ERCP at the University Clinical Center of Kosovo-Prishtina. Before ERCP, all patients received periprocedural 500mg Naproxen single dose rectal administration in prevention of PEP. The levels of amylase, lipase, and CRP were measured before ERCP, and 4/24h after.

The incidence of PEP was 16,67% (5/ 30) – 2 (11,76%) of the male and 3 (23,08%) of the female (p=0,4101). No significant differences between the patients without/with PEP was found related to age (p=0,8674), BMI (p=0,5591) and duration of procedure (p=0,5590). Pancreatic duct wire cannulation happened in 5 (16,67%) patients, while only 2 (40%) of them developed PEP. Amylases levels 24h after ERCP were significantly higher in patients with PEP (p=0,0005). Between patients without/with PEP there were significant differences in lipase levels before/4h/24h after ERCP for p=0,0451 vs. p=0,0278 vs. p=0,005 respectively. Related to CRP levels, no significant difference was found between the groups at any measurement time. Analyzed potential influencing factors didn't show significant influence on efficacy of Naproxen in prevention of PEP after ERCP. More extensive controlled trials are underway in Republic of Kosovo to precise the effects of Naproxen in reduction of PEP after ERCP.

Keywords: Naproxen; nonsteroidal anti-inflammatorydrugs; pancreatic duct cannulation; post-endoscopicretrograde cholangiopancreatography; pancreatitis.

Introduction

Post endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP) [1,2].

Acute pancreatitis (AP) is defined as a new upper abdominal pain, with increased serum amylase and/or lipase levels to at least three times above the normal limit [1].

Studies have found varying incidence rates for this problem, ranging from 4 to 40%. However, post-endoscopic retrograde cholangiopancreatography pancreatitis is severe in 0.1 to 0.5% cases only [2].

Factors predicting post-ERCP pancreatitis (PEP) according to the European Society of Gastrointestinal Endoscopy (ESGE), are female gender, suspected sphincter of Oddi dysfunction, prior episode of pancreatitis, prolonged cannulation time, passing guide wire into pancreatic duct more than once and injection of contrast into the pancreatic duct [3].

Probable mechanisms for PEP include mechanical, chemical, and hydrostatic injuries [4].

One class of prophylactics are nonsteroidal anti-inflammatory drugs (NSAIDs). These agents are potent inhibitors of prostaglandins and phospholipase A2, which play key roles in the pathophysiology of acute PEP. NSAIDs also induce lipoxins and resolvins, which are lipid mediators that control and resolve inflammation. Experimental models have established that these mediators down regulate the expression of proinflammatory genes [5,6].

Although most cases of PEP are clinically mild or moderate in severity, 10% present have severe manifestations [7-10].

Evidence suggests that the patient's inflammatory response to pancreatic duct imaging and instrumentation contribute to the development of PEP [9,11-14].

According to research datas, the naproxen has the best safety compared with another NSAIDs drugs [15,16].

Recently, only one documented study has reported the efficacy of 500 mg rectal naproxen for the prevention of PEP [17].

In our study we aimed to examine the possible influence of selective demographic and clinical factors on efficacy of periprocedural 500 mg Naproxen single dose rectal administration in prevention of PEP in patients after diagnostic or therapeutic ERCP.

Material and methods

This randomized prospective mono-centric clinical study was implemented on 30 patients referred for diagnostic or therapeutic ERCP at the endoscopy unit in abdominal surgery ward of the University Clinical Center of Kosovo-Prishtina during the period of January-April 2022. Before ERCP, all patients received periprocedural 500mg Naproxen single dose rectal administration in prevention of PEP.

According to selected criteria only patients' aged 18 years and older regardless of gender and other demographic characteristics were enrolled. Exclusion criteria understood minimum one of the conditions as:acute pancreatitis, active peptic ulcer disease, rectal disease, aspirin-induced asthma, nonsteroidal anti-inflammatory drug (NSAIDs) induced hypersensitivity, pregnancy, breast feeding, renal disfunctionor history of gastrectomy with billroth's II anastomosis.

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.

As parameters which can potentially influence efficacy of periprocedural Naproxen single dose rectal administration in prevention of PEP we selected gender, age, duration of ERCP procedure, pancreatic duct wire cannulation, BMI, amylase, lipase, and CRP. BMI (kg/m²) was calculated for each patient before the intervention. The levels of amylase, lipase, and CRP were measured before ERCP, 4 hours and 24 h after the procedure. Referent values were for: amylase <100 U/L, lipase<60 U/L, and CRP<5mg/L.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants prior to study enrolment. The Ethical Committee of University Clinical Centre of the Republic of Kosovo approved the implementation of the study.

Statistical analysis

The data obtained with the research were processed in SPSS software package, version 22.0 for Windows. The qualitative series were processed by determining the coefficient of relations, proportions, and rates, and were shown as absolute and relative numbers. 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. Pearson Chi square test was used to determine the association between certain variables in the groups of subjects. Difference test was used to compare the proportions. Mann Whitney U test was used to compare differences between two independent groups (without/ with PEP) when the dependent parameters were either ordinal or continuous, but not normally distributed. A binomial logistic regression was used to predict the possible

influence of selective demographic and clinical factors on efficacy of periprocedural Naproxen administration in prevention of PEP in patients after ERCP. A two-sided analysis with a significance level of p<0,05 was used to determine the statistical significance.

Results

The study sample elaborated 30 patients with diagnostic or therapeutic ERCP who received periprocedural 500mg Naproxen single dose rectal administration in prevention of PEP. From the study group, male were 17 (56,67%) and female 13 (43,33%) with male/female ratio of 1,3:1, and without significant percentage differences between the genders - Difference 13,34% [(-11,4 – 35,9) 95% CI]; p=0,3055) (Table 1).

After the ERCP procedure, PEP was diagnosed in 5 (16,67%) patients from the sample group – in 2 (11,76%) of the male and 3 (23,08%) of the female with no significant association between the gender of the patients and development of PEP (p=0,4101) (Table 1).

Average age of the patients without/ with PEP was 58,12±17,60 with 50% younger than 63 years vs. 62,8±8,23 with 50% younger than 62 years respectively. Elevated value of BMI had 10 (40%) of the patients without PEP, and 3 (60%) of the one with PEP. No significant differences between the patients with/ without PEP was found related to age (p=0,8674), as well as BMI (p=0,5591) (Table 1).

Average duration of procedure among the patients without PEP was 17,60±5,42 minutes, with max of 28 min and 50% of the patients with the procedure was shorter than 17 minutes for Median IQR=17 (14-20). For the patients that developed PEP, the average duration of the procedure was 21,60±10,59 with max of 40 minutes and 50% with the procedure shorter than 19 minutes for Median IQR=19 (15-20). No significant differences between the patients without/ with PEP was found related to duration of procedure (p=0,5590) (Table 1).

Pancreatic duct wire cannulation happened in 5 (16,67%) patients, while only 2 (40%) of them developed PEP. No significant association was found between the pancreatitis duct cannulation and development of PEP (p=0,1251) (Table 1).

Table 1. Analysis of selected demographic and ERCP parameters by PEP status.

Parameters	Post ERCP Pancreatitis - PEP		Total	p
	No	Yes		
N (%)				
Male	15 (88,24%)	2 (11,76%)	17 (56,67%)	[1]p=0,4101
Female	10 (76,92%)	3 (23,08%)	13 (43,33%)	
Total	25 (83,33%)	5 (16,67%)	30 (100%)	
Age (years)				
Mean ±SD	58,12±17,60	62,8±8,23	58,9±16,40	Z=-0,167; p=0,8674
Range	18/82	51/72	18/82	
Median (IQR)	63 (47,5-72)	62 (55,5-70,5)	62,5 (48-62,5)	
BMI				
Mean ±SD	26,43±4,11	27,80±6,12	26,65±4,40	Z=-0,583; p=0,5591
Range	19/35	20,8/36,4	19,4/36,4	
Median (IQR)	26,7 (23,1-28,5)	28,4 (23,3-30,1)	26,8 (23,1-28,7)	
Duration of procedure (minutes)				
Mean ±SD	17,60±5,42	21,60±10,59	18,27±6,49	Z=-0,584; p=0,5590
Range	7/28	14/40	7/40	
Median (IQR)	17 (14-20)	19 (15-20)	17,5 (14-20)	
Pancreatitis duct wire cannulation				
No	22 (88%)	3 (12%)	25 (83,33%)	[1]p=0,1251
Yes	3 (60%)	2 (40%)	5 (16,67%)	

Z=Mann-Whitney U Test [1]Fisher exact test*Significant for p<0,05

Comparison of amylases levels in patients without/ with PEP (before, 4h and 24h after ERCP) showed: a) no significant differences in amylases levels before ERCP related to PEP; b) bordering insignificance after 4h in favor of higher value in patients with PEP (p=0,0549) – elevated amylase value was found in 5 (20%) patients without PEP and in 4 (80%) with PEP; and c) significantly higher amylases levels after 24h in patients with PEP (p=0,0005) – elevated amylase value was found in 5 (20%) vs. 4 (80%) patients without/ with PEP respectively (Table 2).

Between patients without/ with PEP there were significant differences in lipase levels at all three measurement times - before ERCP in favor of significantly lower level in patients with PEP (p=0,0451), as well as at 4h and 24h after ERCP in favor of significantly higher level in patients with PEP compared with the one that didn't develop PEP for p=0,0278 vs. p=0,005 respectively (Table 2).

At all three measurement points (before ERCP, 4 hours and 24 h after the procedure), the levels of CRP were no significantly higher in patients with PEP compared with the one without PEP for (Table 2).

Table 2. Analysis of selected clinical parameters in three measurement times by PEP status.

Parameters	Mean ±SD	Range	Median (IQR)	p
Amylases levels(U/L) - before ERCP				
PEP - no	73,86±37,60	31/141	59 (43,2-105)	Z=1,419; p=0,1559
PEP - yes	43,88±19,44	14/64	51 (36,3-54)	
Amylases levels(U/L) - 4h after ERCP				
PEP - no	83,71±42,58	28/189,1	73 (48-112)	Z=-1,919; p=0,0549
PEP - yes	266,86±226,09	26,1/592	179 (140,1-397)	
Amylases levels (U/L)- 24h after ERCP				
PEP - no	79,55±40,57	30/165	68 (49-97)	Z=-3,478; p=0,0005*
PEP - yes	525,28±186,60	351,2/810	540 (363-562)	
Lipase levels(U/L) - before ERCP				
PEP - no	64,28±44,35	12/193,7	57,8 (30,3-74,5)	Z=2,003; p=0,0451*
PEP - yes	28,36±8,67	15,8/38,2	27,4 (25,8-34,6)	
Lipase levels(U/L) - 4h after ERCP				
PEP - no	62,14±34,62	11,9/147,6	56,7 (36-87,4)	Z=-2,198; p=0,0278*
PEP - yes	619,08±513,09	19/1330	500 (329,3-916,4)	
Lipase levels(U/L) - 24h after ERCP				
PEP - no	58,96±37,52	16,2/175,2	44,8 (38,9-71,5)	Z=-3,478; p=0,0005*
PEP - yes	704,26±224,34	557,4/1080	579 (558,9-746)	
CRP levels(mg/L) - before ERCP				
PEP - no	31,24±43,36	0,2/173,8	13,6 (5,1-32,7)	Z=-0,584; p=0,5590
PEP - yes	49,60±59,02	3,3/146,2	30,6 (5,6-62,3)	
CRP levels(mg/L) - 4h after ERCP				
PEP - no	36,68±51,80	0,1/207,7	14,8 (4,8-36,4)	Z=-1,085; p=0,2778
PEP - yes	53,66±54,12	3,2/144,3	34,3 (29,6-56,8)	
CRP levels(mg/L) - 24h after ERCP				
PEP - no	37,69±40,33	0,9/175,2	18,6 (13-56)	Z=-0,696; p=0,4867
PEP - yes	63,18±61,93	7,49/140,3	44,2 (7,5-116,4)	
Z=Mann-Whitney U Test *Significant for p<0,05				

Binominal logistic regression (Table 3) showed that none of the analyzed potential influencing factors didn't have significant influence on efficacy of single dose rectal administration of Naproxen in prevention of PEP after ERCP. Bordering non significant influence for PEP was found for amylases 4 hours after ERCP (p=0,094), and lipase before and 4 hours after ERCP for p=0,099 and p=0,056 respectively.

Table 3. Binominal logistic regression for predictive role of selective factors on efficacy of single dose rectal administration of Naproxenin prevention of PEP after ERCP.

Factors	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Gender	,811	1,000	,658	1	,417	2,250	,317	15,973
Age	,020	,034	,344	1	,557	1,020	,955	1,090
BMI	,072	,112	,413	1	,521	1,074	,863	1,337
Duration of procedure	,086	,071	1,454	1	,228	1,090	,948	1,254
Pancreatitis duct canulation	1,587	1,101	2,078	1	,149	4,889	,565	42,301
Amylases - before ERCP	(,045)	,031	2,093	1	,148	,956	,899	1,016
Amylases - 4h after ERCP	,017	,010	2,813	1	,094	1,017	,997	1,037
Amylases - 24h after ERCP	,188	44,975	,000	1	,997	1,207	,000	-
Lipase - before ERCP	(,057)	,035	2,723	1	,099	,945	,883	1,011
Lipase - 4h after ERCP	,016	,009	3,663	1	,056	1,016	1,000	1,034
Lipase - 24h after ERCP	,095	27,966	,000	1	,997	1,100	,000	-
CRP - before ERCP	,008	,009	,662	1	,416	1,008	,989	1,027
CRP - 4h after ERCP	,006	,008	,449	1	,503	1,006	,989	1,023
CRP - 24h after ERCP	,011	,010	1,303	1	,254	1,011	,992	1,031

Parameters: Gender (male vs. female); Age (years), Duration of procedure (minutes); BMI (kg/m²); Amylases/Lipase/ CRP (mg/L)
N: with PEP = 5; without PEP=25
Dependent variable: PEP yes vs. no *Significant for p<0,05

Discussion

From the first descriptions the ERCP has evolved in an extraordinary way. The first sphincterotomy was published in 1974 [18-19], followed by development of ERCP as a therapeutic procedure as it is nowdays [20**]**.

ERCP is the procedure of choice for management of biliary tract lesions. This procedure should be used only for specific cases, given the consequences of about 10% rate of complications and a 1% mortality rate [19-20].

The indications for implemetation of ERCP should be clear, sustained and well-based on the evidence.

PEP is the most common severe complication after ERCP. PEP's pathophysiology is due to the secretion of inflammatory mediators and cytokine such as prostaglandins, phospholipase-A2, cyclooxygenasein the peri- and post-procedural period [21,22].

The PEP incidence of 16,7% in our study patients group was higher in comparison to 3-10% reported in the systematic review paper [23].

Our finding of no significant association between the gender of the patients and development of PEP corresponds with the results from another similar studies [17,23, 24].

We found no significant differences between the patients with/without PEP related to age (p=0,8674), as well as BMI (p=0,5591which was also found by other authors as Abdelfatah et al [24].

Our findings of no significantly longer ERCP procedure in patients with PEP compared to patients without PEP corresponds with the results presented by Hatami et al. in their randomized, prospective, double-blind trial [25].

In line with our findings are also the results of El Nakeeb *et all* based on univariate analysis of risk factors and predictors of severity such as age, sex, pancreatic duct cannulation, and time of the procedure for post-endoscopic retrograde cholangiopancreatography pancreatitis. They revealed no significant difference between the pancreatitis group and the non-pancreatitis group [20].

In this study we found no significant differences in amylases levels before ERCP related to PEP, bordering insignificance after 4h in favor of higher value in patients with PEP and significantly higher amylases levels after 24h in patients with PEP. Testoni *et all* concluded that the level of serum amylase measured 4h after endoscopic sphincterotomy was the most reliable predictor of post-ERCP pancreatitis, as more than two-thirds of cases of pancreatitis ocurred among the patients whose 4h amylase level was higher than five times the normal upper limit [26].

Related to our analysis, there were significant differences between the groups related to lipase levels at all three measurement times, all in favor of significantly higher lipase level in patients with PEP compared with the one without PEP. Still, after binominal logistic regression, we only confirm bordering non significant influence of lipase on efficacy of single dose rectal administration of Naproxen in prevention of PEP, before and 4 hours after ERCP. Similar results were presented by other authors where serum lipase level was found more useful than serum amylase level for the early diagnosis of PEP after ERCP [27].

In our clinical trial the level of CRP didn't significantly differ between the patients without/ with PEP. In many other studies we found that the level of CRP is useful for prediction of post endoscopic pancreatitis [28].

Conclusion

In our study we didn't confirm any of the analyzed demographic and clinical factors to be a significant predictor for prophylaxis effects of single dose rectal administration of Naproxen in prophylaxis of PEP after ERCP. Boredering nonsignificant findings related to the influence of amylase and lipase levels on the efficacy of Naproxen before/4h/24h after ERCP may be due to our smaller sample size. A further randomized clinical trials on a larger samples of patients are required to examine this research hypothesis. More extensive trials are underway on the population of Republic of Kosovo to precise the effects of Naproxen in reduction of incidence of PEP after diagnostic or therapeutic ERCP.

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