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RAMAZAN UÇAR

MURAT BIYIK

ESMA UÇAR

İLKER POLAT

SAMİ ÇİFÇİ

See next page for additional authors

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Authors
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Rectal or intramuscular diclofenac reduces the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography

Ramazan UÇAR[1,*], Murat BIYIK[2], Esma UÇAR[1], İlker POLAT[3], Sami ÇİFÇİ[2], Hüseyin ATASEVEN[2], Ali DEMİR[2]

[1]Department of Internal Medicine, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
[2]Department of Gastroenterology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
[3]Division of Internal Medicine, Afyon State Hospital, Afyonkarahisar, Turkey

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Background/aim: Acute pancreatitis is the most common adverse event of endoscopic retrograde cholangiopancreatography (ERCP). We aimed to evaluate the efficacy of intramuscular diclofenac sodium for prophylaxis of post-ERCP pancreatitis (PEP) in comparison to the rectal form.

Materials and methods: One hundred and fifty consecutive patients who underwent ERCP were enrolled in this single-center, prospective, randomized controlled study. Patients were randomized into three groups. The first group received 75 mg of diclofenac sodium via intramuscular route and the second group received 100 mg of diclofenac sodium rectally 30–90 min before the procedure. The third group served as the control group. Patients were evaluated for post-ERCP pancreatitis with serum amylase levels and abdominal pain 24 h after the procedure.

Results: The overall incidence of PEP was 6% (n = 9) and 2% (n = 1) in the intramuscular (IM) and rectal groups, respectively, and 14% in the control group (P = 0.014). Nineteen (12.7%) patients developed post-ERCP abdominal pain (8% in IM, 10% in rectal, and 20% in control group; P = 0.154). Twenty-five (16.6%) patients developed post-ERCP hyperamylasemia (10% in IM, 12% in rectal, and 24% in control group; P = 0.03).

Conclusion: Prophylaxis with diclofenac given rectally or intramuscularly is an effective option for the management of post-ERCP pancreatitis.

Key words: Diclofenac, ERCP, post-ERCP pancreatitis

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure with the highest rate of adverse events among all gastrointestinal endoscopic procedures. Post-ERCP pancreatitis (PEP) is the most common adverse event of ERCP (1). PEP occurs in about 1%–10% of patients undergoing ERCP but most of the cases are mild or moderate (2). Several drugs have been studied for the pharmacologic prophylaxis of PEP, including relaxation of the sphincter of Oddi, reduction of pancreatic secretions, prevention of infection, and restriction of inflammatory response, which yielded controversial results (1).

In recent years, nonsteroidal antiinflammatory drugs (NSAIDs), particularly diclofenac sodium, have been successfully used for PEP prophylaxis. A single administration of diclofenac, by rectal or intramuscular (IM) route, has been studied either before or after the ERCP procedure for prevention of PEP (3–5). Diclofenac is an inexpensive, commonly available, easily administered drug that is safe for single use.

In this study, we aimed to compare the efficacy of IM diclofenac sodium with that of the rectal form for prevention of PEP.

2. Materials and methods

One hundred and fifty patients who underwent ERCP in the Gastroenterology Department between January 2011 and September 2012 were consecutively enrolled in this single-center, prospective, randomized controlled study. Patients with acute pancreatitis using NSAIDs or acetylsalicylic acid during the previous week with creatinine levels above 2 mg/dL, those with a known allergy to diclofenac, pregnant and breastfeeding women, patients who were recently diagnosed with peptic ulcer, and those with a history of endoscopic sphincterotomy were excluded. Patients were consecutively randomized

* Correspondence: mdramazan@gmail.com

into three groups. The first group received 75 mg of diclofenac sodium intramuscularly and the second group received 100 mg of diclofenac sodium via rectal route 30–90 min before the procedure. The third group did not receive any prophylaxis and served as the control group. The study was approved by the local ethics committee and all patients gave written informed consent.

All ERCP procedures were performed by same endoscopist. The endoscopist was blinded to treatment allocation and recorded the following information during the procedure: the difficulty of cannulation, diagnosis made during ERCP, presence of periampullary diverticula, total duration of the procedure, insertion of guide wire into the pancreatic duct, opacification of the pancreas, and adverse events, if any, during the procedure and interventions such as sphincterotomy, balloon dilation, and stenting. Difficult cannulation was defined as needing more than 5 attempts and/or 10 min of manipulation time. We performed suprapapillary fistulotomy with needle knife for patients with difficult cannulation and standard sphincterotomy for all other patients.

Serum amylase levels were measured at 4 and 24 h of the procedure, and oral intake of water was permitted for patients with serum amylase levels less than 3 times the upper limit of normal (ULN) (375 U/L) at 4 h.

Patients were evaluated for PEP according to the criteria described by Cotton et al., which included an increase in serum amylase levels 3 times greater than the ULN and new-onset or worsened abdominal pain lasting more than 24 h after the procedure (6). Post-ERCP hyperamylasemia was considered when serum amylase levels were 3 times greater than the ULN within 24 h after ERCP. Severity of pancreatitis was defined on the basis of the duration of hospitalization after procedure; 2–3 days of hospital stay was required for mild PEP, 4–10 days for moderate PEP, and >10 days for severe PEP and/or necrotizing pancreatitis and any surgical interventions related to PEP (6).

2.1. Statistical analysis

Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The Student t-test and the chi-square test were used for groups showing normal distribution and the Mann–Whitney U test was used for groups with nonnormal distribution. The one-way ANOVA test was used to examine the differences between multiple groups. The Wilcoxon test was used to determine differences between intragroup repeated measures. Continuous variables were expressed as means with standard deviations. Statistical significance was set at $P < 0.05$.

3. Results

A total 150 patients (100 females and 50 males) with a mean age of 60.2 ± 17.6 years were enrolled in the study. The three groups were similar with respect to age, sex, indication, procedures performed during ERCP, diagnosis, and other factors associated with increased risk for PEP, as shown in Tables 1–3.

The mean serum amylase levels were statistically significantly higher ($P = 0.05$) in the control group compared to both diclofenac groups at 4 h [183 ± 38 (SE) U/L in IM group, 214 ± 61 U/L in rectal group, and 487 ± 148 U/L in control group] and at 24 h after ERCP (140 ± 20 U/L in IM group, 211 ± 77 U/L in rectal group, and 463 ± 100 U/L in control group; $P < 0.05$).

Nineteen (12.7%) patients reported new-onset abdominal pain at 24 h after ERCP (n = 4, IM group; n = 5, rectal group; n = 10, control group). The incidence of abdominal pain was higher in the control group compared to the IM and rectal groups, but the difference was not statistically significant ($P = 0.15$). Twenty-five (16.6%) patients developed post-ERCP hyperamylasemia (n = 5, IM group; n = 6, rectal group; n = 14, control group), which occurred significantly more frequently in the control group ($P < 0.05$).

A total of 9 (6%) patients had PEP (n = 1, IM group; n = 1 rectal group; n = 7, control group), which was

Table 1. Characteristics and demographic data of patients.

	Intramuscular (n = 50)	Rectal (n = 50)	Control (n = 50)	P-value
Sex (male/female)	17/33	13/37	20/30	0.334
Age (years)	61.1 ± 16.8	59 ± 18.6	60.5 ± 17.6	0.830
Body mass index (kg/m^2)	26.2 ± 3.0	27.6 ± 3.3	26.5 ± 2.9	0.058
Total bilirubin (mg/dL)	4.1 ± 0.6	4.2 ± 0.8	4.4 ± 0.9	0.954

Data are presented as number/number or mean ± standard deviation, as appropriate.

Table 2. Indications for endoscopic retrograde cholangiopancreatography.

	Intramuscular (n = 50)	Rectal (n = 50)	Control (n = 50)
Choledocholithiasis	40	47	36
Periampullary tumor	7	1	10
Benign biliary stenosis	1	1	-
Other	2	1	4

Data are presented as numbers.

Table 3. Endoscopic findings and therapeutic procedures during endoscopic retrograde cholangiopancreatography.

	Intramuscular	Rectal	Control	P-value
Total duration (min)	24 ± 12	20 ± 11	25 ± 11	0.073
Difficult cannulation	8	11	15	0.309
Insertion of guide wire into the pancreatic duct	15	16	21	0.402
Pancreatic opacification	7	4	-	0.027
Suprapapillary fistulotomy with needle knife	8	9	11	0.619
Diverticula (peridiverticular/intradiverticular papilla)	3/4	9/4	5/4	0.440
Balloon catheter for stone extraction	33	36	39	0.398
Basket catheter for stone extraction	5	6	8	0.662
Lithotripsy	0	4	4	0.118
Biliary stenting	11	6	10	0.413

Data are presented as number, number/number, or mean ± standard deviation, as appropriate.

significantly more common in the control group ($P < 0.05$). Four of them had mild PEP (n = 1, IM group; n = 3, control group) and 5 had moderate PEP (n = 1, rectal group; n = 4, control group).

The median of duration of hospital stay was significantly longer in the control group compared to the diclofenac groups (1 day in IM group, 1 day in rectal group, and 2 days in control group, $P < 0.001$; Table 4).

Four of the patients (2 in IM and 2 in rectal group) had self-limiting bleeding, which stopped spontaneously during the procedure and did not require any intervention. We did not use pancreatic stents in any of the patients, and no adverse effects were observed after administration of a single dose of NSAIDs in the diclofenac groups.

4. Discussion

In the present study we found that: 1) diclofenac, whether administered rectally or intramuscularly, reduced the incidence of PEP; 2) abdominal pain was less common in the diclofenac groups compared to the control group; 3) post-ERCP hyperamylasemia occurred at a significantly lower rate in the diclofenac groups in comparison to the control group; and 4) duration of hospitalization was significantly shorter in both diclofenac groups compared to the control group.

Three metaanalyses, which gathered data from 4 randomized, controlled trials on NSAIDs (two studies each with diclofenac and indomethacin), were published for PEP prophylaxis (7–9). Murray et al. (4) and Khoshbaten et al. (3) reported that 100 mg of diclofenac administered rectally significantly reduced the incidence of PEP. In a recent study by Otsuka et al. in Japanese patients, 50 mg of diclofenac given by the rectal route was found to be effective for prevention of PEP, post-ERCP hyperamylasemia, and abdominal pain (2). Senol et al. administered diclofenac by intramuscular route for preventing PEP for the first

Table 4. Outcome measures of the study groups.

	Intramuscular	Rectal	Control	P-value
Post-ERCP pancreatitis	1	1	7	0.014
Mild	-	1	3	
Moderate	1	-	4	
Severe	-	-	-	
Abdominal pain	4	5	10	0.154
Amylase, at 4 h (U/L)	183 ± 38	214 ± 61	487 ± 148	0.05
Amylase, at 24 h (U/L)	140 ± 20	211 ± 77	463 ± 100	0.006
Post-ERCP hyperamylasemia	5	6	14	0.03
Duration of hospitalization after ERCP (days) (min/median/max)	1/1/4	1/1/3	1/2/8	<0.001

ERCP: Endoscopic retrograde cholangiopancreatography.
Data are presented as number, mean ± standard deviation, or minimum/median/maximum, as appropriate.

time and found that diclofenac nonsignificantly lowered PEP incidence (5). In the current study, the incidence of PEP was equal in the rectal and intramuscular diclofenac groups and significantly lower compared to the control group.

Inflammatory response of the patient due to irritation of the pancreatic duct is an important cause of PEP (10,11). NSAIDs have potent effects on inhibiting phospholipase A_2, which plays a crucial role in the initial steps of the inflammatory cascade (12). The peak serum concentration of diclofenac occurs at 30–90 min after administration and the elimination half-life is 2 h (13). Any concern that diclofenac may mask abdominal pain during evaluation of PEP is unlikely because the analgesic effect of diclofenac is not maintained for 24 h. Diclofenac, which is an NSAID, is an inexpensive, widely available, and easily administered drug and it has a safe adverse effect profile. In the present study, there were no severe adverse effects associated with diclofenac. Rectal administration of diclofenac or indomethacin before or after ERCP has been recommended for prophylaxis of PEP by the most recent guideline of the European Society of Gastrointestinal Endoscopy (ESGE) (1).

In addition to NSAID prophylaxis, in the case of high risk for PEP, prophylactic pancreatic stent placement is recommended by ESGE guidelines (14). However, a metaanalysis showed that prophylactic pancreatic stenting alone was less effective than NSAIDs alone, and the combination of NSAIDs with prophylactic pancreatic stenting did not further decrease the risk of PEP (15). In our study, we did not place any pancreatic stents, because we aimed to evaluate the role of diclofenac for PEP prophylaxis. Additional pancreatic canal implementation could also increase the risk of PEP. There are several pharmacological agents studied for PEP prophylaxis, but findings are controversial. Only glyceryl trinitrate (sublingually) or somatostatin (bolus injection) have been found to be possibly effective agents and might be considered as an option in high-risk cases if NSAIDs are contraindicated and if prophylactic pancreatic stenting is not possible (14).

Although we aimed to compare the effectiveness of IM and rectal forms of diclofenac for prophylaxis of PEP, the incidence of PEP was the same in both groups; hence, no statistical comparison was made between these groups.

Female sex, age less than 60 years, normal serum bilirubin levels, difficult cannulation, and pancreatic opacification are well-known risk factors for PEP. In the current study, these factors were more common in patients developing PEP, but the difference was not statistically significant.

In conclusion, this study showed that both rectal and intramuscular forms of diclofenac are successful in preventing PEP. We think that diclofenac administered rectally or intramuscularly is a safe, inexpensive, and simple method for PEP prophylaxis.

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