Surg Endosc (2017) 31:2317–2324
DOI 10.1007/s00464-016-5234-x

Prophylaxis of pancreatitis with intravenous ketoprofen in a consecutive population of ERCP patients: a randomized double-blind placebo-controlled trial

Fernanda de Quadros Onófrio[1] · Julio Carlos Pereira Lima[1] · Guilherme Watte[2] · Romnei Lenon Lehmen[3] · Daniela Oba[1] · Gabriela Camargo[1] · Carlos Eduardo Oliveira dos Santos[4]

Received: 15 July 2016 / Accepted: 30 August 2016 / Published online: 20 September 2016

Abstract *Background* Acute pancreatitis is the most common complication after ERCP, occurring in about 4 % of the procedures. Only the placement of pancreatic duct prosthesis and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have shown benefit in the prevention of post-ERCP pancreatitis (PEP). Although the benefit of rectal administration of indomethacin or diclofenac is recommended by some studies and society guidelines especially in a selected group of high-risk patients, there is so far, no standardization of time or route of NSAID administration. The aim of the current study is to investigate the role of an intravenous NSAID administered before the procedure for PEP prevention. *Methods* In this randomized double-blind clinical trial, all consecutive patients who underwent ERCP were randomized to receive saline infusion with ketoprofen or saline, immediately before the procedure. *Results* A total of 477 patients were enrolled and completed follow-up. The majority of patients (72.1 %) had bile duct stones, and only 1.5 % had a clinical suspicion of sphincter of Oddi dysfunction. PEP developed in 5 of 253 (2 %) patients in the placebo group and in 5 of 224 (2.2 %) patients in the ketoprofen group ($p = 1.$). *Conclusions* Intravenous administration of ketoprofen immediately prior to ERCP did not result in reduction in PEP in a general population of ERCP patients.

Keywords Acute pancreatitis · Endoscopic retrograde cholangiopancreatography · Anti-inflammatory drug

Pancreatitis is the leading complication of endoscopic retrograde cholangiopancreatography (ERCP), occurring in about 4 % of the cases resulting in considerable morbidity, costs and, rarely, in death [1–5].

Several proposed factors might act independently or in combination to induce PEP, all of these leading to the common endpoint of inflammation. The resultant activation of inflammatory pathways could be targeted by preventive therapies such as technical issues during ERCP or drugs. These include fewer cannulation attempts, use of guide wire—possibly avoiding contrast injections or trauma to the pancreas—and placement of a temporary pancreatic duct stent in high-risk patients. Administration of rectal indomethacin and diclofenac in high-risk patients is a current recommended pharmacological measure for the prevention of PEP [6]. However, the evidence for or against numerous other attempted therapies in selected and non-selected patients is still unclear, and ongoing investigation is required [6].

Ketoprofen is a potent NSAID that inhibits both COX1 and COX2 and when intravenously administered reaches serum peak in minutes, while rectally or orally administered indomethacin or diclofenac will reach peak serum concentrations within 2–3 h [7]. Moreover, the absorption

Electronic supplementary material The online version of this article (doi:10.1007/s00464-016-5234-x) contains supplementary material, which is available to authorized users.

✉ Fernanda de Quadros Onófrio
fqonofrio@gmail.com

[1] Department of Gastroenterology and Hepatology, Santa Casa Hospital/Federal University of Health Sciences of Porto Alegre (UFCSPA), Rua São Francisco, 469/1203, Porto Alegre 90620-070, Brazil

[2] The Post-Graduation Program in Chest Medicine Sciences, Santa Casa Hospital, Porto Alegre, Brazil

[3] Department of Anesthesiology, Santa Casa Hospital, Porto Alegre, Brazil

[4] Department of Gastroenterology and Endoscopy, Santa Casa de Caridade de Bagé, Bagé, Brazil

of rectally introduced indomethacin or diclofenac may be erratic [7], sedated patients would have difficulties in retaining the suppository when it is given after the procedure and it is recommended that the suppository should be introduced after defecation, in order to increase the absorption of the drug.

Most studies [4, 8] that analyzed the use of prophylactic NSAIDs included as high-risk patients a huge proportion of SOD patients (82 % in the study by Elmunzer et al. [8]) and a very high rate of PEP in the placebo group (mean 15 % in 2 different meta-analyses) [9, 10]. Thus, the result of these studies may not apply to most of the patients undergoing ERCP. Recent studies analyzing rectal indomethacin or diclofenac for consecutive ERCP patients who yielded a reasonable PEP rate in the placebo group have not demonstrated a benefit in the use of the drug [11, 12]. Therefore, in this study we tested the use of intravenous ketoprofen immediately prior to ERCP in a consecutive sample of "naïve" papilla patients.

Materials and methods

Subject selection

Eligible subjects were all adults who were scheduled to undergo ERCP at our institution. Risk factors for PEP were specified as cannulation time more than 10 min, contrast injection into the pancreas, guide wire passage to the pancreatic duct, pre-cut, biliary sphincterotomy, pancreatic sphincterotomy, age less than 40 years and female gender.

Exclusion criteria were patients with known contraindication to ketoprofen use, active pancreatitis at the time of ERCP, previous ERCP and refusal to enter in the study.

All patients gave signed informed consent to the procedure and to the study before randomization. The study protocol was approved by the research Ethics Commission of our institution and registered as "Acute pancreatitis prevention after endoscopic retrograde cholangiopancreatography (ERCP) with an anti-inflammatory" in the Brazilian protocol registry under number RBR-6zkm5 k (http://www.ensaiosclinicos.gov.br/rg/RBR-6zkm5k/).

Protocol

The randomization was computer-generated by the www.researchrandomizer.org site in groups of 100 randomized subjects. All the enrolled patients were randomly divided into study group and placebo group. The anesthesiologist (RLL) opened the sealed envelopes, which contained patient's randomization allocation. Cannulation attempts began with contrast or guide wire technique at endoscopist's discretion, and air was used for insufflation in all ERCPs. Pancreatic stents were never used in this trial. Patients in the study group received 100 ml saline infusion with 100 mg ketoprofen during 20 min, immediately before the procedure, while patients in the placebo group received only 100 ml saline solution, during 20 min (both infusions had the same aspect). Patients were sedated with proprofol, midazolam and fentanyl, and hyoscine was administered in order to abolish duodenal peristalsis. All ERCPs were performed by one of the authors (JPL), who perform more than 800 ERCPs annually. Patients, operator (endoscopist), nurses and result observers were blinded to the randomization assignment.

The operator filled out the procedure evaluation form immediately after the procedure. The research team contacted patients by phone or personally 48–72 h after ERCP to fill the follow-up form. Patients who experienced post-ERCP pain underwent laboratory and abdominal imaging evaluation.

The study followed CONSORT guidelines.

Definitions and study outcomes

Contraindications to ketoprofen use were defined as creatinine level >1.4 mg/ml, current or previous peptic ulcer disease, myocardial infarction in the last 3 months or NSAID allergy.

The primary outcome was PEP, which was defined based on consensus definition [13], in which the diagnosis of acute pancreatitis requires new or worsened abdominal pain suggestive of pancreatitis lasting more than 24 h, serum amylase more than three times the upper limit of normal and requiring new hospitalization.

Abdominal pain with no pancreatitis after ERCP was considered a secondary outcome and was defined as pain lasting for 12–24 h in the upper abdomen without pancreatic enzymes elevation greater than three times the upper limit of normal and negative abdominal images. Other procedure-related complications were also evaluated.

Statistical analysis

We estimated that 536 patients (268 per study group) would provide a power of at least 80 % to detect a reduction in the incidence of post-ERCP pancreatitis, from 7 % in the placebo group (half the mean PEP rate observed in the placebo group in the meta-analysis published by Ding et al. [9]) to 2 % in the ketoprofen group, on basis of Fisher's exact test, with a two-sided significance level of 0.05.

Data were presented as mean ± SD or frequency and percentage. We performed associations between variables with the χ^2 tests. For comparing continuous variables, a Student t test or an unequal variance t test was used.

We performed additional exploratory subgroup analyses using multinomial logistic regression analyses [8] to investigate whether demographic components and interventional procedures were associated with abdominal pain without PEP or PEP (reference is no abdominal pain after ERCP and no PEP). The multivariate model was built in these steps: Demographic components and interventional procedures associated with PEP (p less than 0.05) in univariate analysis were included in a multivariate model and considered statistically significant if the overall p value was less than 0.05.

All the subgroup statistical analyses were calculated for interaction effects with ketoprofen and any subgroups (Table 2) ($p > 0.05$) [14].

An interim analysis was planned after the sixth to seventh month of patient recruitment.

Analyses were performed using STATA Intercooled 13.1 (STATA Corporation, College Station, Texas, USA).

Results

Patients

Between August 2013 to February 2014, 562 patients underwent ERCP at our unit (Fig. 1). Of the 500 consecutive cases with no prior ERCP, 477 were enrolled in the study and 23 excluded (10 with ongoing acute pancreatitis [4 in the placebo group], 3 were less than 18 years old [1 in the placebo group] and 10 were lost to follow-up or have inappropriate filled forms [5 in each group]). A total of 396 of these 477 (83.01 %) ERCPs were performed as an outpatient procedure.

Of the 477 enrolled patients, 253 were assigned to and received placebo and 224 ketoprofen. Both arms completed follow-up for primary endpoint and were included in the analysis (Fig. 1).

Baseline characteristics were similar between the two study groups (Table 1). Notably, 72.1 % of the sample was bile duct stone patients, 70.4 % were women and the mean age was 57 years. Sphincter of Oddi dysfunction was suspected in only 1.5 % of patients.

Study outcomes and risk factors for PEP

The primary outcome, PEP occurred in 10 of 477 patients (2.1, 95 % CI: 1.0–3.8). Of these events, 5 of 253 (2.0, 95 % CI: 0.6–4.5) occurred in the placebo group and 5 of 224 (2.2, 95 % CI 0.7–5.1) in the ketoprofen group ($p = 1.$) (Fig. 2). All these 10 patients had mild pancreatitis. There was no difference in length of hospital stay between placebo or ketoprofen groups among these 10 patients.

Abdominal pain lasting for about 24 h after the procedure with no pancreatitis occurred in 38 of 447 patients (8.0, 95 % CI: 5.1–10.1), 23 (9.1, 95 % CI: 5.5–13.3) in the placebo group and 15 (6.7, 95 % CI 3.9–10.8) in the ketoprofen group ($p = 0.33$) (Fig. 2.).

Risk factors associated with mild PEP in the univariate analysis were: time until deep biliary cannulation ≥10 min ($p = 0.04$), contrast injection into the pancreatic duct ($p = 0.04$), pancreatic sphincterotomy ($p < 0.05$) and submucosal contrast depot ($p = 0.02$) (Table 2).

Female gender, use of guide wire and pancreatic duct guide wire passage was related to abdominal pain with no pancreatitis in crude analysis ($p < 0.05$). In adjusted multivariate analysis only female gender was associated with abdominal pain [OR 2.83 (95 % CI 1.42–5.64); $p = 0.003$].

Adverse events

Main adverse events during the study are showed in Table 3. Ketoprofen was not associated with any specific side effect.

Infection occurred in 4 (0.8 %) patients, 3 (1.2 %) in the placebo group and 1 (0.4 %) in the ketoprofen group. Infections reported were urinary tract infection (1), cholangitis (2) and gastroenteritis (1).

Overt bleeding occurred in 8 patients (1.6 %): 4 in the placebo group and 4 in the ketoprofen group ($p = 1.$).

There were 11 deaths at 30-day follow-up, 5 (2.0 %) in the placebo group and 6 (2.7 %) in the ketoprofen group, all in patients with advanced cancer, and none related to the procedure.

Discussion

In this study, intravenous administration of ketoprofen immediately prior to ERCP did not result in a reduction in PEP in a general population of ERCP patients. However, it significantly reduced the frequency of post-procedure abdominal pain in women.

This pain lasting for about 12–24 h after the procedure without laboratory and image evidences of PEP could be caused by excess of intestinal gas (we perform ERCP only with air insufflation), stretching of the mesentery or other ligaments during the procedure or even, subclinical microperforations.

This is the first study that analyzed the use of intravenous ketoprofen in the prevention of PEP. Prior placebo-controlled trials of intravascular valdecoxib, oral diclofenac and intramuscular diclofenac have yielded negative results [15–17]. In a recently published guideline [4], it was stated that only rectally administered indomethacin or

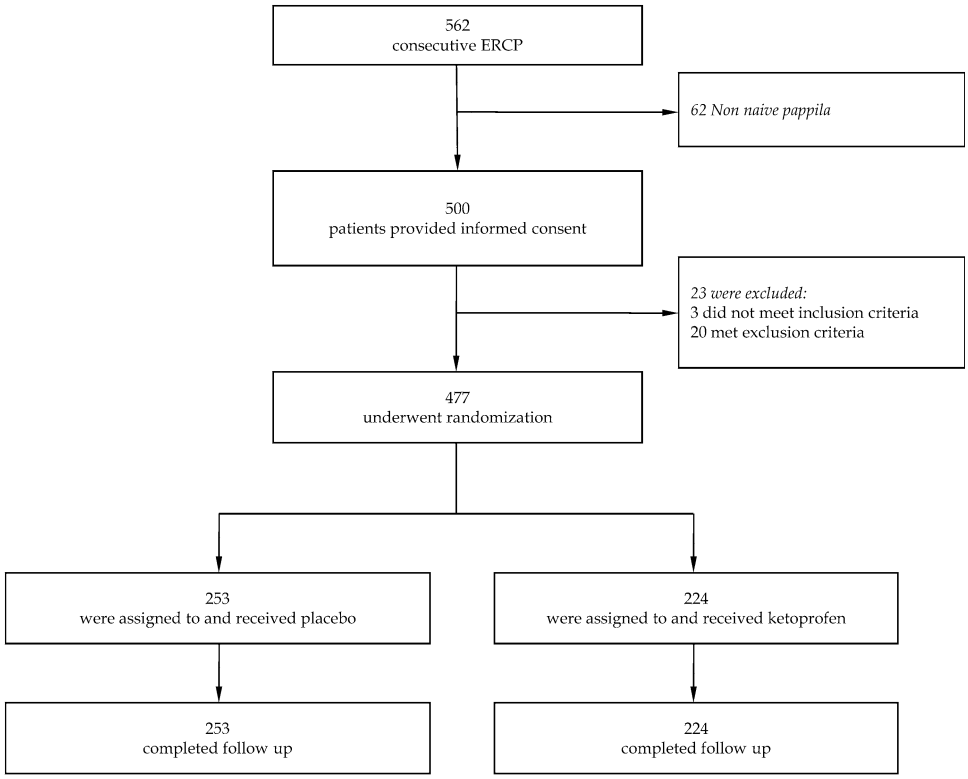

Fig. 1 Diagram of patient flow through the trial

diclofenac immediately before or after the procedure would prevent PEP because peak concentrations on NSAIDs could be attained within 3-hours. For this reason ketoprofen could also be an ideal NSAID in this setting.

From a pharmacology point of view, peak plasma concentrations of diclofenac and indomethacin are attained within 2–3 h after oral intake as well as after rectal administration of these drugs [7]. Moreover, the presence of stools in the rectum may avoid or delay their complete absorption [18], and suppositories are unappealing to many health care providers and may be undesirable to certain patients.

Ketoprofen as well as indomethacin and diclofenac, inhibits the activity of phospholipase A2 that is supposed to play a major role in the pathogenesis of pancreatitis [19]. In a study conducted in vitro, testing 17 pharmacological agents for phospholipase A2 inhibition, ketoprofen inhibited by 90 % the enzyme activity, diclofenac inhibited by 93 % and the strongest effect was reached by indomethacin [20].

Pancreatic injury occurs during ERCP. Thus, the administration of a drug that inhibits the inflammatory cascade before the procedure would seem more logical, preventing damage and therefore, pancreatitis. In addition, the ideal drug would need to be at high concentrations during the procedure, while the pancreas is being injured. Indeed, several experimental studies showed that once the inflammatory cascade is triggered pancreatitis could not be avoided anymore [21].

Glucocorticoids, which are the most potent anti-inflammatory drugs, were also tested for PEP prophylaxis in two meta-analyses that included 6 RCTs and proved ineffective [22, 23]. Diclofenac has a half-life of 2 h, indomethacin of 4 h and ketoprofen of 3–4 h [7]. Since 80 % of PEPs manifest clinically within 3 h after the procedure, drugs with longer half-lives such as indomethacin and ketoprofen would be recommended. For this reason intravenous ketoprofen represents a valid and practical pharmacological option to prevent PEP.

In this single-center sample of ERCP patients with a relatively low incidence of PEP, female sex and younger age were not associated with PEP as traditionally reported in the literature [24–29]. However, the majority of the studies in which PEP was related to these risk factors had a large proportion of presumptive SOD patients [15]. These patients are usually young women, whose bile duct is thin, and, consequently, more difficult to cannulate. Perhaps difficult bile duct cannulation could be the cause of the higher frequency of PEP in these cases.

More than 10 min until bile duct cannulation, contrast injection in the pancreatic duct and contrast depot (all surrogate markers of difficult bile duct cannulation) were associated with PEP in univariate analysis. Since PD contrast injection and PD guide wire passage are not uniform

Table 1 Characteristics of the patients at baseline

Characteristics	Total ($n = 477$)	Placebo ($n = 253$)	Ketoprofen ($n = 224$)	p
Female	336 (70.4)	183 (72.3)	153 (68.3)	0.336
Age (years)	57 ± 19	57 ± 18	58 ± 19	0.710
White	429 (89.9)	222 (88.5)	205 (91.5)	0.280
Diagnoses				0.172
BD stone[a]	243 (50.9)	130 (51.4)	113 (50.4)	
Difficult BD stone[b]	101 (21.2)	55 (21.7)	46 (20.5)	
Neoplasia	63 (13.2)	27 (10.7)	36 (16.1)	
Sphincter of Oddi dysfunction (SOD)	7 (1.5)	2 (0.8)	5 (2.2)	
Other[c]	63 (13.2)	39 (15.4)	24 (10.7)	
Cannulation attempts duration >10 min	78 (16.4)	42 (16.6)	36 (16.1)	0.876
Overall ERCP time (min)[d]	13 ± 11	13 ± 11	13 ± 11	0.928
Use of GW	157 (32.9)	92 (36.4)	65 (29.0)	0.088
Contrast injection in the PD	222 (46.5)	116 (45.8)	106 (47.3)	0.748
Submucosal contrast depot	39 (8.2)	25 (9.9)	14 (6.3)	0.149
PD GW passage	73 (15.3)	41 (16.2)	32 (14.3)	0.561
Pre-cut sphincterotomy/infundibulotomy	81 (17.0)	42 (16.6)	39 (17.4)	0.814
Biliary sphincterotomy	391 (82.0)	201 (79.4)	190 (84.8)	0.128
Pancreatic sphincterotomy	31 (6.5)	18 (7.1)	13 (5.8)	0.562
Placement of biliary stent	78 (16.4)	36 (14.2)	42 (18.8)	0.183

Data are presented as mean ± SD or No. (%)

BD bile duct, *PD* pancreatic duct, *GW* guide wire

[a] Less than 4 stones or smaller than 1.5 cm

[b] 5 or more stones or ≥1.5 cm

[c] Bile duct leakage, benign biliary stricture, biliary cysts, chronic pancreatitis

[d] From scope insertion to scope retrieva

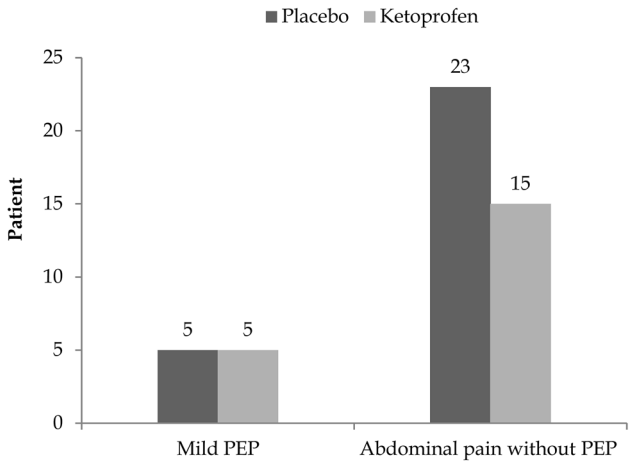

Fig. 2 Comparisons between the placebo and ketoprofen groups demonstrated that there were no statistically significant differences in post-ERCP complications: and mild PEP ($p = 1.$) and abdominal pain without PEP ($p = 0.335$)

(force and amount of contrast of each injection, and which pancreatic zone was reached by the guide wire), the study was designed in a yes or no fashion for these variables.

The fact that none of these surrogate markers of difficult bile duct cannulation has individually reached statistical significance in the multivariate analysis is related to the infrequency of the complication.

Pre-cut papillotomy (with a needle knife papillotome beginning at the papillary roof and avoiding the ostium) was not associated with PEP. However, pre-cut papillotomy using the technique of transpancreatic sphincterotomy was associated with PEP in the univariate analysis. Although initially considered almost a sacrilege by some authors [30–32], transpancreatic access sphincterotomy has been used as an effectively and relatively safe alternative to approach the bile duct [33–35].

In a thorough review of the literature performed by Dumonceau et al. for a consensus statement of the ESGE [4] cannulation time more than ten minutes and suspicion of SOD diagnosis were the most important risk factors for PEP. According to that publication, the pooled incidence of PEP in patients with less than 10 min of cannulation attempt was 3.8 and 10.8 % for those with cannulation attempts for more than 10 min. In the case of SOD, the pooled incidence of PEP was 8.6 versus 2.5 % in those

Table 2 Multinomial logistic regression analysis of demographic components and interventional procedures that were associated with post-ERCP complications among the 477 patients in the RCT

	Abdominal pain without PEP				Mild PEP			
	Crude OR (95 % CI)	*p*	Adjust* OR (95 % CI)	*p*	Crude OR (95 % CI)	*p*	Adjust* OR (95 % CI)	*p*
Female	2.96 (1.51–5.79)	0.002	2.83 (1.42–5.64)	0.003	1.77 (0.49–6.41)	0.379	2.11 (0.54–8.23)	0.278
≥40 years	1.06 (0.47–2.40)	0.882			0.99 (0.20–4.78)	0.997		
Time until deep biliary cannulation ≥10 min	2.03 (0.94– 4.39)	0.070	1.23 (0.44–3.39)	0.684	3.80 (1.04–13.84)	0.043	1.37 (0.20–9.38)	0.744
Use of GW	2.50 (1.28–4.88)	0.007	1.81 (0.72–4.59)	0.205	2.25 (0.64–7.90)	0.206	1.04 (0.16–6.80)	0.962
Contrast injection in the PD	0.83 (0.42–1.61)	0.590	1.46 (0.60–3.55)	0.393	0.20 (0.04–0.99)	0.049	0.23 (0.04–1.28)	0.095
SM contrast depot	1.54 (0.35–6.71)	0.558	1.68 (0.35–7.98)	0.508	0.20 (0.04–0.81)	0.024	0.23 (0.04–1.19)	0.080
PD GW passage	2.95 (1.41–6.17)	0.004	2.86 (0.87–9.38)	0.081	2.74 (0.68–10.90)	0.152	0.38 (0.03–4.73)	0.455
Pre-cut sphincterotomy	1.36 (0.60–3.10)	0.455			2.19 (0.55–8.70)	0.262		
Pancreatic sphincterotomy	1.16 (0.26–5.09)	0.843	3.21 (0.62–16.57)	0.162	0.15 (0.03–0.61)	0.008	0.20 (0.02–1.75)	0.147

Reference is no abdominal pain and no PEP after the procedure

PD pancreatic duct, *GW* guide wire, *SM* submucosal

* Odds Ratio (OR) adjusted for all variables

Table 3 Complications of ERCP

Complications	Total ($n = 477$)	Placebo ($n = 253$)	Ketoprofen ($n = 224$)	*p*
Perforation	1 (0.2)	1 (0.4)	–	1.
Infection	4 (0.8)	3 (1.2)	1 (0.4)	0.626
Overt bleeding	8 (1.6)	4 (1.6)	4 (1.6)	0.954
Abdominal pain (PEP negative)	38 (8.0)	23 (9.1)	15 (6.7)	0.335
Mild post-ERCP pancreatitis	10 (2.1)	5 (2.0)	5 (2.2)	1.
Death <48 h	2 (0.4)	1 (0.4)	1 (0.4)	1.
Death <30 days	9 (1.9)	4 (1.6)	5 (2.2)	0.740
Overall mortality	11 (2.3)	5 (2.0)	6 (2.7)	0.762

Data are presented as No. (%)

without the risk factor. Paradoxically, in studies comparing NSAIDs versus placebo for the prevention of PEP, the frequency of PEP in the placebo group has ranged from 10.3 to 16.8 % (mean = 14.6 %) and in the NSAID group, these figures ranged from 5.1 to 8.9 % (mean = 7.1 %) [9, 10, 36–38]. In our study the PEP rate was 2.1 %. This way, in studies dealing with PEP prevention with NSAIDs, the groups randomized to placebo had a surprisingly high incidence of PEP, even greater than the most important risk factors for PEP, such as SOD and difficult bile duct cannulation. So the incidence of PEP in the placebo groups in these trials was up to 4 times greater than the expected incidence pointed out by the ESGE and ASGE guidelines [4, 5]. Explanations for these high incidences of PEP in placebo patients are still lacking.

Our study has potential limitations: first, its single-center setting and second one endoscopist performing all the procedures. However, these may be advantages of the study

as it reflects real-life practices. Most previous studies have been multicenter and have included several endoscopists with various levels of expertise. However, many other groups have also reported a low PEP incidence [4, 13]. Other criticisms that could be raised against our study are the randomization in groups of 100 patients instead of one sole block of 536 individuals, and we ended up randomizing 11 % less patients than the targeted enrollment. Nonetheless, a planned *interim* analysis at the sixth to seventh month after study beginning showed a consistent trend that the study continuity would not alter the outcome. For reference, to detect a 50 % reduction from 2 to 1 %, more than 5000 subjects would be necessary.

Lastly, in our study, no patient, even the considered at high risk for PEP, received prophylactic pancreatic prosthesis. However, since both groups did not receive it, the study outcomes were not affected.

In summary, intravenously administered ketoprofen immediately prior to the procedure in a consecutive sample of ERCP patients did not reduce the incidence of PEP, even in individuals considered at high-risk for the complication.

Compliance with ethical standards

Disclosures Dr. Julio Carlos Pereira Lima (jpereiralima@terra.com.br) is on the speakers' board of Takeda Pharmaceutical and receives honoraria as consultant of Boston Scientific. The patients' private or public health insurance funded all ERCPs including the drugs used in this trial. Drs. Fernanda de Quadros Onófrio (fqonofrio@gmail.com), Guilherme Watte (g.watte@gmail.com), Romnei Lenon Lehmen (lenon@mail.com), Daniela Oba (oba.daniela@gmail.com), Gabriela Camargo (camargo.gabriela@gmail.com) and Carlos Eduardo Oliveira dos Santos (ddendo@uol.com.br) have no conflicts of interest or financial ties to disclose.

References

1. Wong LL, Tsai HH (2014) Prevention of post-ERCP pancreatitis. World J Gastrointest Pathophysiol 5:1–10
2. Freeman ML, Guda NM (2004) Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc 59:845–864
3. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Spirito F, Pilotto A, Forlano R (2007) Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 102(8):1781–1788
4. Dumonceau JM, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, Marek T, Baron TH, Hassan C, Testoni PA, Kapral C (2014) European society of gastrointestinal endoscopy (2014) prophylaxis of post–ERCP pancreatitis: European society of gastrointestinal endoscopy (ESGE) guideline—updated june 2014. Endoscopy 46:799–815
5. ASGE Standards of Practice Committee, Anderson MA, Fisher L, Jain R, Evans JA, Appalaneni V, Ben-Menachem T, Cash BD, Decker GA, Early DS, Fanelli RD, Fisher DA, Fukami N, Hwang JH, Ikenberry SO, Jue TL, Khan KM, Krinsky ML, Malpas PM, Maple JT, Sharaf RN, Shergill AK, Dominitz JA (2012) ASGE Standards of Practice Committee: complications of ERCP. Gastrointest Endosc 75:46–473
6. Thaker AM, Mosko JD, Berzin TM (2015) Post-endoscopic retrograde cholangiopancreatography pancreatitis. Gastroenterology Report 3:32–40
7. Insel PA (1996) Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Gilman AG, Limbird LE (eds) Goodman&Gilman's. The pharmacological basis of therapeutics. Mc-graw hill, New York, pp 617–657
8. Elmunzer BJ, Sheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SM, Nicholson S, Fogel EL, U.S. Cooperative for Outcomes Research in Endoscopy (USCORE) (2012) A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. New Engl J Med 366:1414–1422
9. Ding X, Chen M, Huang S, Zhang S, Zou X (2012) Nonsteroidal anti-inflammatory drugs for prevention of post-ERCP pancreatitis: a meta-analysis. Gastrointest Endosc 76:1152–1159
10. Dai HF, Wang XW, Zhao K (2009) Role of nonsteroidal anti-inflammatory drugs in the prevention of post-ERCP pancreatitis: a meta-analysis. Hepatobiliary Pancreat Dis Int 8:11–16
11. Levenick JM, Gordon SR, Fadden LL, Levy LC, Rockacy MJ, Hyder SM, Lacy BE, Bensen SP, Parr DD, Gardner TB (2016) Rectal indomethacin does not prevent post-ERCP pancreatitis in consecutive patients. Gastroenterology 150(4):911–917
12. Hauser G, Blažević I, Salkić N, Poropat G, Giljača V, Bulić Z, Štimac D (2016) Diclofenac sodium versus ceftazidime for preventing pancreatitis after endoscopic retrograde cholangiopancreatography: a prospective, randomized, controlled trial. Surg Endosc [Epub ahead of print]
13. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nick N (1991) Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 37:383–393
14. Kent DM, Rothwell PM, Ioannidis JP (2010) Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 11:85–95
15. Park SW, Chung MJ, Oh TG, Park JY, Bang S, Park SW, Song SY (2015) Intramuscular diclofenac for the prevention of post-ERCP pancreatitis—a randomized trial. Endoscopy 47:33–39
16. Bhatia V, Ahuja V, Acharya SK, Garg PK (2011) A randomized controlled trial of valdecoxib and glyceryl trinitrate for the prevention of post-ERCP pancreatitis. J Clin Gastroenterol 45:170–176
17. Cheon YK, Cho KB, Watkins JL, McHenry L, Fogel EL, Sherman S, Schmidt S, Lazzell-Pannell L, Lehman GA (2017) Efficacy of diclofenac in the prevention of post-ERCP pancreatitis in predominantly high-risk patients: a randomized double-blind prospective trial. Gastrointest Endosc 66:1126–1132
18. Torriani MS, Silva RG, Santos L (2003) Vias de administração: o cuidado do farmacêutico na orientação do uso dos medicamentos. In: Santos L, Torriani MS, Barros E (eds) Medicamentos na prática da farmácia clínica. Artmed, Porto Alegre, pp 51–59
19. Nevalainen TJ, Hietaranta AJ, Gronroos JM (1999) Phospholipase A2 in acute pancreatitis: new biochemical and pathological aspects. Hepato-Gastroenterology 46:2731–2735
20. Mäkelä A, Kuusi T, Schröder T (1997) Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. Scand J Clin Lab Invest 57:401–407
21. Tiemen S, Steinberg WM (2010) Acute pancreatitis. In: Feldman M, Friedman LS, Brandt LJ, Sleisenger, MH (eds) Sleisenger & Fordtran's gastrointestinal and liver disease:

pathophysiology/diagnosis/management, 9th edn. Saunders Elsevier, Philadelphia, PA, p 959–983
22. Bai Y, Gao J, Shi X, Zou D, Li Z (2008) Prophylactic corticosteroids do not prevent post-ERCP pancreatitis: a meta-analysis of randomized controlled trials. Pancreatology 8:504–509
23. Zheng M, Bai J, Yuan B, Lin F, You J, Lu M, Gong Y, Chen Y (2008) Meta-analysis of prophylactic corticosteroid use in post-ERCP pancreatitis. BMC Gastroenterol 8:6
24. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MD, Ryan ME, Shaw MJ, Lande JD, Pheley AM (1996) Complications of endoscopic biliary sphincterotomy. N Engl J Med 335:909–918
25. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A (1998) Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc 48:1–10
26. Williams EJ, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, Lombard M (2007) Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. Endoscopy 39:793–801
27. Masci E, Mariani A, Curioni S, Curioni S, Testoni PA (2003) Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography: a meta-analysis. Endoscopy 35:830–834
28. Freeman ML, DiSario JA, Nelson DB, Fennerty MD, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP (2001) Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 54:425–434
29. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA (2001) Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol 96:417–423
30. Herreros de Tejada A, Calleja JL, Díaz G, Pertejo V, Espinel J, Cacho G, Jiménez J, Millán I, García F, Abreu L, UDOGUIA-04 Group (2009) Double-guidewire technique for difficult bile duct cannulation: a multicenter randomized, controlled trial. Gastrointest Endosc 70:700–709
31. Wang P, Zhang W, Liu F, Zs Li, Ren X, Fan ZN, Zhang X, Lu NH, Sun WS, Shi RH, Li YQ, Zhao Q (2010) Success and complication rates of two precut techniques, transpancreatic sphincterotomy and needle-knife sphincterotomy for bile duct cannulation. J Gastrointest Surg 14:697–704
32. Halttunen J, Keränen I, Udd M, Kylänpää L (2009) Pancreatic sphincterotomy versus needle knife precut in difficult biliary cannulation. Surg Endosc 23:745–749
33. Weber A, Roesch T, Pointner S, Born P, Neu B, Meining A, Schmid RM, Prinz C (2008) Transpancreatic precut sphincterotomy for cannulation of inaccessible common bile duct: a safe and successful technique. Pancreas 36:187–191
34. Yoo YW, Cha SW, Lee WC, Kim SH, Kim A, Cho YD (2013) Double guidewire technique vs transpancreatic precut sphincterotomy in difficult biliary cannulation. World J Gastroenterol 19:108–114
35. Miao L, Li Q, Zhu M, Ge XX, Yu H, Wang F, Ji GZ (2015) Endoscopic transpancreatic septotomy as a precutting technique for difficult bile duct cannulation. World J Gastroenterol 21:3978–3982
36. Yaghoobi M, Rolland S, Waschke KA, McNabb-Baltar J, Martel M, Bijarchi R, Szego P, Barkun AN (2013) Meta-analysis: rectal indomethacin for the prevention of post-ERCP pancreatitis. Aliment Pharmacol Ther 38:995–1001
37. Yuhara H, Ogawa M, Kawaguchi Y, Igarashi M, Shimosegawa T, Mine T (2014) Pharmacologic prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: protease inhibitors and NSAIDs in a meta-analysis. J Gastroenterol 49:388–399
38. Sethi S, Sethi N, Wadhwa V, Garud S, Brown A (2014) A meta-analysis on the role of rectal diclofenac and indomethacin in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. Pancreas 43:190–197