Clinical trial

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Rectal Diclofenac administration for prevention of post-Endoscopic Retrograde Cholangio-Pancreatography (ERCP) acute pancreatitis. Randomized prospective study

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Abstract

Introduction. Post-Endoscopic Retrograde Cholangio-Pancreatography pancreatitis (PEP) is a relevant (1-4%) complication of biliopancreatic operative endoscopy. Rectal nonsteroidal anti-inflammatory drugs (specifically, 100 mg of diclofenac) have shown promising prophylactic activity in PEP. The aim of our prospective study is to report whether prophylactic oral versus rectal suppository versus intramuscular diclofenac versus placebo are able to reduce the incidence and the severity of ERCP-induced pancreatitis.

Materials and Methods. in this randomized, double-blinded, prospective study, 100 patients (49 male, 51 female), similar with regard to indication for ERCP, were enrolled between January 2016 and November 2017 to undergo ERCP in the Section of General and Thoracic Surgery of University Hospital of Palermo. They were randomized into five groups, respectively 20 patients with placebo by mouth; 20 patients with 50 mg diclofenac sodium enteric-coated capsules by mouth; 20 with 100 mg rectal suppository diclofenac, 20 with 75 mg/3 ml intramuscular diclofenac sodium, 20 with 75 mg/3 ml intramuscular diclofenac sodium and 20 with 75 mg/3 ml intravenous diclofenac. All drugs were administered 30 to 90 minutes before ERCP. All clinical data were collected one day before and 2, 12 and 24 hour after ERCP.

Results. data were prospectively collected and to demonstrate the preventive effect of rectal diclofenac on PEP, a two-by-two table and chi-square test with Yates correction were used: the incidence of PEP was significantly lower ($p < 0.001$) in the rectal diclofenac group respect to other groups and, in the same way, the incidence of post-ERCP pain was significantly lower in the rectal diclofenac group than in the other groups ($p = 0.001$) and patients discharge was consequently earlier ($p < 0.01$).

Conclusions. 100 mg dose rectal diclofenac administered 30-60 minutes before ERCP can effectively prevent PEP. ***Clin Ter 2019; 170(5):e332-336. doi: 10.7417/CT.2019.2156***

Key words: *Diclofenac, ERCP, pancreatitis, complication, prevention*

Introduction

Pancreatitis is a well known ERCP-related complication (1-4% in average risk patients in unselected prospective series, but can exceed 20% in high risk patient subset) after endoscopic retrograde cholangiopancreatography (ERCP) and carries substantial morbidity and long hospitalization, although mortality is rare (1-3); it is of mild or moderate severity in approximately 90% of cases (4).

Risk factors for developing post-ERCP pancreatitis (PEP), extracted from reviews and meta-analyses, may be: female sex, young age, suspected sphyncter of Oddi disfunction (SOD), prior PEP, recurrent pancreatitis, pancreatic duct injection, pancreatic sphincterotomy, balloon dilatation, anatomic alteration, difficult or failed cannulation, precut sphincterotomy and ampullectomy (3-8).

The aim of this randomized, double-blinded, prospective study was to determine whether prophylactic oral versus rectal suppository versus intramuscular diclofenac versus placebo will reduce the incidence and the severity of PEP.

Methods

100 patients, similar with regard to indication for ERCP, as described in table 1, were enrolled between January 2016 and November 2017 as they were seen for therapeutic ERCP in the Operative Endoscopic Surgery Unit of General and Thoracic Surgery Section on Teaching Hospital "Paolo Giaccone" in Palermo. Exclusion criteria were: (1) acute pancreatitis within the preceding 72 hours before ERCP, (2) current treatment with aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), (3) allergy history to diclofenac or other NSAIDs; (4) contrast allergy, (5) impaired renal function (serum creatinine > 2 mg/dL), (6) known liver cirrhosis, (7) previous biliary sphincterotomy, (8) patient with peptic ulcer, and (9) patients with rectal disease.

LIST OF ABBREVIATION:
- **PEP =** post- endoscopic retrograde cholangio-pancreatography pancreatitis
- **ERCP =** endoscopic retrograde cholangiopancreatography
- **SOD =** sphincter of Oddi disease/disfunction
- **NSAIDs =** nonsteroidal anti-inflammatory drugs

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After informed consent was obtained, enrolled patients were randomized to receive diclofenac (Voltaren®, Novartis Pharma, Italy) in different route of administration, with equivalent doses and pharmacokinetic action:

– GROUP A (20 patients): placebo by mouth, 50 mg (30 to 90 minutes before ERCP);
– GROUP B (20 patients): 50 mg diclofenac sodium enteric-coated capsules by mouth (30 to 90 minutes before ERCP);
– GROUP C (20 patients): 100 mg rectal suppository diclofenac (30 to 90 minutes before ERCP);
– GROUP D (20 patients): 75 mg/3 ml intramuscular diclofenac sodium (30 to 90 minutes before ERCP).
– GROUP D (20 patients): 75 mg/3 ml intravenous diclofenac sodium (30 to 90 minutes before ERCP).

Demographic data at admission and group division are summarized in table 1.

The ethic committee of our University Hospital approved unreservedly the study design and the randomization.

All ERCP were performed by the same endoscopic team constituted by experienced endoscopists (G.G.) with Olympus TJF 145 side-view duodenoscopes, performed under conscious sedation with midazolam and fentanyl, under respiratory and cardiac monitoring.

Biliary cannulation was attempted by using wire-guided technique with standard three-lumen sphincterotome after the intravenous administration of hyoscine butylbromide 20 mg/ml. Deep cannulation of the common bile duct (CBD) was considered successful when the sphincterotome was inserted deeply into the CBD with guidewire-assisted technique and a cholangiogram was obtained. When biliary cannulation was not achieved by standard sphincterotome (cannulation more than three attempt, cannulation time more than 5 minutes or unintentional pancreatic duct cannulation more than three times), we used needle-knife precut papillotomy.

After the procedure, patients continued fasting until the next morning. Serum amylase levels were measured before ERCP, at 4, 12 and 24 hours after the procedure. If the course was uneventful and exams were negative, then the patient resumed a free oral diet and was discharged the day after procedure.

Results

The operative results of ERCP, divided into previous five groups (A-E), are described in table 2.

Moreover, patients has been classified as high risk if they had any of the high-risk parameters as identified by Freeman (female, < 60 years, suspected SOD, recurrent pancreatitis, pancreatic duct injection, pancreatic sphincterotomy, difficult or failed cannulation, precut sphincterotomy); they were classified as low risk if the primary indication of ERCP was biliary stone, stricture, or bile leak(9).

Post-ERCP data were prospectively collected at the time of the procedure and 24 to 72 hours after discharge (table 2) and to demonstrate the preventive effect of rectal diclofenac on PEP, a two-by-two table and chi-square test with Yates correction were used (Table 3).

In the present trial, of all the patients, 11/100 (11%) developed PEP. The incidence of PEP was significantly lower ($p < 0.001$) in the rectal diclofenac group (no case observed) respect to other groups.

Table 1. Demographic data at the admission

	Group A (oral placebo)	**Group B (oral Diclofenac)**	**Group C (rectal Diclofenac)**	**Group D (intramuscular Diclofenac)**	**Group E (intravenous Diclofenac)**
Number of pts	20	20	20	20	20
M:F	11:9	10:10	8:12	9:11	11:9
Mean age (range)	58.6 (55-72)	60.1 (55-71)	59.8 (54-75)	61.2 (60-77)	60.3 (51-76)
Chronic pancreatitis	0	0	0	0	0
Indications	Biliary stones 17/20 = 85% Biliary cancer 2/20 = 10% Pancreatic cancer 1/20 = 5%	Biliary stones 17/20 = 85% Biliary cancer 1/20 = 5% Pancreatic cancer 2/20 = 10%	Biliary stones 17/20 = 85% Biliary cancer 1/20 = 5% Pancreatic cancer 2/20 = 10%	Biliary stones 16/20 = 80% Biliary cancer 1/20 = 5% Pancreatic cancer 3/20 = 15%	Biliary stones 17/20 = 85% Biliary cancer 0/20 Pancreatic cancer 3/20 = 15%
Mean WBC 10^3/µL before procedure (NV 4-11)	8.62±1.3	8.19±1.6	8.57±1.8	9.45±1.3	8.96±1.2
Mean Amy U/l before procedure (NV 11-54)	45±2	51±3	48±2	65±2	61±3
Mean Lip U/l before procedure (13-60)	15±2	21±1	18±2	22±1	17±1

Amy = serum amylase Lip = serum lipase

Table 2. Operative results of ERCP

	Group A (oral placebo)	Group B (oral Diclofenac)	Group C (rectal Diclofenac)	Group D (i.m. Diclofenac)	Group E (e.v. Diclofenac)
Difficult cannulation (≥ 3 attempts or > 5 minutes)	2/20 = 10%	3/20 = 15%	2/20 = 10%	2/20 = 10%	2/20 = 10%
Small bile duct (< 10 mm)	1/20 = 5%	2/20 = 10%	2/20 = 10%	2/20 = 10%	1/20 = 5%
Guidewire in Wirsung	0	1/20 = 5%	1/20 = 5%	0	1/20 = 5%
Pancreatography	0	0	0	0	0
Biliary sphyncterotomy	20/20 = 100%	20/20 = 100%	20/20 = 100%	20/20 = 100%	20/20 = 100%
Needle-knife fistulotomy	1/20 (5%)	1/20 (5%)	1/20 (5%)	2/20 (10%)	1/20 (5%)
Biliary stent placement	2/20 = 10%	2/20 = 10%	2/20 = 10%	3/20 = 15%	3/20 = 15%
Post-ERCP pancreatitis Mild pancreatitis Moderate pancreatitis Severe pancreatitis	**4/20 (20%)** 2/20 (10%) 2/20 (10%) 0	**3/20 (15%)** 1/20 (5%) 2/20 (10%) 0	**0** 0 0 0	**3/20 (15%)** 2/20 (10%) 1/20 (5%) 0	**1/20 (5%)** 1/20 (5%) 0 0
Amyl 2 ULN at 4 hours	4/20 (20%)	3/20 (15%)	0	3/20 (15%)	1/20 (5%)
Amyl 2 ULN at 12 hours	4/20 (20%)	2/20 (10%)	0	2/20 (10%)	1/20 (5%)
Amyl 2 ULN at 24 hours	3/20 (15%)	3/20 (15%)	0	2/20 (10%)	1/20 (5%)
Transient hyperamy (≤ 2 ULN at 4 hours)	3/20 (15%)	4/20 (20%)	2/20 (10%)	2/20 (10%)	1/20 (5%)
Post-ERCP pain	3/20 (15%)	3/20 (15%)	0	1/20 (5%)	0
Adverse reaction to Diclofenac ®	No	No	No	No	No
Dismission on 1st POD	14/20 (70%)	12/20 (60%)	18/20 (90%)	15/20 (75%)	19/20 (95%)
Dismission on 2nd POD	4/20 (20%)	2/20 (10%)	2/20 (10%)	1/20 (5%)	1/20 (5%)
Dismission after 2nd POD	2/20 (10%)	6/20 (30%)	-	4/20 (20%)	-

POD = post-operative day

Table 3.p value of PEP (Chi-square with Yates correction)

	Group A vs Group B	Group A vs Group C	Group A vs Group D	Group A vs Group E	Group B vs Group E	Group C vs Group E	Group D vs Group E	Group B vs Group D	Group C vs Group D	All groups vs Group C
***p* value**	0.3865	< 0.001	0.3865	< 0.001	0.581	< 0.001	< 0.001	0.6579	< 0.001	< 0.001
OR	0.49	0.04	0.49	0.01	0.1	0.01	0.012	1	0.02	0.01

Moreover, the severity of PEP was mild in 6 patients and moderate in other 5 patients.

After ERCP, transient asymptomatic hyperamylasemia was observed in 2/20 patients (10%) in the rectal diclofenac group and in 10/80 patients (12.5%) in the other groups (p = 0.4559). 7 patients with PEP also experienced post-ERCP pain, and the incidence of post-ERCP pain was significantly lower in the rectal diclofenac group than in the other groups (7.8% vs 37.7%, respectively; p = 0.001).

Also, patients discharge was earlier in the rectal diclofenac group (20/20 patients discharged within the second day post-procedure) than the other groups (12/80 = 15%, p < 0.01, discharged after the second post-ERCP day).

In all 11 cases, post-ERCP acute pancreatitis has been treated with medical therapy with complete resolution and dismission before the fifth post-procedure day.

There were no adverse events related to diclofenac in all groups.

The cost per dose of rectal diclofenac was 1.35 € for single 100 mg suppository.

Discussion

In 1993, Khan IH described a case of acute pancreatitis following the use of diclofenac for a painful arthropathy(10).

Since then, paradoxically, has gradually grown the number of studies that have demonstrated the role of diclofenac in the prevention of PEP, definable as a new acute onset of pancreatic-type abdominal pain (persistent, severe, epigastric pain often radiating to the back) with amylase or lipase at least three times the normal rate more than 24 hours after an ERCP requiring hospital admission or a prolongation of planned admission and with characteristic findings of acute pancreatitis on contrast-enhanced CT and, less commonly, magnetic resonance imaging or transabdominal ultrasonography(4).

Severity of post-ERCP pancreatitis is graded based on length of hospital admission and need for intervention and it can be divided into mild, moderate and severe(11).

In 2007, a systematic survey of 21 studies involving 16855 patients (1987-2003) found a 3.47% occurrence of

PEP, with mild, moderate and severe respectively 45%, 44% and 11% of cases with 3% of deaths(12); more recent data reports similar incidence of PEP (4.2 4.4%)(13,14), diagnosed mild, moderate, and severe type in 69%, 23%, and 8%, respectively(14).

It is widely accepted that the local and systemic inflammatory response induced by ERCP is the physiopathological event that triggers PEP and it has been proposed that phospholipase A2 plays a pivotal pathogenesic role of this inflammatory response, regulating proinflammatory mediators such as prostaglandins, leukotrienes, and platelet-activating factors; in vitro assays show that non-steroidal anti-inflammatory drugs (NSAIDs) as diclofenac are potent inhibitors of phospholipase A2 (15).

In fact, many reports have shown that NSAIDs, including diclofenac, reduce experimental pancreatitis-driven lethality in rodents (2) and three recent meta-analyses of four prospective randomized placebo-controlled trials confirmed that rectal administration of 100 mg diclofenac immediately before the procedure was effective in reducing pancreatitis, with a pooled relative risk after administration of 0.36 (95% CI: 0.22-0.60). Moreover, Murray showed that 100 mg of rectal diclofenac administered to high-risk patients (i.e., patients undergoing pancreatography or with documented sphincter of Oddi dysfunction) upon arrival in the recovery area significantly reduced the incidence of post-ERCP pancreatitis(7/110 (6.4%) *vs* 17/110 (15.5%) in the placebo group). Similarly, Khoshbaten showed that 100 mg of rectal diclofenac administered to high-risk patients upon arrival in the recovery area was superior to placebo in reducing the incidence of post-ERCP pancreatitis(2/50 (4%) *vs* 13/50 (26%) in the placebo group (2).

In a very recent italian multivariate analysis of a single center, the only risk factor for PEP is the high number of cannulation and the logistic binary regression reveals, as ulterior risk factor, the pancreatic injection of contrast (16).

Furhtermore, in a subset of patients, is well estabilished that cost-effective measure to prevent PEP is also the mechanical prevention with small-caliber pancreatic stents (3 or 5 French) after reiterated cannulation of main pancreatic duct(4,17,18).

Our study is associated with some potential limitations. First, because of the prospective design, there was a potential for selection bias. In the early study period, ERCP was more frequently performed without the administration of diclofenac. This might have improved the operator's technical skill during the latter period. However, ERCP with the administration of diclofenac became more popular later in the study period, although there were no significant differences in the baseline characteristics of the patients. Second, the prevention of PEP with NSAIDs has been previously reported; nevertheless, our study only investigated the use of diclofenac.

Conclusions

Post-ERCP pancreatitis appears unavoidable, even in the hands of expert endoscopists, but potentially preventable. A comprehensive and multidisciplinary approach should be employed by all who perform ERCP and strategies can be broadly divided into 5 areas: (1) patient selection, (2) risk stratification of patients undergoing ERCP and meaningful use of this information in clinical decision-making, (3) atraumatic and efficient procedural technique, (4) pharmacoprevention, and (5) prophylactic pancreatic stent placement.

Our study showed that a single rectal administration of diclofenac, 30 to 90 minutes before ERCP, is an efficacious and safe measure for reducing the incidence and the severity of post-ERCP pancreatitis and it is better than diclofenac sodium enteric-coated capsules by mouth and intramuscular diclofenac sodium.

Disclosure

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Competing interest section

All the Authors declare that they have no conflict of interest.

Auhtor's contribution

G.G. and L.M.A.I. conceived and designed the study
G.G., B.D.O. and F.S. collected data
G.G., P.V.D., M.A. and B.D.O. analyzed and interpreted data
G.G. and L.M.A.I. have been involved in drafting the manuscript and revised it critically
G.G., P.V.D., F.S. and L.M.A.I. have given final approval of the version to be published
All authors read and approved the final manuscript

Declaration of Helsinky

The Authors have respected the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

Ethics and Informed Consent

This article contains studies with human subjects, approved by Ethical Committee Palermo 1 of University of Palermo (protocol n. 54/2015). The consent is clearly available, with supporting data, in our database.

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