Original Article

Rectal diclofenac for prevention of post-endoscopic retrograde cholangiography pancreatitis

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Background: Acute pancreatitis is an important complication of endoscopic retrograde cholangiography (ERC), occurring between 1–10% of patients. Several randomized controlled trials and meta-analyses have demonstrated the effectiveness of nonsteroidal anti-inflammatories (NSAIDs) such as diclofenac and indomethacin as a post-ERC pancreatitis (PEP) prophylaxis. The aim is to determine if the rectal diclofenac use reduces the PEP rate.

Methods: Retrospective cohort study. Subjects were included who underwent ERC for different indications in a tertiary center between January 2015 and June 2016. Two groups were analyzed: group A (without diclofenac use) and group B (with use of diclofenac as PEP prophylaxis). Biodemographic, technical and mortality variables were measured.

Results: The total cohort was 116 patients, 67 in group A and 49 in group B. The average age was 61.9±17.8 and 58.3±15.8 years, respectively (P=0.2606). Gender distribution showed a women predominance in both groups (P=0.933). Of the technical variables measured, the precut showed a statistically significant relationship to PEP (P=0.013). Of the total cohort, 8.6% developed acute pancreatitis after an ERC: four in group A and six in group B (P=0.196). In those who developed PEP (n=10), six patients developed severe acute pancreatitis (SAP). The average hospitalization for PEP was 32.2±34 days (P=0.881). No patients died, not were there any adverse reactions to the drug.

Conclusions: Rectal diclofenac administered at the beginning of the ERC did not reduce the PEP rate in this patients cohort.

Keywords: Endoscopic retrograde cholangiography (ERC); pancreatitis; prophylaxis; diclofenac; post-endoscopic retrograde cholangiography pancreatitis (PEP)

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Introduction

Acute pancreatitis is an important complication of endoscopic retrograde cholangiography (ERC), occurring in 1–10% of patients.

Most patients develop mild to moderate pancreatitis, and only between 0.3–0.6% require some type of surgery (1,2).

Several theories exist regarding the post-ERC pancreatitis (PEP) pathogenesis, but the most accepted is the occurrence of a mechanical trauma on papilla or the pancreatic sphincter, temporarily obstructing the pancreatic juice release. Another theory suggests that the increase in hydrostatic pressure in the pancreatic duct due to the

injection of contrast or saline solution damages parenchyma (3,4). Regardless of the mechanism, an events cascade begins which results in the proteolytic enzymes activation, causing pancreas autodigestion and acinar secretion (5) alteration. This inflammatory cascade activation is the cause of local and systemic effects. The proposed surgeries to prevent PEP seek to break this inflammatory cascade (3,6,7).

Several alternatives, both mechanical and pharmacological, have been assessed as a PEP prevention, but without success. Nonsteroidal anti-inflammatories (NSAIDs) are powerful inhibitors of phospholipase A2, which is fundamental for the inflammatory cascade activation (8).

Several randomized controlled trials and meta-analyses have demonstrated the effectiveness of NSAIDs such as diclofenac and indomethacin as PEP prophylaxis.

Our aim is to evaluate whether the administration of rectal diclofenac before the ERC reduces PEP rate.

Methods

Design

Retrospective cohort study.

Population

This study was conducted at a tertiary center in Temuco, Chile, between January 2015 and June 2016 (18 months). Two groups were analyzed (n=116) that underwent an ERC for different indications. All the patients who had an ERC were included; there were no exclusion criteria. Group A contained patients who underwent an ERC without diclofenac, and in group B diclofenac was used as PEP prophylaxis.

From August 2015, rectal diclofenac (Laboratorio Chile) was administered to all patients undergoing an ERC as PEP prophylaxis at the beginning of the procedure. Prior to this period, no prophylaxis was used.

Management

Two members of the hepatobiliopancreatic surgery team (JSA and HLM) perform ERC 2–3 times per week in the hospital. On most occasions they are the members of the team during the procedures, and decisions are made jointly.

About the bile duct cannulation techniques, the team uses papillotomy or a biliary cannula with a hydrophilic guide. The precut is used when three unsuccessful bile duct cannulation attempts have been made or cannulation or repeated contrast injections have been used in the Wirsung duct.

After the procedure the patient remains with nothing by mouth for approximately 12 hours. A clinical assessment occurs and if the patient is asymptomatic, refeeding is started (9).

The use of pancreatic prostheses to prevent PEP was not used routinely and according to the surgeon's preference.

Other measures such as adrenalin instillation on the mucosa or lidocaine were not routine.

The team does not do rescue ERC in a case where patients have PEP in the early post-ERC period.

In our center, we do not perform routine post-ERC amylase or lipase control, only according to the patient's clinical picture.

PEP refers to patients with suggestive abdominal pain and serum amylase and/or lipase levels three times higher than normal laboratory values.

Study variables

Biodemographic variables and technical variables of ERC and mortality were described.

(I) Biodemographic variables: age, gender.

(II) Technical variables: difficult cannulation, thin bile duct, cannulation/Wirsung contrast, biopsy, sphincterotomy, prosthesis, PEP, indications for ERC in both groups.

Sample size

The study by Khoshbaten (10) was used to calculate the sample size, which showed a 4.4% pancreatitis rate in the diclofenac group and 26% in the placebo group. With a statistical significance of 95% and a power of 80%, a sample of 42 patients per group was obtained, with a total of 84 patients.

Statistical tools

Descriptive statistics were used with central tendency and dispersion measure, and analytical statistics with a *t*-test for continuous variables and chi^2 or Fisher's exact test for dichotomous variables. The database was done in Excel® and the analysis was performed in Stata® 10.0, (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP). EPIINFO was used to calculate the

Table 1 Indications of ERC in both groups

Indication ERC	Group A (n=67)	Group B (n=49)	P value
Choledocholithiasis	59	44	0.770
Papillary tumor	5	3	0.542
Benign bile duct stenosis	1	0	0.578
Cholangiohydatidosis	1	0	0.578
Biliopleural fistula	1	0	0.578
Biliary fistula	0	1	0.422
Klatskin tumor	0	1	0.422

ERC, endoscopic retrograde cholangiography.

Table 2 Technical characteristics of ERC

Technical characteristics ERC	Group A	Group B	P value
Papillotomy (n=87)	49	38	0.587
Precut (n=15)	13	2	0.013
Sphincterotomy (n=10)	3	7	0.064
Difficult cannulation (n=19)	13	6	0.303
Thin bile duct (n=29)	15	14	0.447
Cannulation Wirsung (n=5)	4	1	0.294
Wirsung contrast (n=12)	7	5	0.609
Installation of prosthesis (n=29)	16	13	0.745
Biopsy sampling (n=8)	6	2	0.262
Balloon sphincteroplasty (n=22)	13	9	0.888

ERC, endoscopic retrograde cholangiography.

sample size.

Ethical aspects

The study protocol was approved by the scientific ethics committee of the Araucanía South Health Service (Chile) and by the research group of the Department of Surgery Traumatology and Anesthesiology at the Universidad de la Frontera. All persons gave their informed consent prior to their inclusion in the study (ID: 004). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

The total cohort was 116 patients. Group A (without diclofenac) contains 67 patients and group B (with diclofenac) contains 49 patients.

The indications of ERC for the cohort in both groups were similar, with choledocholithiasis being the main indication, followed by papillary tumors (*Table 1*).

Within measured biodemographic variables, the gender distribution showed a women predominance in both groups, with no significant differences between the two groups (68% *vs.* 69%) (P=0.933). The average age was similar in groups A and B, 61.9±17.8 and 58.3±15.8 years, respectively (P=0.2606).

Of all patients, 8.6% developed post-ERC acute pancreatitis: four patients in group A and six patients in group B (P=0.196).

Table 2 illustrates the relationship between ERC technical variables and PEP outcome. Only the precut demonstrated

Table 3 Characteristics and indicators in the PEP group

Characteristics	Group A	Group B	P value
PEP	4	6	0.196
Age (average ± SD, years)	50±13.8	58.6±11.3	0.349
Female	3 (75%)	5 (83%)	0.667
Days of hospitalization (average ± SD, days)	30±23.3	33.6±42.3	0.881
SAP	3 (75%)	3 (50%)	0.714
Apache II	8±3.5	9±3.6	0.709
PCR	23.7±26.2	190±158.5	0.125
Req. CPU	2 (50%)	2 (33%)	0.548
Mortality	0	0	

PEP, post-endoscopic retrograde cholangiography pancreatitis; PCR, C-reactive protein; CPU, critical patient unit; SAP, severe acute pancreatitis.

a statistically significant relation (P=0.013).

The patients who developed PEP (n=10), six patients developed severe acute pancreatitis (SAP) (three in group A and three in group B), and four patients developed mild acute pancreatitis (MAP), one in group A and three in group B with diclofenac use.

The average PEP hospitalization was 32.2±34.3 days, with no statistically significant differences between groups A and B (P=0.881). Four patients required a CPU bed; two in group A and two in group B (P=0.548).

The average APACHE II in the PEP group was 8±3 and 9±3, in groups A and B respectively (P=0.709). The average PCR was 23.7±26.2 and 190.2±158.5 in groups A and B respectively (P=0.125) (*Table 3*).

No patients died and there were no adverse reactions to the drug.

Discussion

PEP is one of the most frequent ERC complications and its prevention is a crucial topic to reduce the morbimortality in this patient group.

A meta-analysis in 2008 already showed the effectiveness of rectal NSAIDs in the PEP prevention (11).

Although the etiopathogenic mechanism is not absolutely clear, the prevention mechanism suggests that diclofenac acts at the inflammatory reaction level produced by the irritation of the pancreatic duct, because NSAIDs have a powerful inhibitory effect on phospholipase A2, a crucial element in the inflammatory cascade that produces acute pancreatitis.

Several agents have been studied with promising results; however, they include drugs not available anywhere in the world (gabexate and somatostatin) (12). By contrast, in addition to its clinical benefit, diclofenac is a low-cost drug, widely available, easy to administer and with a favorable side-effect profile, making it an attractive option.

The aim of the study was to verify if this simple PEP prevention measure could be replicated in a public hospital in southern Chile.

The PEP rate was higher in this report (8.6%) than in a previous report provided by our group (0.5%) (9). This is probably related to the greater complexity of the cases.

Our study showed that a 100 mg dose of rectal diclofenac administration at the beginning of the procedure does not significantly reduce the PEP incidence. We had no adverse reactions to diclofenac nor mortality in our study.

Among the technical variables, a factor we consider important is that ERC is performed in the presence of two liver and pancreas surgeons (JSA and HLM) in most cases. This allows for team decision-making in difficult cases and to protocolize certain technical aspects like papillotomy size, use of precuts or use of balloon sphincteroplasty.

Although there is evidence showing that the use of rectal diclofenac reduces PEP rate, recent reports question its use in all patients undergoing an ERC.

A recent study with a sample of 1,000 patients with use of diclofenac compared to 1,000 historical controls without the use of diclofenac showed a PEP rate of 2.8% with no significant differences between the groups (13).

Among the possible explanations for the lack of reduction in the PEP rate with rectal diclofenac is the reduced effect in the obese patients group, a very frequent reality in our hospital and unfortunately this variable was not recorded in the present study (14).

The stratification of the PEP risk and the use of diclofenac only in the high-risk group are controversial and evidence shows contradictory results (7,13).

The combination of rectal diclofenac and other therapies that have shown effectiveness in reducing PEP rate seems attractive. One of the most economical therapies is crystalloid infusion in the peri-ERC period. Some works show that this association could have an effect on reducing PEP rate (15).

Our group will initiate a randomized clinical trial to assess whether the association of the crystalloid infusion in the peri-ERC period and rectal diclofenac reduces PEP rate.

There are some other tools that can be used to prevent PEP, such as the use of pancreatic prostheses in patients with repeated cannulations or opacification of the Wirsung duct (16-19). In the patients who present abdominal pain in the post-ERC period, the rescue ERC being performed by installing a Wirsung prosthesis could reduce the severity of PEP (20-22). We do not use these tools routinely, but we are starting a protocol to evaluate their effectiveness in our center.

Conclusions

The pancreatitis rate post-ERC was 8.6%% (10/116) is similar to what has been described in the literature.

Rectally administered prophylactic diclofenac at the beginning of the ERC does not reduce the rate of PEP compared with the patients on whom the prophylaxis was not used.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-19-395). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the scientific ethics committee of the Araucanía South Health Service (Chile) and by the research group of the Department of Surgery Traumatology and Anesthesiology at the Universidad de la Frontera. All persons gave their informed consent prior to their inclusion in the study (ID: 004). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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