TITLE PAGE

Title: Efficacy of rectal indomethacin plus aggressive hydration as prophylaxis to prevent post-ERCP pancreatitis at a secondary-care teaching hospital: a randomized controlled trial.

Short title: Prophylaxis against Post-ERCP pancreatitis.

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Abstract

Background

Post-ERCP pancreatitis (PEP) is the most frequent and serious complication of ERCP, affecting approximately 4-10% of patients worldwide and resulting in significant morbidity and annual health-care-costs. The pathophysiology involves enzyme activation triggered by mechanical obstruction, hydrostatic injury, and inflammation mediated by prostaglandins. Rectal non-steroidal anti-inflammatory drugs (NSAIDs) inhibit this inflammatory cascade, and aggressive hydration (AH) mitigates acidosis and inflammation. This study aimed to evaluate the effectiveness of combined prophylaxis (rectal indomethacin + AH) in reducing PEP incidence and post-procedure serum amylase and lipase levels.

Methods

A single-center randomized controlled trial (RCT) enrolled 60 eligible patients (n=31 prophylaxis, n=29 control). The prophylaxis group received 100 mg rectal indomethacin 30 min pre-ERCP combined with aggressive hydration using intravenous Hartmann's solution (3 mL/kg/hr during ERCP; 20 mL/kg bolus post-procedure; followed by 3 mL/kg/hr for 8 hours). The primary outcome was the incidence of PEP, defined by consensus criteria (new or worsened abdominal pain and enzyme levels ≥ 3x the upper limit of normal at 24 hours). Serum amylase and lipase levels were measured 4 hours post-ERCP.

Results

The incidence of PEP was significantly lower in the prophylaxis group (3%) compared to the control group (41%) (p=0.000378). This corresponded to a Relative Risk of 12.83 (95%CI, 1.77-92.5), indicating patients without prophylaxis were nearly 13 times more likely to develop PEP. Post-ERCP lipase levels were significantly lower in the prophylaxis group (p=0.0358), suggesting a reduced inflammatory response.

Conclusion

Combined prophylaxis with rectal indomethacin and aggressive hydration provides robust evidence for significantly reducing PEP incidence. Given the high baseline PEP rate observed in the control group, adopting this prophylaxis as a standard of care is strongly recommended, particularly for high-risk patients.

Keywords: Post-ERCP pancreatitis, PEP, Rectal Indomethacin, Aggressive Hydration, Ringer's Lactate, ERCP Prophylaxis.

INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is one of the most important and contemporary procedures for managing biliopancreatic diseases (1). It was introduced to the medical community in 1968, following the first description of endoscopic cannulation of the ampulla of Vater. Technical and technological advancements led, six years later, to the first endoscopic sphincterotomy, marking the beginning of significant progress in the diagnosis and treatment of the biliopancreatic region and its related structures (2).

ERCP remains the gold standard for treating diseases affecting the biliopancreatic ducts, choledocholithiasis being the most common indication, for which sphincterotomy is the most frequently performed procedure (3).

Although ERCP is highly beneficial on a large scale when treating predominantly obstructive pathologies, it carries risks that may considerably increase morbidity and mortality. One of the most common and currently leading complications is post-ERCP pancreatitis (PEP), affecting approximately 4-10% of patients undergoing the procedure (1, 4, 5).

Careful patient selection based on clinical indications, risk-benefit evaluation, anatomical considerations, and endoscopist expertise is essential to maximize safety and efficacy (1, 2). PEP is classified by severity into mild, moderate, and severe forms. The Atlanta classification defines clinical and systemic patterns from onset and at 48 hours or later, providing a more accurate severity assessment (5).

The pathophysiology involves mechanical obstruction or hydrostatic injury that causes premature activation of pancreatic enzymes, leading to local inflammation and potential systemic effects (5). Causes include physical blockage by stones or tumors, trauma, and

edema of the ampulla from instrumentation, as well as contrast-induced duct irritation. Key factors that trigger inflammation include mucosal injury from cannulation, irritation from contrast media, prostaglandin activation leading to cytokine release, and activation of pancreatic zymogens (4, 5).

The procedure-related risk factors to PEP include difficult cannulation, defined by the “5-5-1” rule (more than 5 minutes, 5 attempts, or more than 1 accidental pancreatic duct cannulation). Preventing unnecessary ERCPs through appropriate patient evaluation is pivotal to reduce complications (5).

Post-ERCP serum levels of amylase and lipase are useful early detectors of pancreatitis and enable timely interventions to improve outcomes (2, 6).

Rectal indomethacin before ERCP has been shown to reduce the incidence of PEP (7-9), especially when combined with aggressive hydration using Hartmann’s solution during and after the procedure. Indomethacin is a non-steroidal anti-inflammatory drug that inhibits cyclooxygenase, reducing prostaglandin synthesis, thus attenuating the inflammatory cascade associated to ERCP. On the other hand, aggressive hydration’s proposed mechanisms include liver metabolism of lactate, producing bicarbonate to correct acidosis and inhibition of NF-kB transcription, thereby mitigating inflammation (10, 11).

Therefore, it is essential to evaluate the effectiveness of the prophylaxis with rectal indomethacin and aggressive hydration to reduce the frequency of PEP and the serum levels of amylase and lipase.

METHODS

To determine if a prophylactic dose of rectal indomethacin plus an aggressive hydration scheme reduces the incidence of post-ERCP pancreatitis at our Institution, a randomized controlled study (RCT) was designed in the surgery department of a secondary-care teaching hospital. The study was conducted from March to October 2024 and included patients of both genders, aged 18 years or older, without contraindications to the use of indomethacin or aggressive hydration, who required ERCP and agreed to participate in the study, being randomly assigned using a computer-generated random number table. Exclusion criteria included patients with cardiac or renal alterations, while elimination criteria comprised anatomical abnormalities precluding the procedure, surgical complications, and death within 24 hours due to causes other than post-ERCP pancreatitis.

The sample size calculation was performed using the EPIDAT statistical software, estimating a population proportion with an average of 80 ERCP procedures based on the Institution's surgical records. Considering an expected 30% of patients presenting amylase alterations, a confidence level of 95%, and a 5% precision, a total of 60 patients were required, divided into two study groups; 29 patients in the control group and 31 in the experimental (prophylactic) group.

After ethics committee approval and with support from the endoscopic surgery service, eligible patients were identified and informed of the study objectives, procedures, potential risks, and benefits. After obtaining written informed consent, patients were assigned to their respective groups according to the randomization scheme (Annex 1).

Patients in the prophylaxis group received 100 mg of rectal indomethacin 30 minutes before the ERCP procedure, combined with intravenous Hartmann’s solution administered at 3 mL/kg/hr during the procedure (5). A 20 mL/kg bolus was given post-

procedure, followed by continuous hydration at 3 mL/kg/hr for 8 hours (5, 10). The control group underwent ERCP without prophylactic treatment.

Throughout the study period, both groups were closely monitored, with vital signs and clinical data related to their pathology continuously assessed.

Serum amylase and lipase levels were measured 4 hours after the endoscopic procedure in both groups.

Data were recorded in an Excel database and analyzed using EPI INFO version 7.3.5. Descriptive statistics included absolute and relative frequencies, while inferential analysis utilized Student's t-test and Chi-square test, considering a p-value less than 0.05 as statistically significant. Results are presented in tables and graphical formats.

The study was carried out in strict compliance with the ethical standards of the Hospital's Research Ethics Committee (approval number 2024-000344) in accordance with the Helsinki Declaration of 1975 and its last update of 2024 in Helsinki, and following the international guidelines for good clinical practice.

RESULTS

A total of 60 patients undergoing ERCP were included in the study. Of these, 51.67% (31 patients) were allocated to the prophylaxis group, receiving rectal indomethacin and aggressive hydration, while 48.33% (29 patients) comprised the control group without prophylaxis (Table 1).

Regarding sex, the distribution between both groups was even, with 61% females and 39% males in the prophylaxis group, and 69% females and 31% males in the control group. While mean age in the prophylaxis group was 50 ± 16 years, compared to 54 ± 17 years in the control group (Table 1).

The clinical conditions for requesting ERCP included cholangitis, choledocholithiasis, post-surgical biliary disease, common bile duct stenosis, biliary injury, biliary pancreatitis, suspected bile duct tumor, stent exchange, T-tube removal control, migrated stent, and pancreatic tumor. The distribution based on the group in which patients were randomized is shown in Table 2.

The pre- and post-ERCP behavior of serum markers for pancreatitis is illustrated in Table 3, where we find an important post-ERCP increase in both amylase and lipase, but reaching statistical significance in the last one ($t = -2.15$, $p = 0.0358$).

Regarding the incidence of post-ERCP pancreatitis, only one patient (3%) in the prophylaxis group developed the condition, compared to 12 patients (41%) in the control group. Chi-square analysis showed a value of 12.64 with a highly significant p-value of 0.000378. The relative risk was 12.83 (95% CI, 1.77–92.5), indicating that patients without prophylaxis were up to 13 times more likely to develop post-ERCP pancreatitis compared to those who received prophylaxis (Table 3).

DISCUSSION

This study evaluates the cost-benefit impact of implementing established protocols combining rectal indomethacin and aggressive hydration in patients undergoing ERCP to reduce the risk of post-ERCP pancreatitis. The comparison between a prophylaxis group and a control group was performed through randomization.

Patient distribution between the groups was balanced (51.67% with prophylaxis; 48.33% without), providing a reliable basis for comparison. The majority of participants in both groups were female (61% in the prophylaxis group; 69% in the control group). Although a higher female proportion was observed, X^2 analysis did not reveal a statistically significant difference regarding sex distribution. Similarly, mean ages were comparable between groups, with no statistically significant differences, indicating that age distribution likely did not influence the observed outcomes.

Post-surgical diagnoses were analyzed, revealing choledocholithiasis as the most frequent diagnosis in both groups. However, no statistically significant differences in diagnosis distribution were found between groups, suggesting that prophylaxis does not impact the baseline distribution of conditions in the study population.

The most compelling findings relate to pancreatic enzyme levels (amylase and lipase) pre- and post-ERCP. Post-ERCP amylase levels were higher in the control group but did not reach statistical significance ($p=0.0623$). In contrast, post-ERCP lipase levels were significantly lower in the prophylaxis group ($p=0.0358$), suggesting that prophylaxis may be associated with a reduced inflammatory response as reflected by lipase levels.

The incidence of post-ERCP pancreatitis was markedly lower in the prophylaxis group (3%) compared to the control group (41%). This difference was statistically significant ($p=0.000378$) with a relative risk of 12.83 (95% CI, 1.77-92.5), indicating that patients without prophylaxis are nearly 13 times more likely to develop pancreatitis following

ERCP. These results are striking compared to international literature, where incidence rates rarely exceed 7% in high-volume centers. These data reinforce that the combination of rectal indomethacin and aggressive hydration substantially reduces the occurrence of post-ERCP pancreatitis.

Conclusion

This study provides robust and significant evidence supporting the benefits of combined prophylaxis with rectal indomethacin and aggressive hydration in patients undergoing ERCP, with a significant reduction in the incidence of post-ERCP pancreatitis.

Significantly lower lipase levels in the prophylaxis group and the nearly 13-fold risk reduction compared to controls underscore the urgency of implementing these preventive measures, especially in healthcare stings like ours, where post-ERCP pancreatitis incidence far exceeds international benchmarks. Given these findings, this prophylaxis approach can be established as a standard of care in patients classified as high-risk.

While this study prompts greater interest in investigating the local patient population and risk factors, it also invites further research into variables such as chronicity of clinical presentations, socio-economic status, or limited access to healthcare facilities.

In summary, prophylaxis with combined rectal indomethacin and aggressive hydration presents a solid and highly recommended preventive strategy that should be adopted as a standard protocol to reduce health risks and hospitalization costs associated with prolonged stays.

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TABLES

Table 1. Distribution of patients by group, sex, and age

Variable	Prophylaxis Group	Control Group
Proportion of total (n=60)	31 (51.67%)	29 (48.33%)
Female	19 (61%)	20 (69%)
Male	12 (39%)	9 (31%)
Mean age (years ± SD)	50 ± 16	54 ± 17

Table 2. Clinical conditions requiring ERCP

Clinical condition	Prophylaxis Group	Control Group
Cholangitis	3 (9.68%)	0 (0.00%)
Cholangitis w/choledocholithiasis	2 (6.45%)	0 (0.00%)
Choledocholithiasis	18 (58.06%)	23 (79.31%)
Post-surgical biliary disease	2 (6.45)	0 (0.00%)
Common bile duct stenosis	1 (3.23%)	0 (0.00%)
Biliary injury	0 (0.00%)	1 (3.45%)
Biliary pancreatitis	1 (3.23%)	0 (0.00%)
Suspected bile duct tumor	1 (3.23%)	0 (0.00%)
Stent exchange	0 (0.00%)	1 (3.45%)
T-tube removal control	1 (3.23%)	0 (0.00%)
Migrated stent	0 (0.00%)	1 (3.45%)
Pancreatic tumor	2 (6.45%)	3 (10.34%)

Table 3. Serum markers and incidence of post-ERCP pancreatitis

Variable	Prophylaxis Group (n=31)	Control Group (n=29)	p-value
Post-ERCP amylase	↑ (not significant)	↑ (not significant)	NS
Post-ERCP lipase	↑ significant	↑ significant	0.0358
Incidence of pancreatitis (%)	3% (1 patient)	41% (12 patients)	0.000378
Relative risk (95% CI)	—	12.83 (1.77–92.5)	—