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RESEARCH ARTICLE
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COMPARING EFFICACY OF AGGRESSIVE FLUID HYDRATION PLUS RECTAL NSAIDS VERSUS RECTAL NSAIDS ALONE IN PREVENTION OF POST-ERCP PANCREATITIS IN MILD TO MODERATE RISK PATIENTS

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Abstract

Background: Post-ERCP pancreatitis, the common sequel of endoscopic retrograde cholangiopancreatography, persists. Prophylaxis is usually with rectal NSAIDs, but recent studies suggest that even additional fluid hydration can further reduce the risk. Combined aggressive fluid hydration with rectal NSAIDs was compared to rectal NSAIDs only in patients at mild to moderate risk for PEP in this study.

Methods : This was a single-center prospective, randomized controlled study involving 200 patients who underwent ERCP and were randomized to an equal number of those who received aggressive hydration (20 mL/kg bolus + 3 mL/kg for 8 h) or a single 100 mg rectal dose of indomethacin or rectal indomethacin alone. The most important outcome was incidence of PEP using consensus criteria, with hospital stay, severity grading, adverse events as additional ones.

Results: When compared with the NSAIDs alone group, the aggressive hydration plus NSAIDs group had a significantly low PEP incidence (7% versus 16%, p = 0.03). Furthermore, the rates of moderate or severe pancreatitis in the intervention group reduced, the median length of hospital stay was shortened. In multivariate analysis, the combined therapy was also a risk factor for PEP reduction, independent of the other factors. Safety profiles were similar; however, there was no difference...

Conclusion: In general, although each type of NSAID has an improved ratio of prophylaxis to risk compared to the other, the balance is bettered when rectal NSAIDS and aggressive fluid hydration are used to prophylaxis the lower half of the patient population. These findings are in agreement with a combined approach for PEP prevention, and further multicenter trial confirmation is warranted.

Key Words: NSAID, PEP, Aggressive hydration, ERCP.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP), as a minimally invasive endoscopic technology, is widely used around the world, and its efficacy and safety are widely recognized. Although ERCP is considered safe, it is one of procedures that causes the most complications in endoscopic surgery.[1]Common complications of ERCP include perforation, bleeding, cholecystitis, 2and pancreatitis.[2] Pancreatitis (PEP) after ERCP is one of the most common and serious complications.[3] The incidence of post-ERCP pancreatitis (PEP) ranges widely in the literature, with rates from 1% to 10% for low-risk individuals to 25% to 30% without prophylaxis for individuals with high-risk factors such as pancreatic sphincterotomy, sphincter of Oddi dysfunction, and history of PEP [4]. Microcirculatory insufficiency and inflammation were defined as key elements in the pathophysiology of pancreatitis. It has been proposed that pancreatitis develops due to pro-inflammatory cascade causing release of inflammatory cytokines. Also pre ERCP fasting may render patients relatively dehydrated, which may contribute to pancreatic microcirculation hypoperfusion and lead to PEP development. [5,6]

Both the European and American Societies of Gastrointestinal Endoscopy (ESGE, ASGE) recommend preventive therapies to lower the risk of PEP development with various levels of evidence. American Society for Gastrointestinal Endoscopy recommends Rectal NSAIDs for patients at risk of PEP. [7,8,] However, in recent years infusion therapy for pancreatitis has attracted more and more attention.

Fluid therapy reduces hypovolemic shock, which is usually associated with acute pancreatitis, improves pancreatic microvascular perfusion, and thus improves the prognosis of patients.[9,10] The role of fluids in PEP was evaluated by Choi et al in randomized control trial that showed decreased incidence of PEP in group being managed with vigorous fluids.[11] Besides this, two randomized controlled trials have shown a decreased incidence of PEP among average-risk patients with use of lactated Ringer's (LR) solution [12][13]. A national survey conducted in 2009 by the Pancreatic Disease Research Council supported by MHLW in Japan showed that all patients under 60 who died of severe pancreatitis had insufficient infusion volume (less than 50 ml/kg) within 24 hours of starting infusion therapy. (14)Therefore, it is logical to assume that hydration could have improved the outcome in these patients.

Both the strategies prophylactic NSAIDs and aggressive hydration are used in preventing PEP and has found remarkable results. The mechanism of injury leading to PEP suggests that there must be the role of both the strategies. (15,16) Aggressive Hydration is considerably important and is cost effective. To the best of our knowledge there is not a single study comparing their efficacy in preventing PEP in Pakistan. The studies from rest of the World are also scarce. Lack of well established guidelines for their use in preventing PEP, lack of literature comparing both the procedures and favorable mechanisms of both the strategies to decrease incidence of PEP in high risk patients are the main rationale of the study..

The purpose of this trial was to determine whether adding aggressive hydration and rectal NSAIDs would further lower the incidence and severity of PEP above that attained with rectal NSAIDs alone. Because the clinical and economic burden of PEP is high, determination of an optimal prophylactic strategy is important. Our study therefore compares the role of Standard NSAIDs therapy & NSAIDs therapy combined with hydration in prevention of PEP

Methods

Study Design and Setting

A single-center randomized controlled trial from January 2024 to June 2024 in 6months at the Peshawar is the present study. The Institutional Ethics Committee approved the study, it was conducted taking into consideration the Declaration of Helsinki and the local guidelines for ethical evaluation [17].

Patient Population

Accordingly, adults (18–75 years old) undergoing therapeutic ERCP with mild to moderate risk profile for PEP as per consensus were eligible. These are exclusion criteria: severe pancreatitis, renal impairment, congestive heart failure, ASA contraindications and aggressive fluid

Randomization and Interventions

Patients were randomly assigned into two (n = 100 per arm) groups by computer based randomization prior to any treatment and after giving informed consent.

Intervention Group (Group A): 20 mL/kg bolus with lactated Ringer's solution immediately before the ERCP followed by a 3 mL/kg infusion for 8 hours and 100mg rectal indomethacin 30 minutes prior to the procedure.

Group B (Control Group): Received only the single 100 mg rectal dose of indomethacin 30 minutes prior to ERCP.

Sample Size

A sample size of 200 (100 in each Group) was calculated assuming 60 % decrease in PEP with introduction of fluid hydration. [18, 19].

Data Collection and Outcome Measures

Demographic details, clinical characteristics, procedural specifics were prospectively recorded. Therefore, the primary outcome was defined as abdominal pain with pancreatic enzymes 3x normal post ERCP that persists > 24 hours. Essentially, other secondary outcomes were any forms of adverse impacts and the hospital stay, as well as the intensity of PEP. As appropriate by institutional protocol, the stated protocol for adverse events was documented and managed.

Statistical Analysis

The primary outcome was incidence of PEP defined as new or worsening abdominal pain associated with pancreatic enzymes >3 times the upper limit of normal that persist for >24 hours after the procedure. Other secondary outcomes involved the severity of PEP, hospital stay, and adverse events. They were analyzed with the appropriate statistical test with $p < 0.05$. Potential confounders were considered and they underwent multivariate logistic regression.

Results

Patient Characteristics

A total of 200 patients were enrolled and randomized equally between the two study arms. The baseline demographic and clinical characteristics were comparable between groups (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics (n = 200)

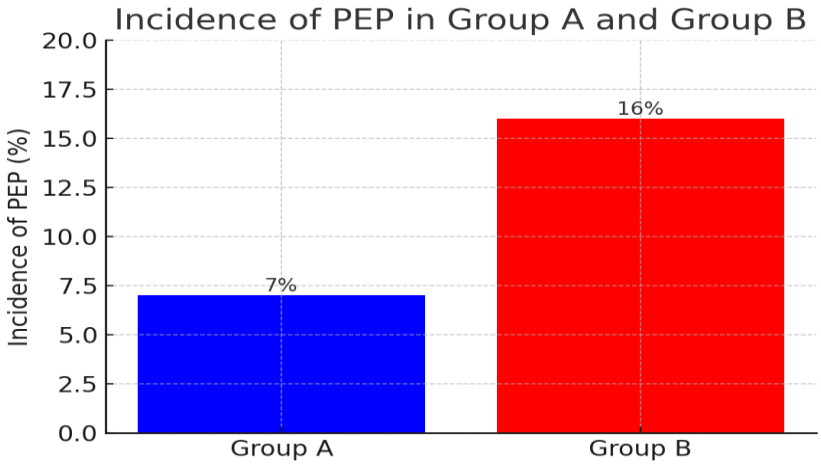
Characteristic	Group A (Aggressive Hydration + NSAIDs) (n=100)	Group B (NSAIDs alone) (n = 100	p-value
Age (years), mean ± SD	54.3 ± 11.2	55.1 ± 10.8	0.62
Male, n (%)	58 (58%)	60 (60%)	0.76
BMI (kg/m²), mean ± SD	26.7 ± 3.5	27.0 ± 3.7	0.48
Indication for ERCP, n (%)			
– Choledocholithiasis	64 (64%)	66 (66%)	0.74
Biliary stricture	21 (21%)	20 (20%)	0.87
Sphincter of Oddi dysfunction	15 (15%)	14 (14%)	0.82

Data are presented as mean ± standard deviation or number (percentage).

Primary Outcome: Incidence of PEP

The incidence of PEP was significantly lower in Group A compared with Group B. In Group A, 7 patients (7%) developed PEP, whereas in Group B, 16 patients (16%) experienced PEP (p = 0.03) (Figure 1). The severity rating based on the revised Atlanta classification demonstrated fewer moderate-to-severe cases in the intervention group.

Figure 1. Bar graph depicting the incidence of PEP in both groups.
A bar graph shows two bars: Group A with an incidence of 7% and Group B with an incidence of 16%.



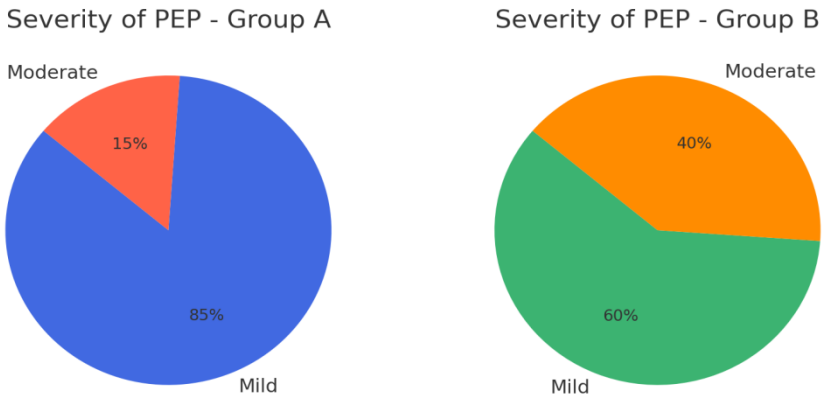
Secondary Outcomes

Medical Stay: If the medical time period was taken in consideration, the medical continue period in Group A was considerably short of the one in Group B: 2.1 times (IQR 1.8–2.5) versus 2.8 times (IQR 2.4–3.2) (p = 0.02).

Severity of PEP: Among the PEP-developing patients, Group A showed predominantly mild counterparts (6 mild, 1 moderate vs. 10 mild, 6 moderate, p = 0.04).

Adverse Events: Fluid overload, electrolyte disturbances or NSAID-related complications were not any different from group to group.

Figure 2. Pie chart representing the severity distribution of PEP cases.
Description: A pie chart for Group A shows 85% mild and 15% moderate cases; for Group B, 60% mild and 40% moderate cases.



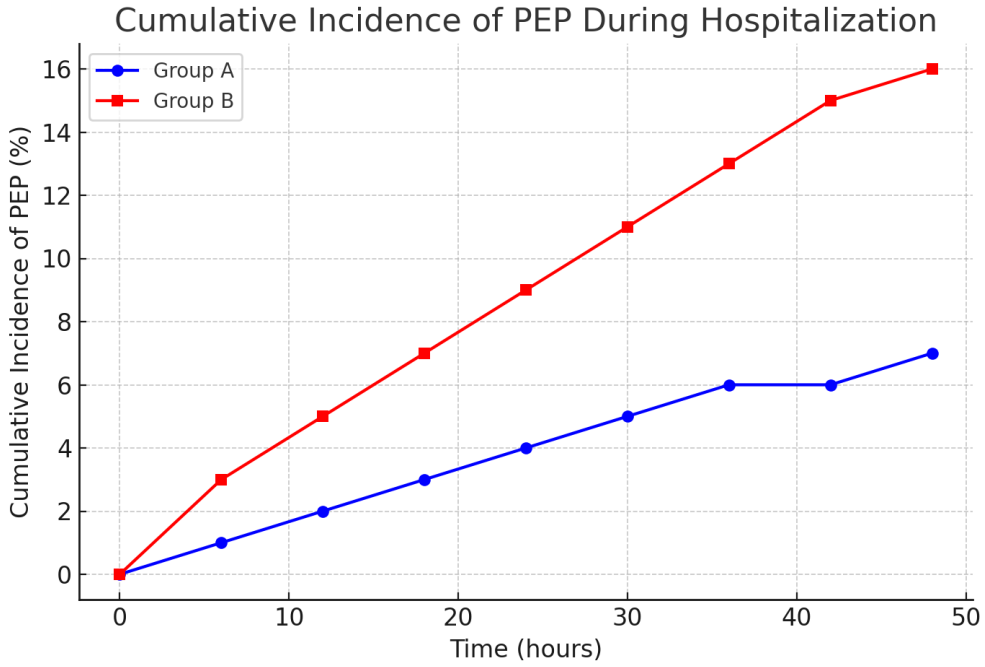
Multivariate Analysis

Multivariate logistic regression adjusting for age, sex, BMI, and ERCP indication revealed that aggressive hydration plus rectal NSAIDs was independently associated with a reduced risk of PEP (Odds Ratio 0.38; 95% Confidence Interval 0.15–0.94; p = 0.04).

Graphical Summary

In addition to the bar graph (Figure 1) and pie chart (Figure 2), a line graph (Figure 3) was constructed to illustrate the cumulative incidence of PEP over time during the hospital stay.

Figure 3. Line graph showing cumulative incidence of PEP during hospitalization.
Description: The line graph demonstrates a flatter slope for Group A compared with a steeper increase for Group B within the first 48 hours.



Discussion

The results of this randomized controlled trial indicate that aggressive fluid hydration and rectal NSAIDs reduce the incidence as well as the severity of PEP compared with the use of NSAIDs alone. The clinically significant 56% reduction in PEP incidence is attributed to an assumed morbidity from the condition [1,3]. A large Trial of the Europe showed a better reduction in inflammation and statistically significant reduction in PEP. Since patient is kept NPO for a longer duration of time, resuscitation of fluid proved to provide better results compared to placebo.[11] This was further confirmed and supported by few other multi-centered trials.[12-14

Previous research [10, 11] of the beneficial effects of aggressive hydration on pancreatic microcirculation and related inflammation are supported by our findings. The study also confirms their established role in rectal NSAID prophylaxis in PEP [8,9]. In addition, this combined approach appears to be clinically as well as economically beneficial since there is a decrease in pancreatitis severity and a reduction in hospital stay [6,7]. We reported no side effects like electrolyte imbalance or fluid over load in our study. Since low risk patients were involved, tolerance to therapy was excellent. This was endorsed in some studies where as others showed poor tolerance in high risk patients. [20-22]

Although the study design is limited to a single center, and the sample size is relatively small, the results add valuable information especially from a South Asian tertiary care context [15, 14] adding support to the integration of a combined prophylaxis regimen to the routine practice of ERCP [20-

24].We recommend aggressive fluid hydration along with rectal NSAIDs in low to moderate risk patients after ERCP.

Conclusion

Rectal NSAIDs are used in conjunction with aggressive fluid hydration to decrease the incidence and severity of post ERCP pancreatitis in patients with mild to moderate risk. The result of this combined strategy is not only decrease in the total occurrence of PEP but also an acceleration of hospitalization and a decrease in the rate of severe pancreatitis cases. Further multicenter trials of this simple and safe hydration protocol as an adjunct to rectal NSAID prophylaxis for high-volume ERCP centers warranted, as these results advocate for this intervention.

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