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Original Research Article

PER RECTAL INDOMETHACIN V/S DICLOFENAC TO PREVENT POST ERCP PANCREATITIS- A COMPARATIVE STUDY

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ABSTRACT

Background: Two promising medications for preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) are rectal indomethacin and diclofenac. It is still debatable if they have a preventive impact on PEP in individuals at ordinary risk. We conducted a prospective observational trial with these two drugs and observed their effects with respect to the incidence of post-operative abdominal pain and discomfort, of pre and post-operative serum amylase and lipase levels and the hospital stay in days after per rectal administration with indomethacin and diclofenac.

Materials and Methods: A total of 46 patients undergoing ERCP were randomised into two groups for post ERCP per rectal suppository placement. Participants' baseline plasma amylase and lipase levels were measured prior to ERCP using blood samples, and these results were compared to post-intervention levels after 24 hours. Pain score was measured using VAS scale of pain. Length of stay at the hospital after developing PEP less than 3 days was considered to be mild, 4–10 days moderate and more than 10 days or complications requiring a pancreatectomy was considered as severe.

Results: Both the groups were comparable with regards to pre and post-op amylase and lipase levels. Mean post-op pain as measure by VAS score at 24 hours after surgery was comparable. Mean hospital stay was comparable between study groups. Incidence of post-ERCP pancreatitis was comparable and observed as 8.7% each in both groups. In both study groups, one case each of mild and moderate pancreatitis seen. Incidence of adverse reactions was observed to be more in cases of Indomethacin group (26.5% vs 4.3%; p-0.069).

Conclusion: The efficacy of indomethacin compared with diclofenac was similar, however, more adverse reactions were associated with use of Indomethacin. In conclusion, study recommends per rectal administered of NSAIDs, preferrable diclofenac before in every patient (without renal failure) undergoing ERCP.

Keywords: ERCP, Pancreatitis, NSAIDS, Post ERCP.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) plays an ever-expanding role in the management of diseases involving the bile duct and pancreatic duct but, as an invasive procedure, it carries significant risks to the patient. The most common complication is acute pancreatitis, which is reported to occur in 2–10% of patients overall (ranging from 2–4% in low-risk patients up to 8–40% in high-risk patients).[1,2] A recent meta-analysis of 108 randomized, controlled trials (RCTs) reported an overall incidence of 9.7%, with a mortality rate of 0.7%.[3]

The exact mechanism for pancreatitis though poorly understood, the proposed theories are injury, oedema, or perforation of the pancreatic sphincter, bile duct, or ampulla by instrumentation or from thermal injury produced by electrocautery causing mechanical obstruction. It has also been suggested that infection

plays a part, due to the possible introduction of luminal contamination into the ducts.[1]

The resultant cascade of inflammation includes the premature intra-acinar activation of zymogens into proteolytic enzymes, chemo-attraction of inflammatory cells, and the release of inflammatory mediators and cytokines. This cascade can be limited to local inflammation or initiate a systemic inflammatory response syndrome (SIRS).[1]

Numerous attempts have been made, over several decades, to prevent post- ERCP pancreatitis or limit its severity, although only a few strategies have been proven effective and subsequently accepted into clinical practice. There are several approaches that are employed to reduce the occurrence of this complication. The first is careful patient selection in order to avoid unnecessary exposure to ERCP and its accompanying risks, using instead newer, less-invasive diagnostic modalities when indicated. Second is the use of epidemiological data to identify the most important risk factors for the development of pancreatitis. High-risk patients may warrant specific preventive endoscopic procedures, such as pancreatic duct stent placement. Risk stratification may also prompt referral of high-risk patients to expert providers. Finally, there are ongoing efforts to identify pharmacological agents that provide effective medical prophylaxis against pancreatitis, with promising recent developments regarding non-steroidal anti-inflammatory agents (NSAIDs).[4]

NSAIDs are potent inhibitors of phospholipase A2, cyclooxygenase and neutrophil– endothelial interactions which are believed to play an important role in the pathogenesis of acute pancreatitis. NSAIDs also induce lipoxins and resolvins, which are lipid mediators that control and resolve inflammation. Experimental models have established that these mediators down regulate the expression of proinflammatory

Genes.[5,6]

Rectal NSAIDs prevent PEP more effectively than oral NSAIDs, perhaps because they act more rapidly and have a larger bioavailability.[7] Many studies have shown that prophylactic rectal NSAIDs such as diclofenac and indomethacin effectively reduce the incidence of pancreatitis without any severe NSAID-related side effect.[8-12]

Diclofenac and Indomethacin are two commonly used NSAIDs for prevention of post- ECP Pancreatitis. Diclofenac has overall higher bioavailability and pain control than indomethacin.[14] Side effects like nausea, vomiting, ulcers, dizziness, visual disturbances, hearing disturbances, etc. were seen more with indomethacin than diclofenac.[15]

Despite being the two most commonly used drugs, there are no clear consensus on efficacy of one over the other. The aim of the present study was thus to evaluate the efficacy of per-rectal diclofenac or indomethacin for the prevention of PEP in adult patients undergoing ERCP.

MATERIALS AND METHODS

Inclusion Criteria

1. Patients undergoing ERCP.
2. Either gender with age of >18 years.
3. Patients willing to give written informed consent and follow study related procedures.

Exclusion Criteria

1. Any previous history of pancreatitis.
2. Pregnant or lactating.
3. History of active peptic ulcer, asthma, or any previous allergic reaction to aspirin or NSAIDs.

Thus a total of 46 subjects undergoing ERCP were randomly divided into one of the following two groups (23 each) using computer generated random numbers over a period of 2 years:

Group D – Per rectal Diclofenac

Group I - Per rectal Indomethacin

Methodology

In this prospective observational study, a total of 46 patients undergoing ERCP, satisfying the inclusion criteria and exclusion criteria were enrolled.

Before ERCP, participant's blood samples were obtained to measure the baseline plasma amylase, lipase, levels.

Immediately after ERCP, patients received 100mg diclofenac, or 100mg indomethacin suppositories, according to their randomized group placement.

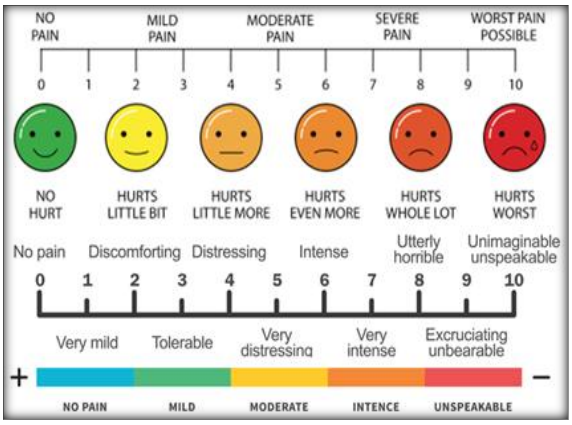
Post intervention blood samples were obtained 24 hrs after ERCP to measure amylase, lipase levels.

Post ERCP Pancreatitis (PEP) was defined according to consensus criteria as more than 3 fold increase in amylase and lipase compared with the baseline limit levels 24 hrs after the procedure, and accompanied by abdominal pain, discomfort leading to prolonged hospitalization.

A patient's length of stay at the hospital after developing PEP less than 3 days considered to be mild PEP, a stay of 4–10 days considered moderate, whereas a stay more than 10 days or the presence of complications requiring a pancreatectomy was considered as severe.

Instruments/ questionnaires used for data collection

- Pre- and post-operative serum amylase and lipase levels.
- VAS pain score scale.



Statistical Analysis

All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-Square test with Continuity Correction for all 2 X 2 tables and Fisher's exact test for all 2 X 2 tables. Quantitative data was represented using Mean ± SD. Analysis of Quantitative data between the two groups was done using unpaired t-test if data passed 'Normality test' and by Mann-Whitney Test if data failed 'Normality test'. A p-value < 0.05 was taken as level of significance. Results were graphically represented where deemed necessary. SPSS Version 21.0 was used for most analysis and Microsoft Excel 2010 for graphical representation.

RESULTS

Two groups of 23 were made for each drug with mean age being 50.92 years with no difference between study groups (p-0.67).

Mean duration of the procedure was 39.57 mins, with no difference between study groups (p-0.52).

Both the groups were comparable with regards to pre-op and post-op amylase and lipase levels (p>0.05).

Table 1: Distribution of study groups as per gender

ADRs	Group		Total
	D	I	
Female	16	15	31
	69.6%	65.2%	67.4%
Male	7	8	15
	30.4%	34.8%	32.6%
Total	23	23	46
	100.0%	100.0%	100.0%
	p- value-1.0		

Out of the total 46 cases, 67.4% were females and 32.6% were males (p>1.0).

Table 2: Mean Comparison of pre-op amylase and lipase levels among study groups

Pre-op Level	Group	N	Mean	SD	P-value
Amylase	D	23	44.95	10.99	0.49
	I	23	47.12	10.89	
Lipase	D	23	31.46	7.70	0.51
	I	23	32.99	7.62	

Both the groups were comparable with regards to pre-op amylase and lipase levels(p>0.05)

Table 3: Mean comparison of post-op amylase and lipase levels among study groups

Post-op Level	Group	N	Mean	SD	P-value
Amylase	D	23	82.56	27.91	0.81
	I	23	84.37	23.88	
Lipase	D	23	60.23	23.61	0.94
	I	23	59.78	17.45	

Both the groups were comparable with regards to post-op amylase and lipase levels(p>0.05)

Table 4: Mean comparison of post-op pain score among study groups

VAS Score	Group	N	Mean	SD	P-value
	D	23	5.46	1.18	0.213
	I	23	4.93	1.52	

Mean post-op pain as measure by VAS score at 24 hours after surgery was comparable between study groups (D vs I: 5.46 vs 4.93; p-0.213).

Table 5: Mean comparison of hospital stay among study groups

Hospital Stay in Days	Group	N	Mean	SD	P-value
	D	23	1.96	0.82	0.69
	I	23	2.07	1.09	

Mean hospital stay was comparable between study groups (D vs I: 1.96 vs 2.07; p-0.69).

Table 6: Comparison of study groups as per incidence of post ERCP pancreatitis

Post ERCP Pancreatitis	Group		Total
	D	I	
No	21	21	42
	91.3%	91.4%	91.3.%
Yes	2	2	4
	8.7%	8.7%	8.7%
Total	23	23	46
	100.0%	100.0%	100.0%
	p- value-1.0		

Incidence of post-ERCP pancreatitis was comparable and observed as 8.7% each in both groups (p-1.0).

Table 7: Comparison of study groups as per adverse reactions

ADRs	Group		Total
	D	I	
Dizziness	0	2	2
	0.0%	8.7%	4.3%
Nausea	1	4	5
	4.3%	17.4%	10.9%
None	22	17	39
	95.7%	73.9%	84.8%
Total	23	17	39
	100.0%	100.0%	100.0%
	p- value-0.069		

In both the study groups, we observed one case each of mild and moderate pancreatitis each (p- 1.0).
Incidence of adverse reactions was observed to be more in cases of Indomethacin group (26.1% vs 4.3%; p-0.069). Incidence of adverse reactions among Cases receiving Indomethacin and diclofenac is as follows: dizziness (8.7% vs 0%) and nausea (17.4% vs 4.3%).

DISCUSSION

Numerous attempts have been made, over several decades, to prevent post- ERCP pancreatitis (PEP) or limit its severity, although only a few strategies have been proven effective and subsequently accepted into clinical practice. In present study, we aimed to evaluate the efficacy of per-rectal Diclofenac or Indomethacin for the prevention of PEP in adult patients undergoing ERCP.
Sethi S et al,[16] did a meta-analysis of seven randomized, controlled trials involving 2133 patients. The meta-analysis showed that rectal NSAIDs decreased the overall incidence of PEP (risk ratio, 0.44; 95% confidence interval, 0.34-0.57; P <0.01). No differences of the adverse events attributable to NSAIDs were observed.
Patai Á et al,[17] did a meta-analysis of 4741 patients from 17 trials. The study showed that diclofenac or indomethacin significantly decreased the risk ratio (RR) of PEP to 0.60 (95% confidence interval [CI], 0.46-0.78; P = .0001). The efficacy of indomethacin compared with diclofenac was similar (P = 0.98). The efficacy of indomethacin or diclofenac did not differ according to timing (P = .99) or between patients with average-risk and high-risk for PEP (P = .6923). Study also observed that rectal route was very effective (P = .0005).
Yu S et al,[18] in another meta-analysis of 10 RCTs, including 2928 patients observed that rectal indomethacin and diclofenac were associated with a significant reduction in the overall risk of PEP compared with control intervention [relative risk (RR) = 0.62; 95% confidence interval (CI): 0.46–0.83] in average-risk patients. Subgroup analyses showed that both rectal indomethacin (RR = 0.67; 95% CI: 0.49– 0.94) and diclofenac (RR = 0.42; 95% CI: 0.23–0.75) were effective in the prevention of PEP. Indirect comparison showed no significant difference between the effectiveness of the two drugs in the prevention of PEP (RR = 1.607; 95% CI: 0.824–3.136).
Other investigations on the prevention of PEP administration of NSAIDs have recently been conducted. The majority of earlier research has validated the function of indomethacin and diclofenac in lowering the prevalence of PEP as mentioned above. A recent large-sample retrospective analysis, however, found that diclofenac did not lower the incidence of PEP in low-risk patients when compared to the control group, in contrast to earlier research. Furthermore, Levenick et al. discovered that indomethacin did not lower the incidence of PEP in a recent RCT research.[19] To the best of our knowledge, no extensive RCT trials have directly compared diclofenac and indomethacin to examine how the two medications differ in terms of their potential to prevent PEP.
According to Makela et al., indomethacin was more effective than diclofenac at reducing PLA2 activity in the serum of individuals suffering from acute pancreatitis.[20] Additionally, indomethacin is not vulnerable to significant first-pass metabolism, whereas diclofenac is, with only 50–60% of the drug entering the systemic circulation intact. Given these results, it is logical to hypothesize that indomethacin might be a more effective option for preventing PEP than diclofenac.
To date, only one clinical trial Mohammad Alizadeh AH et al has directly compared the efficiency of rectal indomethacin and diclofenac in the prevention of PEP among unselected patients.[21] However, in that study, PEP was defined as a more than 300% increase in amylase and lipase levels compared with the baseline value, with a less than three-fold increase in the upper normal limit levels, 24 h after the procedure, accompanied by abdominal pain, leading to prolonged hospitalization.[21]
Allopurinol, diclofenac, gabexate, glyceryl trinitrate, indomethacin, nafamostat, octreotide, somatostatin, and ulinastatin have been compared for protection against PEP in a network meta-analysis of RCTs. There were no discernible changes in the effectiveness of diclofenac, gabexate, glyceryl

trinitrate, indomethacin, somatostatin, and ulinastatin compared to a placebo, according to the results.[22]

Adverse Reactions

Incidence of adverse reactions was observed to be more in cases of Indomethacin group (26.1% vs 4.3%; p-0.069). Incidence of adverse reactions among Cases receiving Indomethacin and diclofenac is as follows: dizziness (8.7% vs 0%) and nausea (17.4% vs 4.3%). Montaño Loza et al,[23] in a study of rectal indomethacin observed an incidence of nausea and vomiting as 17%. Murray B et al,[24] in their study of rectal diclofenac observed the overall incidence of ADRs as 7% with incidence of nausea and vomiting as 5%. Shil BC et al,[25] in a comparative trial observed no difference between study groups with regards to adverse reactions. Yu S et al,[22] in their meta-analysis observed no difference in two drugs in terms of adverse reaction profile.

CONCLUSION

Prophylactic use of rectal NSAIDs reduces the incidence and severity of Post ERCP pancreatitis. The efficacy of indomethacin compared with diclofenac was similar, however, more adverse reactions like nausea and dizziness were associated with use of Indomethacin. In conclusion, present study recommends per rectal administered of NSAIDs, preferrable diclofenac before in every patient (without renal failure) undergoing ERCP.

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