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ORIGINAL ARTICLE

Comparison of severity of pancreatitis with and without diclofenac sodium in post ERCP patients.

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ABSTRACT… Objective: To compare the diclofenac sodium intramuscular prophylaxis given with standard treatment in patients having ERCP was compared with standard treatment alone with respect to frequency and severity of pancreatitis within 48 hours after the procedure. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Gastroenterology, Hepatology, and GI Endoscopy, SZABMU, Pakistan Institute of Medical Sciences, Islamabad. **Period:** August 2021 and April 2022. **Material & Methods:** The study enrolled 160 patients with obstructive jaundice with or without pruritus (20-70 years). Each group consisted of 80 patients. A prophylactic dose of 75 mg of diclofenac sodium was administered intramuscularly to Group A in addition to standard treatment, while standard treatment was given to Group B alone. The standard treatment for PEP was antibiotics (Cefoperazone/Sulbactam 2g IV) for both groups. IV dormicum (midazolam) was given to both groups as sedation. All patients were tested for lipase and amylase after the procedure to detect any complications. They were also monitored for abdominal pain at 4 and 24 hours after the procedure. **Results:** In patients of Group A (n=80), the mean age was 47.1 years ± 8.4 SD, whereas in patients in Group B (n=80), the mean age was 47.5 years ± 7.4 SD. In Group A, 3.8% of patients (n=3/80) developed PEP, while 11% (n=11/80) developed PEP (p=0.025). Intramuscular diclofenac sodium was more efficient at preventing PEP when compared to the control group on standard treatment alone, on all of the following parameters: (1) the proportion of patients that did not develop PEP, (2) the rate of patients that developed PEP, and (3) the average quantity of days that patients were sick. In both groups A and B, the PEP diagnosis was mild and the patients were discharged within 2-3 days of diagnosis. PEP efficacy was not significantly different across age groups or genders in both treatment groups (p>0.05). **Conclusion:** Diclofenac sodium is significantly more effective than standard treatment alone for intramuscular pancreatitis prophylaxis after ERCP.

Key words: Diclofenac Sodium, ERCP, Post ERCP Pancreatitis.

INTRODUCTION

Endoscopic retrograde Cholangiopancreatography (ERCP) is a specialized endoscopic technique. A side-viewing upper endoscope is guided into the duodenum, which allows instruments to be passed into the bile and pancreatic ducts. A contrast medium is injected to opacify the structures for proper visualization under radiography.[1,2] PEP is the most common serious complication observed after ERCP.[1] There are various factors that have been proposed in the induction of PEP. The two most important ones are instrumentation-related mechanical injury and contrast-related hydrostatic injury.

In a systematic review of more than 2000 high-risk patients, the overall incidence of PEP was found to be 14.7%.[2] In most of them, the PEP was of mild severity (8.6%), PEP of moderate severity was found in 3.9% and severe PEP was found in 0.8% of patients. the mortality rate was 0.2%.[3] Early diagnosis of PEP is important and diagnosis of PEP is generally established when a patient with signs and symptoms of pancreatitis (e.g., abdominal pain and tenderness) has elevated pancreatic enzymes (i.e., amylase and lipase).[4,5] In an attempt to reduce the incidence of PEP, several measures have been assessed with close attention to good ERCP technique, which is fundamentally important. There are

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some guidelines that recommend routine use of pharmacologic prophylaxis in the form of NSAIDs.[6,7]

Several clinical trials reported the efficacy of NSAIDs in preventing PEP. In a meta-analysis of 17 trials with over 4700 patients, the use of either indomethacin or diclofenac by any route reduced the risk of PEP (RR 0.60, 95% CI 0.46-0.78). Timing of NSAID dosing (i.e., before or after ERCP) did not affect the risk of PEP.[8] In another study including more than 400 patients, the use of rectal indomethacin was found to be associated with a lower risk of PEP (OR 0.36, 95% CI 0.17-0.75).[9]

A recent trial by Ucar R, et al assessed the effectiveness of diclofenac sodium (intramuscular versus rectal) for reducing the incidence of PEP and compared it with the control group.[1] They found that administration of intramuscular diclofenac sodium resulted in an incidence of 6% of PEP as compared to 1% after administration of rectal diclofenac, while in the control group the incidence of PEP was found to be 14% ($P = 0.014$). They further demonstrated that 12.7% (10% in rectal, 8% in IM and 20% in controls; $P>0.05$). Elevated serum amylase levels were seen in 16.6% (12% in rectal, 10% in IM and 24% in controls; $P<0.05$).[1]

MATERIAL & METHODS

The Ethical Review Board at Shaheed Zulfiqar Ali Bhutto Medical University (F1.1/2015/ERB/SZABMU/795) approved the study. All participants provided written informed consent to participate in this study between August 2021 and April 2022 and it was conducted at the Department of Gastroenterology, Hepatology, and GI Endoscopy, SZABMU, Pakistan Institute of Medical Sciences, Islamabad. Using the WHO sample size calculator, 80 patients were allocated to each group. Parameters used were as follows; Significance level 5%, test power 80%, proportion of first population (P1) 2%, and proportion of second population (P2) 14%.[1]

In this study, patients were enrolled by non-probability consecutive sampling. The study included patients of all genders between the ages of 20 and 70. ERCP was performed on all patients enrolled in the study. This study excluded patients with acute pancreatitis treated with NSAIDs or acetylsalicylic acid within the last week, patients with peptic ulcer disease, those who had undergone an endoscopic sphincterotomy, pregnant and nursing women, those previously diagnosed with CCF or CKD, as well as those who were on antiplatelet or anticoagulant therapy. A lottery method was used to randomly divide the patients into two groups: diclofenac sodium intramuscular (Group A) and control group (Group B). PEP prophylaxis was administered to both groups with antibiotics (Cefoparazone/Sulbactam 2g IV). Dormicum (midazolam) was given to both groups as sedation.

In Group A, 75 mg of diclofenac sodium intramuscularly was administered as an add-on prophylactic therapy. After the procedure, patients' amylase and lipase levels were measured at 4 and 24 hours afterward, and abdominal pain was monitored to ensure no discomfort occurred. According to standard criteria, PEP was diagnosed. Since the study conducting doctor collected data within 24 hours of admission, a longer follow-up period was not necessary to address the compliance issue. A pre-designed proforma was used to record all the information.

A SPSS version 17 program was used to analyze the data. The descriptive statistics were calculated for all variables, including age, gender, and the severity of PEP. The frequency and percentages of PEPs were calculated based on gender, severity, and PEP type. The mean and standard deviation for age, serum lipase, and serum amylase were estimated in both groups at four hours and twenty-four hours. The frequency of PEP was compared between two groups using the chi-square test. It was considered statistically significant if the P value was less than 0.05.

RESULTS

In the present we enrolled one hundred and sixty ($n=160$). Mean age was 47.1 years ± 8.4 SD in Group A patients and it was 47.5 years ± 7.4 SD

in group B patients as shown in Table-I.

In group A, 42.5% (n=34/80) patients had age between 20-45 years and 57.5% (n=46/80) had age between 46-70 years.In group B, 43.8% (n=35/80) patients had age between 20-45 years and 56.3% (n=45/80) patients had age between 46-70 years as shown in Table-I.

Gender distribution was similar in both groups. In Group A there were 63.8% (n=51/80) males and 36.3% (n=29/80) females and in group B there were 66.3% (n=53/80) males and 33.3% (n=27/80) females as shown in Table-I.

Factors	Group A N = 80	Group B N = 80
Mean Age	47.1±8.4	47.5±7.4
Distribution of Age		
20-45 years	34 (42.5%)	35 (43.8%)
46-70 years	46 (57.5%)	45 (56.3%)
Gender		
Male	51(63.8%)	53(66.3%)
Female	29 (36.3%)	27 (33.8%)

Table-I. Baseline demographic characteristics

There was no significant difference between the two groups in the level of amylase four hours after the procedure; 261.6 U/L ± 57.6 SD in group B patients versus 266.8 U/L ± 57.9 SD in Group A patients; (p=0.566) as shown in Table-II. There was no significant difference in mean serum lipase levels as well, between patients in Group A (1061.1 U/L ± 279.3 SD) and Group B (1018.6 U/L ± 281.5 SD) (p=0.345) as shown in Table-II.

Patients in Group A had a mean serum amylase level of 137.7 U/L ± 84.6 SD at 24 hours postoperatively, and patients in Group B had a mean serum amylase level of 170.3 U/L ± 132.1 SD (p=0.065, Table 9). Group A patients had a mean lipase level of 326.1 U/L ± 116.4 SD at 24 hours, while those in group B had a mean lipase level of 362.1 U/L ± 137.2 SD (p=0.071) as shown in Table-II.

Of the 80 patients in group A, 3 (=3.8%) were found to have PEP. Conversely, of the 80 patients in group B, 11 (=13.8%) were found to have PEP (p=0.025) as shown in Table-II. The use of diclofenac sodium for intramuscular prophylaxis of PEP was significantly more efficacious than the standard treatment alone when comparing both groups. PEP diagnosed in all the patients of Group A and B was of mild severity and patients were discharged within 2-3 days from hospital.

Factors	Group A N = 80	Group B N = 80	P-Value
Serum Amylase (U/L)			
4 hours	266.8±57.9	261.6±57.6	0.566
24 hours	137.7±84.6	170.3±132.1	0.065
Serum Lipase (U/L)			
4 hours	1061.1±279.3	1018.6±281.5	0.345
24 hours	326.1±116.4	362.1±137.2	0.071
Diagnosis of PEP	3 (3.8 %)	11 (13.8 %)	0.025

Table-II. Post procedure monitoring of the cases

DISCUSSION

The results of our study are comparable to those published previously. A recent study by Ucar et al evaluated the effectiveness of diclofenac sodium (intramuscular versus rectal) in reducing PEP incidence.[1] With intramuscular diclofenac sodium, the incidence of PEP was 6%, while with rectal diclofenac it was 1%, while with control the incidence was 14% (P = 0.014). The study also found 12.7% (10% in rectal, 8% in IM, and 20% in controls; P>0.05). 16.6% of patients (12% in rectal, 10% in IM, and 24% in controls) had elevated serum amylase levels.[1]

A similar study by Senol et al demonstrated that diclofenac sodium (intramuscular) along with fluid replacement is effective for preventing PEP.[12] A total of 80 patients were enrolled and randomized into two groups who were scheduled for ERCP. The patient group received intramuscular diclofenac sodium (75 mg loading dose) followed by an infusion of isotonic saline (5-10 ml/kg/hr) for 4 hours after ERCP, while the other group received only isotonic saline (500 ml). The study found that 12.5% of patients treated with extra diclofenac and 17.5% of those treated with normal saline had PEP. PEP incidence was lowered by administering IM diclofenac along with fluid replacement, according to the authors.

Contrasting results have been demonstrated in two other similar studies. Park et al assessed the

effectiveness of diclofenac sodium (intramuscular) in reducing PEP risk.[13] They randomized the patients who were planned to undergo ERCP into two groups. One received 90mg of diclofenac (intramuscular) soon after the procedure and the other was the placebo group. Their results showed that PEP was developed in 11.8% (n=20) patients after administration of intramuscular diclofenac and in 12.7% (n=22) patients in the placebo group (P>0.05). Authors concluded that administration of diclofenac sodium (intramuscular) had no additional benefit in the prevention of PEP.

Rana et al investigated the effectiveness of diclofenac sodium (intramuscular) in reducing PEP risk and severity in 383 patients who were to undergo ERCP, compared to saline taken as a placebo.[14] According to their results, 12.2% of patients developed PEP. After conservative treatment, all patients recovered. There was no statistically significant difference between two groups in the incidence of PEP (12.7% versus 11.8%; P = 0.87), which contradicts our results.

The use of oral diclofenac sodium for the prevention of PEP has been investigated by some authors. A study by Cheon et al evaluated the effect of diclofenac sodium (oral) on the risk and severity of PEP in 207 patients undergoing ERCP (102 control, 105 oral diclofenac) and compared with a control group.[15] According to their results, 16.4% of patients developed PEP. There was no statistically significant difference in the incidence of PEP between the two groups (16.7% in the control group versus 16.2% in the oral diclofenac group; P >0.05). Ishiwatari investigated the effectiveness of diclofenac sodium (oral 50 mg) in reducing PEP risk among 407 (202 control, 205 oral diclofenac) patients undergoing ERCP compared with placebo.[16] There was no significant difference in PEP incidence between the two groups (9.8% in the oral diclofenac group and 9.4% in the placebo group, P > 0.05).

Their analysis included 21 randomized controlled trials with 6854 patients. Patients used NSAIDs pre-ERCP 50% of the time (n=3427) and did not use NSAIDs 50% of the time (n=3427). A meta-analysis was conducted by Serrano JPR to assess the efficacy of NSAIDs in preventing PEP.[16,17] Two large meta-analyses have been published recently on the use of NSAIDs for PEP prevention. An analysis of pooled data showed that patients who took NSAIDs prior to ERCP (n=250) had a lower risk of PEP than those who did not (n=427). Furthermore, only diclofenac or indomethacin use was found to reduce PEP (6.8 % vs. 13 %).[17]

In another meta-analysis, Lyu et al evaluated the role of NSAIDs in reducing the risk of PEP using 21 RCTs.[18] PEP incidence was significantly reduced by NSAIDs (p< 0.00001). Post-ERCP administration of indomethacin reduced the incidence of PEP more effectively (p 0.05) than pre-ERCP administration (p 0.003). Diclofenac administration post-ERCP (p = 0.35) was less effective than pre-ERCP administration (p = 0.001). Only patients receiving NSAIDs via the rectal route (p 0.00001) were found to have a significant reduction in PEP risk.

Compared with placebo, intramuscular diclofenac sodium significantly reduced the incidence of PEP in this study and at least two other studies. The frequency of PEPs was not significantly reduced by intramuscular diclofenac sodium compared to placebo therapy in other studies. In several studies, oral diclofenac was not found to reduce PEP incidence. The majority of evidence supports the use of rectal NSAIDs containing diclofenac sodium or indomethacin and it recommended that in the future, oral plus rectal diclofenac sodium therapy should be compared with rectal monotherapy, and future studies should be conducted.

CONCLUSION

Diclofenac sodium is significantly more effective than standard treatment alone for intramuscular pancreatitis prophylaxis after ERCP.

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