

Comparison of stent and indomethacin suppository efficacy in the prevention of acute pancreatitis after ERCP

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Abstract. *Objective:* We aimed to compare stent and indomethacin suppository efficacy in the prevention of acute pancreatitis after ERCP. *Materials and Methods:* 76 high-risk patients undergoing ERCP were included in the study. The patients were divided into three groups as indomethacin group, stent group and control group. Indomethacin group (n = 32) received 100 mg rectal indomethacin immediately after ERCP. A 5F pancreatic stent was applied to the stent group (n = 16) during ERCP. No prophylaxis was given to the control group (n = 28). *Results:* There was no difference between the groups in terms of age and gender. ERCP pancreatitis was seen in 9.2% (7/76) of the patients. The incidence of ERCP-induced pancreatitis (PEP) was 3.1% (1/32) in the indomethacin group and 21.4% (6/28) in the control group. PEP was not seen in the stent group (0/16). The incidence of PEP was significantly lower in the indomethacin group than in the control group (p = 0.043). However, no significant difference was found between the stent and control groups, stent and indomethacin groups in terms of PEP frequency (p = 0.072, p = 0.90 respectively). *Conclusion:* According to the results of our study, rectal indomethacin administration decreased the frequency of PEP in high-risk patients. However, there was no significant difference in PEP prophylaxis between the stent and indomethacin groups.

Key words: Endoscopic retrograde cholangiopancreatography, post-ERCP pancreatitis, non-steroidal anti-inflammatory drug, indomethacin

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the important endoscopic procedures used in the diagnosis and treatment of biliary tract and pancreatic duct diseases. With this method, the ampulla of the second part of the duodenum is cannulated by dilating or sphincteromy. The biliary system and / or pancreatic duct can be visualized under fluoroscopy by administering contrast material after cannulation. In addition, in cases such as stone, stenosis, malignancy, it includes the procedure of dropping

the stone and / or opening the stenosis using baskets or balloon catheters and placing a stent in the stenosis area if necessary(1,2).

Regardless of the mechanism that initiates the events in acute pancreatitis, the increase in pressure in the pancreatic duct and the extravasation of pancreatic enzymes to the extra-duct tissue as a result of damage to the duct causes local and systemic effects(3,4). The first and most important symptom is abdominal pain that starts suddenly and is localized to the epigastrium. Later, the pain may be in the form of a belt and may spread to the back. The pain is continuous and may be blunt or

stinging. The most common causes of acute pancreatitis are gallstones, alcohol, and trauma. In addition to these, stenosis in the pancreatic duct, gland infections, hyperlipoproteinemia, hyperparathyroidism, etc. are the other causes of pancreatitis. The cause may not be determined in approximately 5-7% of cases. Among the causes of pancreatitis, gallstones and chronic alcoholism constitute 60-80% of all pancreatitis cases(5,6). Another reason for pancreatitis is pancreatitis due to ERCP procedure. It is the most common complication of ERCP. In many studies, the percentage of ERCP pancreatitis has been reported as 1.2-8%. The most common test used for ERCP pancreatitis screening is the measurement of serum amylase activity. The diagnosis of ERCP pancreatitis was first made by Cotton et al. Made by. It has been modified by later studies(7-9). According to this consensus, new onset or increased abdominal pain, 3 or more than 3 times higher amylase value 24 hours after ERCP, clinical conditions requiring hospitalization or prolonging the duration of stay for 2 days were evaluated as pancreatitis (8). There are risk factors depending on the patient and technique in the development of pancreatitis due to ERCP (10). Patients with high risk of developing ERCP pancreatitis can be prophylaxis with post-ERCP medical agents (e.g. nonsteroidal anti-inflammatory drugs) or endoscopic methods (e.g. pancreatic duct stent placement)(11).

There are publications about the use of indomethacin and stent placement in the pancreatic duct after the procedure in reducing the risk of ERCP pancreatitis (7). However, there have not been enough studies comparing indomethacin treatment with the method of stent placement in the pancreatic duct. In this study, we aimed to compare indomethacin treatment with the method of stent placement in the pancreatic duct in the prevention of ERCP pancreatitis. In addition, we examined the relationship of these two methods with the group that was not given any prophylaxis.

Material and Methods

In this study, it was planned to compare the effectiveness of indomethacin and stent in patients with high risk for the development of ERCP pancreatitis. The study was initiated after obtaining approval from

the Erciyes University Faculty of Medicine Ethics Committee (Ethics committee decision no: 2013/419, Date: 02.07.2013). Human and patient rights were respected in all phases of the study. Single center, clinical, prospective, and controlled study; 76 patients with ERCP indications for diagnosis and treatment were included consecutively. Patients who were diagnosed with biliary pancreatitis and had high amylase values before ERCP were excluded from the study.

Patient Selection and Data Collection

Patients in the high-risk group for ERCP pancreatitis were determined according to the high-risk patient criteria specified by the European Society of Gastrointestinal Endoscopy (ESGE) (7).

- Young female patient
- Normal bilirubin levels
- Patients with a previous history of pancreatitis
- Patients who have repeatedly tried biliary cannulation and pancreatic cannulation.
- Pre-cut sphincteromyia
- Balloon dilation of the biliary sphincter
- Pancreatic sphincterotomy
- Patients who received contrast injection into the pancreatic duct were included in the study.

Cannulation performed in 10 minutes or more by an experienced endoscopist was considered as power cannulation. Persistent and severe abdominal pain requiring hospitalization after the procedure, amylase values higher than the upper limit of at least 3 times the upper limit and the duration of these values for at least 24 hours were accepted as ERCP pancreatitis criteria. In this direction; Hemogram, total bilirubin, direct bilirubin, AST, ALT, ALP, GGT, amylase and lipase values were measured 6 and 24 hours after the procedure.

The patients included in the study were divided into three groups. 32 patients in the first group; Immediately after the procedure, 100 mg of indomethacin was administered rectally as suppository. This group was followed as the indomethacin group. A prophylactic pancreatic stent was placed in 16 patients in the second group during the ERCP procedure. Patients in this group were named as stent group. In the third

group, 28 patients were not given any treatment other than their routine medications before, during and after the procedure, and no attempt was made. These patients were accepted as the control group.

Devices Used in Processes

In our study, Olympus branded Exera 2 cv-180 device was used for videoduodenoscopy and ERBE ICC 200 Cut / Coag device was used for endoscopic electrocauterization during ERCP procedure. Radiological imaging was performed with Philips BV 300 model x-ray machine. For sphincterotomy, Boston Scientific 5.5 F, 30 mm sphincterotomes, Endomed brand 16 mm diameter 3 lumen catheter as balloon catheter, Cook brand 28 mm diameter 220 cm as basket catheter. catheter was used. Boston Hydra Jaguwire brand 0.035 in x 0.50 cm angle type guide wire was used as a guide wire. Cook brand 5F, 3cm, 5cm, 7cm stent was preferred as pancreatic stent.

As laboratory tests, biochemical parameters such as amylase, lipase, AST, ALT, ALP, GGT, total bilirubin, direct bilirubin were studied with spectrophotometric method on ABOTT brand ARC HECT device. Hemogram values were studied with the laser technique in the SIEMENS brand ADVIA 2120.

Statistical Analysis

SPSS (Statistical Package For Social Science) 15.0 Statistical package program was used for the statistical analysis of the data. 25th and 75th percentile values were used as locative criteria for distribution. Relationships between demographic data were investigated by Chi-Square test and Kruskal-Wallis Test. Comparison of variables that fit the normal distribution between

groups was made with Student's T test. Wilcoxon Signed Ranks test and Friedman test were used for the comparison of repeated measurements. $P < 0.05$ value was considered statistically significant.

Results

Of the 76 patients included in the study, 45 were women and 31 were men. Of the patients in the indomethacin group, 20 (62.5%) were female, 12 (37.5%) were male; 9 (56.3%) of the patients in the stent group were female and 7 (43.8%) were male; 16 (57.1%) of the patients in the control group were female and 12 (42.9%) were male. There was no significant difference between the three groups in terms of gender distribution (Table 1). The ages of the patients participating in the study varied between 18 and 80.

The mean age of the indomethacin group was 56.50 (37.25--68.25), the mean age of the stent group was 54.00 (49.00--68.75), and the mean age of the control group was 47.50 (38.50--59.75). There was no significant difference between the three groups in terms of age (Table 1).

Groups were compared in terms of laboratory parameters. It was observed that there was no significant difference in the laboratory parameters measured at 0, 6.24 hours between all three groups. The data are summarized in Table 2.

An increase of at least 3 times the upper limit of the serum amylase value 24 hours after the procedure and abdominal pain that started or became severe enough to require hospitalization were evaluated as ERCP pancreatitis (7). Accordingly, 7 of 76 patients included in the study developed ERCP pancreatitis. 5 (76.4%) of the 7 patients who developed ERCP pancreatitis were

Table 1. Gender Distribution and Average Age of Patients

| n | | Indomethacin | | Stent | | Control | | Total | p |
|-------------|--------|------------------------|------|------------------------|------|------------------------|------|-------|-----------------------------|
| | | % | n | % | n | % | n | % | |
| Gender | Female | 20 | 62.5 | 9 | 56.2 | 16 | 57.1 | 45 | 0.86 59.2 40.8 100 |
| | Male | 12 | 37.5 | 7 | 43.8 | 12 | 42.9 | 31 | |
| | Total | 32 | 100 | 16 | 100 | 28 | 100 | 76 | |
| Age (years) | | 56.50 (37.25-68.25) | | 54.00 (49.00-68.75) | | 47.50 (38.50-59.75) | | | 0.113 |

Table 2. Comparison of Laboratory Parameters of Groups

| | Indomethacin Group | Stent group | Control group | p value |
|---|---------------------------|---------------------------|---------------------------|----------------|
| Hgb (before) (12-18) g/dl | 13 (12–13.75) | 13 (11,25–13) | 13 (12–14) | 0.22 |
| Leukocyte(before) (4.8-10.8) 10³/μL | 7175 (5945–8380) | 7485 (5932–8032) | 6981 (5945–8150) | 0.714 |
| Plt (before) (130000-400000) 10³/μL | 237000 (197750–310500) | 269000 (253750–319250) | 293000 (206750–368500) | 0.42 |
| Amylase (before) (25-140) μ/L | 46 (30–66) | 60 (42–77) | 65 (41–80) | 0.70 |
| Lipase (before) (8-78) μ/L | 26 (13–40) | 35 (12–87) | 25 (19–49) | 0.61 |
| AST (before) (0-40) μ/L | 70 (29–132) | 69 (33–182) | 120 (49–266) | 0.22 |
| ALT (before) (0-55) μ/L | 94 (26–164) | 136 (58–353) | 245 (57–421) | 0.36 |
| T.Bil (before) (0.2-1,2) mg/dl | 1.2 (0,5–6,8) | 1.0 (0.75–5,8) | 2.0 (0,6–5,1) | 0.94 |
| D.Bil (before) (0-0,5) mg/dl | 0.5 (0,3–4,5) | 0.5 (0,3–4,1) | 1.4 (0,3–3,6) | 0.90 |
| Alp (before) (40-150) μ /lt | 192 85–264 | 197 122–387 | 218 172–441 | 0.64 |
| GGT (before) (12-64) μ/L | 271 73–505 | 411 197–607 | 455 120–683 | 0.75 |
| Amylase (sixth hour) (25-140) μ/L | 113 (54–183) | 125 (55–307) | 137 (58–370) | 0.70 |
| Lipase (sixth hour) (8-78) μ/L | 113 (29–214) | 104 (44–320) | 124 (26–563) | 0.89 |
| Amylase (twentyfourth hour) (25-140) u/L | 86 (43–190) | 145 (49–303) | 117 (63–593) | 0.68 |
| Lipase (twentyfourth hour) (8-78) μ/L | 54 (20–198) | 102 (39–356) | 72 (26–976) | 0.92 |

female and 2 (28.6%) were male. Of the 69 patients who did not develop ERCP pancreatitis, 40 were female and 29 were male. Statistically, there was no difference in gender distribution between patients with and without ERCP pancreatitis ($P = 0.69$).

When the patients with and without ERCP pancreatitis were compared in terms of age, alcohol and smoking history, gallstones, pancreatitis attack, ERCP history, history of previous cholecystectomy, there was no significant difference between the two groups ($p > 0.05$). In the groups with and without ERCP pancreatitis, as expected in the comparison of laboratory parameters (values measured before ERCP, 6 hours and 24 hours after ERCP), amylase and lipase values

at the 6 and 24 hours post-ERCP in those who developed ERCP pancreatitis were higher. When the groups were compared with the control group in terms of the development of ERCP pancreatitis, the difference between indomethacin and control groups was statistically significant ($p = 0.043$).

Development of ERCP pancreatitis was significantly lower in the indomethacin group compared to the control group (Table 3). When the stent group was compared with the control group, development of ERCP pancreatitis was not observed in the stent group, while this difference between the control group was not statistically significant ($p = 0.072$) (Table 4). Indomethacin and stent groups were evaluated statistically

Table 3. Development of ERCP Pancreatitis in Indomethacin and Control Groups

| | EP (-) | | EP (+) | | Total | | <i>p</i> |
|--------------|--------|------|--------|------|-------|-----|----------|
| | n | % | n | % | n | % | |
| Indomethacin | 31 | 96.9 | 1 | 3.1 | 32 | 100 | 0.043 |
| Control | 22 | 78.6 | 6 | 21.4 | 28 | 100 | |
| Total | 53 | 88.3 | 7 | 11.7 | 60 | 100 | |

Table 4. Development of ERCP Pancreatitis in Stent and Control Groups

| | EP (-) | | EP (+) | | Total | | <i>p</i> |
|---------|--------|------|--------|------|-------|-----|----------|
| | n | % | n | % | n | % | |
| Stent | 16 | 100 | 0 | 0 | 16 | 100 | 0.072 |
| Control | 22 | 78.6 | 6 | 21.4 | 28 | 100 | |
| Total | 38 | 86.4 | 6 | 13.6 | 44 | 100 | |

Table 5. Development of ERCP Pancreatitis Between Indomethacin and Stent Groups

| | EP (-) | | EP (+) | | Total | | <i>p</i> |
|--------------|--------|------|--------|-----|-------|-----|----------|
| | n | % | n | % | n | % | |
| Indomethacin | 31 | 96.9 | 1 | 3.1 | 32 | 100 | 0.900 |
| Stent | 16 | 100 | 0 | 0 | 16 | 100 | |
| Total | 47 | 97.9 | 1 | 2.1 | 48 | 100 | |

among themselves, no significant difference was observed ($p > 0.05$) (Table 5).

Discussion

It was observed that a total of 9.2% of 76 patients included in the study and 3.1% of patients in the indomethacin group developed ERCP pancreatitis. No development of ERCP pancreatitis was observed in the stent group. In our study, 5 (76.4%) of 7 patients who had post-ERCP pancreatitis were female and 2 (28.6%) were male. Although most of the patients who developed ERCP pancreatitis were women, no significant difference was found when evaluated statistically. It was thought that this result might be due to the low number of patients and the fact that the majority of the patients included in the study were women.

In a meta-analysis by Masci et al., Female gender was found to be a risk factor for the development of ERCP pancreatitis, and it was reported that ERCP pancreatitis may develop 2 times more than men. It

was thought that oddi sphincter dysfunction (OSD) and gallstones seen in women increase the risk of ERCP pancreatitis (12). Placement of a stent in the pancreatic duct in high-risk patients is an accepted and agreed prophylaxis method for the development of ERCP pancreatitis (7, 13). However, pancreatic stent placement requires a high degree of endoscopic experience and is not always possible due to the anatomical structure. For this reason, non-invasive prophylactic methods have been sought and many medical agents have been tried. Based on the pathophysiological events in the development process of ERCP pancreatitis, sphincter relaxants, protease inhibitors, anti-inflammatory agents, anti-oxidant agents, anti-secretory agents, low osmolar contrast agents were used (7,14,15).

Based on the inflammatory cascade, which is one of the possible mechanisms in the development of acute pancreatitis, many studies have been published on phospholipase A2 inhibitor NSAIDs and it is stated in the ESGE guideline that NSAIDs can be used in ERCP pancreatitis prophylaxis (14) NSAIDs are

cheap, easily available, easy to apply and low. It became the preferred drug group due to its effect profile.

When NSAIDs are tested *in vitro*, it has been detected as a potent inhibitor of PLA2 in the serum of patients with acute pancreatitis. PLA2 catalyzes the hydrolysis of phospholipids in the cell membrane by causing the production of many inflammatory mediators. Indomethacin and diclofenac PLA2 (Phospholipase A2) are the two NSAIDs with the strongest inhibitory properties (16).

Indomethacin reaches peak concentration in suppository form within 30 to 90 minutes after administration. The elimination half-life is 2 hours. After oral administration, the time to reach the peak plasma level takes 1 to 4 hours, and its bioavailability can only be 50% or 60% due to the first pass effect (17).

Therefore, the suppository form of indomethacin should be preferred in studies. We preferred rectal indomethacin in our study due to its existing features. In a study conducted in 2003, the development of ERCP pancreatitis was 6.4% in the NSAID group and 15.5% in the placebo group. It has been suggested that NSAIDs reduce the incidence of ERCP pancreatitis (18).

Immediately after this study, the effectiveness of rectal indomethacin in reducing the incidence of ERCP pancreatitis and hyperamylasemia was investigated in the study conducted by Montano Loza A et al. 150 patients were included in the study, and the patients were randomly divided into two groups. 75 patients were included in the study group and rectal indomethacin was given 2 hours before the ERCP, and the control group was given a placebo glycerin suppository two hours before the ERCP. ERCP pancreatitis developed in 4 (5.3%) of 75 patients in the study group and in 12 (16%) of 75 patients in the control group (19). Another randomized clinical trial conducted in 2007 was conducted by Sotoudehmanesh et al. 490 patients were included in the study, 245 were divided into the indomethacin group and 245 as the placebo group. It was observed that 7 out of 245 patients in the indomethacin group and 15 of 245 patients in the placebo group developed ERCP pancreatitis. As in the previous study, indomethacin was used before the procedure (20). This study also showed that the use of indomethacin before ERCP significantly reduces the risk of ERCP pancreatitis. In

a meta-analysis published in 2009, 6 controlled clinical trials were examined. 648 patients out of 13300 patients were accepted as placebo and 652 patients were accepted as NSAID group.

In the NSAID group, 271 patients received diclofenac and 381 patients received indomethacin. As a result of the analysis, it was stated that the risk of ERCP pancreatitis was very low in the NSAID group compared to the placebo group. No drug-related side effects were observed in any of the 6 clinical studies reviewed. It has been stated that the use of a dose of medication is safe, following observations that side effects such as gastrointestinal ulceration and bleeding may occur after long-term use (17). In our study, no side effects were noted in patients in the indomethacin group. In a multicenter, prospective study conducted by Elmunzer et al between 2009 and 2011, 602 high-risk patients were followed. 50 mg of indomethacin was administered rectally to 295 patients immediately after ERCP, and 307 patients in the control group were given a placebo suppository rectally, just after ERCP pancreatitis. The incidence of ERCP pancreatitis in all patients was 13.1%, in the indomethacin group, the incidence of ERCP pancreatitis was 9.2% (27/295) and 16.9% (52/307) in the control group. It has been observed that the use of rectal indomethacin significantly reduces pancreatitis compared to placebo (21).

In our study, ERCP pancreatitis was found as 3.1% in the indomethacin group compared with the control group, and ERCP pancreatitis was found as 6% in the control group. In conclusion, it was observed that the incidence of ERCP pancreatitis tended to decrease in the indomethacin group. According to our study, the use of rectal indomethacin is an effective method in ERCP pancreatitis prophylaxis in high-risk patients. The selection of all criteria used in our study by adhering to the ESGE guideline distinguishes this statistically significant result from other studies.

Another possible mechanism in the development of ERCP pancreatitis is impairment in pancreatic secretion drainage and increased pressure in the main pancreatic duct. One of the most important causes is mechanical obstruction due to edema formation or oddi sphincter spasm due to ampulla manipulation. The idea of placing a stent in the pancreatic duct

for protection from ERCP pancreatitis has also been developed to ensure continuity in pancreatic secretion flow (22). The first randomized study was conducted by Tarnasky et al. Pancreatic stent efficacy has been shown in patients with OSD (23).

As a result of randomized studies, it was recommended to be used in ERCP pancreatitis prophylaxis in the 2010 ESGE guideline (14). Although there are practical difficulties in the stent-dependent pancreatic duct, such as restenosis, stent migration, and the need for a second endoscopic procedure for stent removal, many studies have shown that ERCP reduces the incidence of pancreatitis (7,24,25).

In the study conducted by Xiao-Ping Pan et al. Between 2008 and 2009, they divided 40 high-risk patients who underwent ERCP into stent and control groups. 4 out of 20 patients in the stent group developed ERCP pancreatitis, and 14 out of 20 patients in the control group developed ERCP pancreatitis. It has been reported that stenting to the pancreatic duct is an effective protection method in ERCP pancreatitis (26). In the study of Sofuni et al., 407 patients selected as high risk; 203 in the stent group and 204 in the non-stent group. The frequency of ERCP pancreatitis was 7.9% (16/213) in the stent group, and 15.2% (31/204) in the non-stent group ($p = 0.021$) (27). In the study conducted by Yoshiaki Kawaguchi et al in 120 high-risk patients, the rate of ERCP pancreatitis was found to be 1.7% in the stent group and 13.3% in the non-stent group (28).

In our study, while ERCP pancreatitis was never seen in the stent group, it was found in 6% of the control group. Although the incidence of pancreatitis was different among the patients, this difference was not statistically significant. The fact that this rate was not statistically significant may be due to the low number of cases in the control group.

Studies have shown that both indomethacin or NSAIDs in general, and pancreatic stent are effective methods in ERCP pancreatitis prophylaxis. However, which method should we choose in which patient group? Should we use stents or NSAIDs? Is there a significant difference between the effectiveness of both methods when compared with each other? Controlled studies, in which we can find adequate answers to their questions, are still not conducted today. In

a meta-analysis published by Akbar et al in 2013, it was questioned whether rectal NSAIDs could replace prophylactic pancreatic stenting in preventing ERCP pancreatitis. It has been reported that the use of rectal NSAIDs is more effective than the use of pancreatic stents (29).

In another meta-analysis, rectal indomethacin was found to be much more effective in the group in which no prophylaxis was used in preventing ERCP pancreatitis than the group using only pancreatic stents (30).

Considering the stent complications that may be encountered in the clinic, even if it is rare, abdominal radiographs taken for stent follow-up, and a second endoscopic procedure that may be required for stent removal, the result determined in the meta-analysis may be interesting. Considering the cost of the stent and the time spent on the procedure, it will be useful to carry out further studies on this subject.

At the end of our study, the effectiveness of indomethacin against the control group was shown, but although pancreatitis did not occur in the stent group, its effectiveness against the control group could not be found to be statistically significant, probably due to the low number of cases. However, it is of great importance as it is the first controlled clinical study to compare indomethacin and stent effectiveness in the literature. In this respect, the design of our study, the criteria used in our patient selection, the time of indomethacin application, and our attention to pancreatic stent selection will guide the studies to follow.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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