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Effect of Somatostatin Plus Diclofenac in Comparison with Diclofenac Before ERCP on the Pancreatitis Double Blinded Randomized Clinical Trial

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Abstract: *Background/Aims:* Despite many therapeutic attempts, post-retrograde cholangiopancreatography pancreatitis (PEP) has remained as a major challenge in interventional endoscopy. This study aimed to compare the effects of intravenous somatostatin plus rectal diclofenac with rectal diclofenac alone in the prevention of PEP. *Methods:* In a double-blind, randomized clinical trial, patients candidate for ERCP who accepted the study protocol were enrolled in the study between 2019 and 2021. The exclusion criteria include a history of pancreatobiliary surgery, ERCP, acute pancreatitis, contraindication, sensitivity to somatostatin, diclofenac, and pregnancy. PEP was defined as abdominal pain with elevated amylase level. Patients who received intravenous somatostatin plus diclofenac and diclofenac alone enrolled in case group and control group respectively. Patients were followed up for 24h after the procedure. Data regarding demographic, clinical presentation and laboratories results were recorded and compared. *Results:* A total 186 patients were enrolled, 91 in the case group and 95 as controls. There was no statistically significant difference between the two groups in terms of PEP incidence, complications or changes in serum amylase level ($p > 0.05$). *Conclusion:* Rectal diclofenac combined with intravenous somatostatin was superior to rectal diclofenac alone to prevent PE, but without a statistically significant difference, which is probably due to the synergic effect of somatostatin and diclofenac.

Keywords: Diclofenac, ERCP, Post-ERCP Pancreatitis, Somatostatin

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has been used as a main tool for diagnostic and therapeutic approach in pancreatobiliary disorders [1]. However, despite significant advances in endoscope technology, ERCP technique has little changes over the past decades [2]. Furthermore, post-ERCP pancreatitis (PEP) is still the most common complication [3]. PEP has been reported to occur in up to 15% of patients, which can lead to serious complications such as systemic inflammatory response syndrome (SIRS), pancreatic necrosis and even mortality. Therefore, prevention of PEP has high significant and importance [4, 5].

Various protocols with different routes or time of administration have been introduced including proper hydration, intravenous somatostatin, intravenous or rectal non-steroidal anti-inflammatory drugs (NSAIDs) such as

indomethacin and diclofenac and etc. [5–7]. Rectal diclofenac in different dosages has been used successfully in some studies. Rainio M et al. [8] and Otsuka et al. [9] reported that 100 mg and 25-50 mg rectal diclofenac have significant inhibitory effects on PEP.

Furthermore, Somatostatin has been administrated in some studies, but its effect has remained inconclusive. Somatostatin is usually recommended in high-risk patients [10]. Zhao Li-na et al. evaluated the outcome of somatostatin before or after ERCP. They reported that pre-ERCP somatostatin may be effective in reducing the risk of PEP in high-risk patients [11]. Also, Wang G. et al. in a meta-analysis reported that prophylactic use of intravenous somatostatin can decrease the occurrence of PEP significantly, post-ERCP amylasemia and abdominal pain in high-risk patients [12]. Somatostatin induces the release of hormones such as growth hormone, insulin and pancreatic polypeptide, as well as internal secretion of exocrine glycine and mucosal exocrine cyclase amylase, and heparin. Also, it shows inhibitory effects on the absorption of glucose, fats and amino acids [13].

Both rectal diclofenac and intravenous somatostatin injection have been shown to prevent PEP according to some investigations, but comparing the effect of combined rectal diclofenac and intravenous somatostatin with diclofenac alone has been less paid attention.

2. Methods

2.1. Subjects

This was a double-blinded randomized clinical trial performed in the endoscopy department of Firoozgar Hospital (Iran University of Medical Sciences, Tehran, Iran). At first a total of 255 patients were candidate for ERCP entered in this study. The endoscopist, the assistant, and patients were blind to study. Inclusion criteria included a logical indication for ERCP, PEP, age ≥18 years, intact ampulla, and no contraindication or sensitivity to somatostatin or diclofenac. Exclusion criteria included age ≤18 years, pregnancy, acute pancreatitis, active bleeding, and history of sphinvterotomy, decline to participate, and contraindication to use NSAIDs, any sensitivity to somatostatin or diclofenac.

An informed written consent was obtained from all patients before enrolment. The study protocol were according the Helsinki declaration. Patients were free to leave the study at any point without affecting their routine care. Data kept confidential. The study protocol was approved by the ethics committee of IUMS (IR.IUMS.REC.1397.290).

2.2. Design and Intervention

The random block method was used for sampling. Patients were divided into two groups. Group A: received intravenous bolus somatostatin (50µg, Eumedica) plus diclofenac suppository (case group) and group B: received rectal diclofenac alone (control group). In the control group, 5 mL distilled water (SUPA Medical Co, Iran) was also administered. Patients in both groups received 100 mg diclofenac suppository ten minutes before ERCP.

Baseline demographic characteristics were obtained using a researcher-made questionnaire including the patient's age, sex, blood pressure, medical history/underlying diseases (cardiovascular diseases, cerebrivascular accidents, pancreatic cancer, other cancers, hyperlipidemia, diabetes, cholecystectomy, pregnancy/breast feeding), ERCP indications, and adverse events if present.

2.3. Data Collection

The complications and outcomes recorded during and post ERCP. Post ERCP complications including abdominal pain, pancreatitis, ampulla cannulation, perforation, bleeding and stenting in the two study groups. To evaluate abdominal pain, fever, nausa, vomiting, the serum amylase level was recorded 6 and 24 hours after ERCP in the two study groups.

2.4. Statistical Analysis

The Fisher exact test was used to evaluate the primary outcome. SPSS version 21 (SPSS Inc. Chicago, Il, The USA) was used for data analysis. A non-parametric chi-square testing was used to analyze categorical data. Students't-test or Mann-Whitney test was used to compare the two groups regarding abdominal pain, PEP and etc. P values below 0.05 were considered as statistically significant.

3. Results

3.1. Study Sample

In total 255 patients met initial screening, among which 58 patients according to exclusion criteria were excluded. So, 197 patients were enrolled in the study, in group A 98 patients received diclofenac suppository and intravenous bolus somatostatin, and in group B 99 received rectal diclofenac suppository alone. 7 and 4 patients in groups A and B didn't continue study respectively and 186 patients complete the study, see Figure 1 for screening details.

3.2. Outcomes

The 91 patients entered in the case group (40 males and 51 females). Also, 95 patients in the control group (44 males and 51 females). In addition, 14 patients (7 in each group) had a history of pancreatic cancer, 3 hyperlipidemia (1 in group A and 2 in group B) and diabetes mellitus in 26 (9 in group A and 15 in group B). The indications of ERCP were biliary duct stone in 98 (52.6%), a suspicion to malignancy in 21 (11.2%), cholangitis in 3 (1.6%) and etc. The two groups were not significantly different in terms of age, sex, lactation status, underlying diseases, cerebrovascular accidents, pancreatic cancer and other cancers, hyperlipidemia, hypertension, diabetes and cholecystectomy (Table 1).

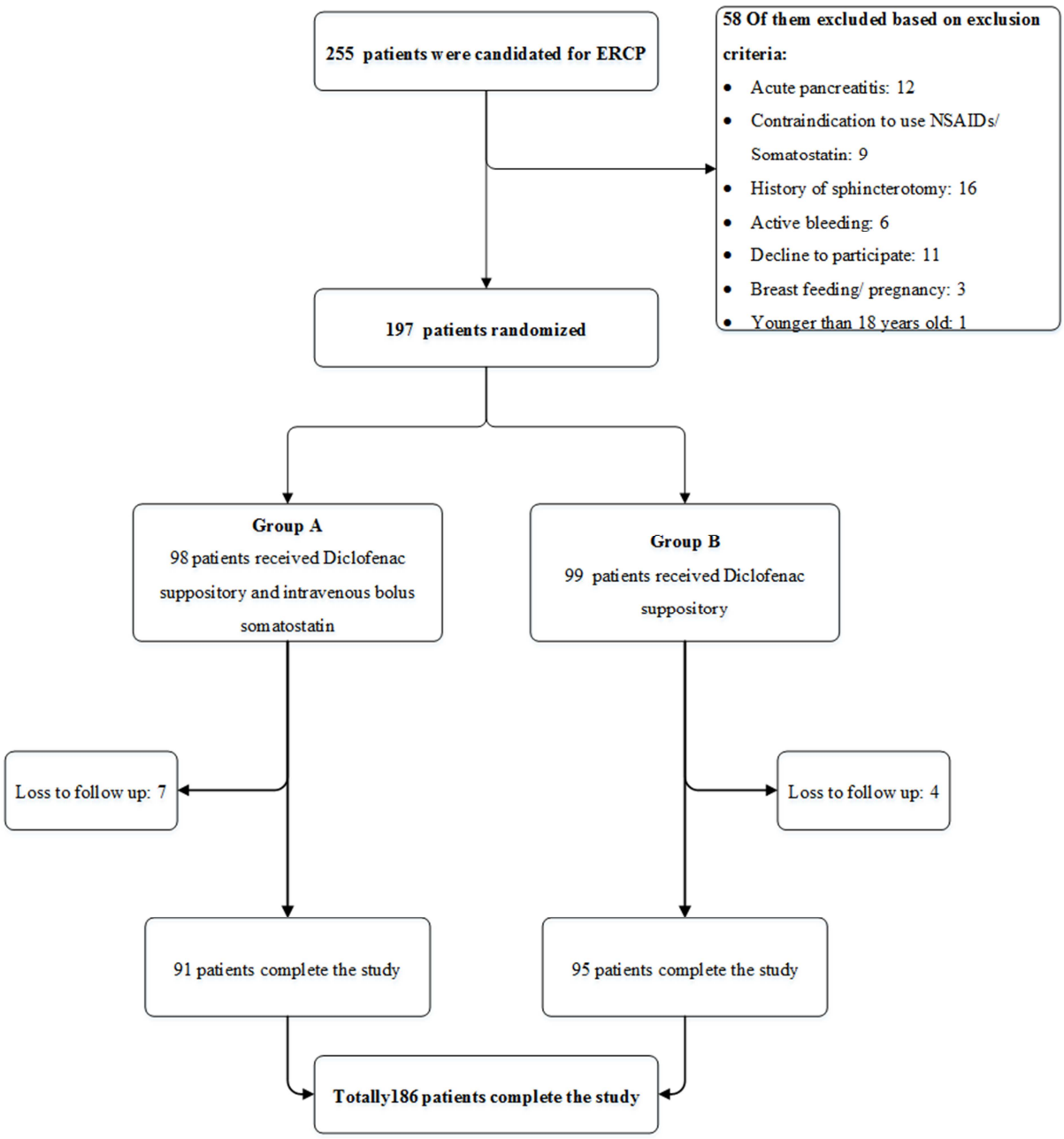

Figure 1. *Flow-chart diagram of the selection and screening of patients for inclusion in this study.*

Table 1. *Baseline demographic characteristics in the two study groups.*

Examined variables		Somatostatin + Diclofenac Suppository Group	Diclofenac suppository group	P-Value
		Number (percent)	Number (percent)	
Gender	Male	40 (44)	44 (46.3)	0.74*
	Female	51 (56)	51 (53.7)	
Age	Under 40 years	20 (22)	19 (20)	0.11*
	59-60 years	28 (30.8)	18 (18.9)	
	Over 60 years	(47.3) 43	(61.1) 58	
Breastfeeding	Yes	2 (2.2)	3 (3.2)	0.67*
	No	(97.8) 89	(96.8) 91	
Underlying diseases	Yes	(51.6) 47	58 (61.1)	0.19*
	No	(48.4) 44	37 (38.9)	
Cerebrovascular accidents	Yes	(28.6) 26	(32.6) 31	0.54*
	No	65 (71.4)	64 (47.4)	
Pancreatic cancer	Yes	7 (7.7)	7 (7.4)	0.95*
	No	84 (92.3)	87 (92.6)	

Examined variables		Somatostatin + Diclofenac Suppository Group	Diclofenac suppository group	P-Value
		Number (percent)	Number (percent)	
Other cancers	Yes	5 (5.5)	6 (6.3)	0.81*
	No	86 (94.5)	89 (93.7)	
Hyperlipidemia	Yes	1 (1.1)	2 (2.1)	0.58*
	No	90 (98.9)	73 (79.9)	
blood pressure	Yes	21 (23.1)	25 (26.3)	0.60*
	No	70 (73.7)	70 (76.9)	
Diabetes	Yes	9 (9.9)	15 (15.8)	0.23*
	No	82 (90.1)	80 (84.2)	
Cholecystectomy	Yes	24 (26.4)	13 (13.7)	0.03*
	No	67 (73.6)	82 (86.3)	
Retrograde cholangiopancreatography (ERCP) indications	Gallstones	59 (64.8)	39 (41.1)	0.01**
	Malignancy	8 (8.8)	13 (13.7)	
	Cholangitis	3 (3.3)	0 (0)	
	Pancreatitis	0 (0)	2 (1.2)	
	Pancreatitis cancer	6 (6.6)	10 (10.5)	
	Simultaneous malignancy of the gallbladder and common bile duct	16 (16.8)	16 (17)	
	Biliary sludge	3 (3.3)	10 (10.5)	
	Cholangiocarcinoma	1 (1.3)	5 (5.3)	

*Chi-square test
**Fisher's exact test

Moreover, abdominal pain was reported in 22 patients (8 in group A and 14 in group B), pancreatitis in 22 patients (8 in group A and 14 in group B) and duodenal perforation in 4 (3 in group A and 1 in group B). The prevalence of PEP was lower in the case group. Despite the fact, there was no statistically significant difference in terms of pain, PEP, ampoule cannulation, perforation and bleeding between the two groups (p>0.05) (Table 2).

Table 2. *Comparison of post-ERCP complications in the two study groups.*

Side effects		Somatostatin + Rectal Diclofenac Suppository Group	Diclofenac suppository group	P-Value
		Number (percent)	Number (percent)	
Pain	Yes	8 (8.8)	14 (14.7)	0.2
	No	83 (91.2)	81 (85.3)	
Pancreatitis	Yes	8 (8.8)	14 (14.7)	0.2
	No	83 (91.2)	81 (85.3)	
Water ampulla cannulation 1	Successful	89 (97.8)	94 (98.9)	0.53
	Unsuccessful	2 (2.2)	1 (1.1)	
Water ampulla cannulation 2	Retrograde cholangiopancreatography (ERCP) (1)	89 (97.8)	92 (96.8)	0.68
	Retrograde cholangiopancreatography (ERCP) (2)	2 (2.2)	3 (3.2)	
Perforation	Yes	3 (3.3)	1 (1.1)	0.29
	No	88 (96.7)	94 (98.9)	
Bleeding	Yes	4 (4.4)	3 (3.2)	0.65
	No	87 (95.6)	92 (96.8)	
Stenting	Yes	42 (46.2)	29 (30.5)	0.02
	No	49 (53.8)	66 (69.5)	

Moreover, the median of serum amylase level 6 hours after the intervention were 165 and 124 U/L in groups A and B, which decreased to 112 and 98 U/L after 24 hours, respectively. However, there was no statistically significant difference between the two groups in terms of amylase level and its changes from baseline to 24 hours after ERCP (p>0.05) (Table 3).

Table 3. *Comparison of serum amylase levels after retrograde cholangiopancreatography (ERCP) in the two study groups.*

Amylase levels (time)	Somatostatin + Diclofenac Suppository Group	Diclofenac suppository group	P-Value
	Median (Interquartile range)	Median (Interquartile range)	
Base level	52 (56)	49 (49)	0.3*
6 hours after retrograde cholangiopancreatography (ERCP)	165 (198)	14 (14.7)	0.05*
24 hours after retrograde cholangiopancreatography (ERCP)	112 (202)	94 (98.9)	0.15*
Changes in 6 hours after retrograde cholangiopancreatography (ERCP)	85 (134)	49 (138)	0.44*
Changes in 24 hours cholangiopancreatography (ERCP) after retrograde	51 (158.5)	30 (143)	0.42*

4. Discussion

The usefulness of ERCP has been increased dramatically over time. Despite the fact, PEP as an important complication has gained much attention in the recent years. Female patients with younger age, a past history of PEP, dysfunction of the Oddi sphincter, balloon expansion, extensive manipulation during the procedure, pancreatic sphincterotomy, operator low experience, etc. have been considered as risk factors of PEP [5, 14, 15].

In our study, the incidence of PEP was 11.8% in all the study participants. The rate of PEP in our study was in line with a systematic review on 13296 patients with an overall PEP rate of 9.7% [16]. Moreover, the study of Bai et al. showed a higher rate of ERCP complications [17], which could be due to different sample size. Moreover, five gastroenterologists work at our endoscopy center with more than 10 years' experience to perform ERCP, which is probably the reason for lower rate of PEP in our investigation.

Acute pancreatitis is the most important complication after ERCP. According to the present study, the incidence of PEP was higher in the control group compared to the experimental one, but without a statistically significant difference. Probably, intravenous injection of somatostatin reduced pancreatic secretion and consequently duct pressure and the intensity of Oddi's sphincter contraction or inhibited proteolytic enzymes or free radical release. Diclofenac was associated with an incidence of 14.7% pancreatitis in our study.

Among the drugs studied in preventing PEP, diclofenac as a nonsteroidal anti-inflammatory which inhibits prostaglandin synthesis and phospholipase A2 has attracted much attention in the recent investigations [18–21]. However, the exact role of prostaglandins in PEP is not clear [22]. In addition, NSAIDs administration in animal models of acute pancreatitis has shown conflicting results [23]. In our study, administration of 100 mg diclofenac suppository before ERCP did not significantly reduce pancreatitis incidence in patients.

Katsinelos et al. in 2012 compared the efficacy of a diclofenac and somatostatin combination with placebo in the prevention of PEP in more than five hundred patients. The overall incidence of PEP was lower in the case group compared to the controls (4.7% vs. 10.4%) [24]. This is in line with the present study regarding the rate of PEP, which highlights the value of a synergic therapy.

Furthermore, Elbaih et al. [25] compared the effects of diclofenac with somatostatin to prevent PEP. They reported that pancreatitis occurred in 8% of patients receiving diclofenac (100 mg diclofenac 30 minutes before surgery) and 12% in the somatostatin group (250 µg of somatostatin 30 minutes before surgery), without a statistically significant difference ($p > 0.05$). This is somewhat consistent with the results of our study. The lower incidence of pancreatitis in our study compared to Elbaih et al. investigation might be due to concurrent use of diclofenac and somatostatin, which had a synergistic effect to reduce PEP. Furthermore, Bai et al. compared the efficacy of a bolus before or somatostatin infusion after ERCP in 908 patients. PEP occurred in 7.5% of patients in the control group and 4.0% in the somatostatin group. They showed the efficacy of somatostatin to prevent PEP [17].

A systematic review published by Wang et al. in 2018 evaluated fifteen RCTs in adults that compared the effect of somatostatin with placebo in PEP prevention. They claimed that Somatostatin was able to reduce the incidence of PEP and abdominal pain, especially in high-risk patients but not in low-risk ones. They suggested that the optimum decision plan would be administration of a bolus somatostatin one hour before ERCP followed by an infusion for ten hours after the procedure [12].

In our study, there was no statistically significant difference between the two groups in terms of amylase level and its changes from baseline to 24 hours after ERCP ($p > 0.05$). In fact, amylase levels showed similar changing trends in both groups. Hyperamylasemia after ERCP did not persist, and returned to normal levels within 24 to 48 hours.

Considering our promising results, the use of a combination of somatostatin and diclofenac is recommended to prevent PEP in patients who are high risk for PEP. It is suggested to examine different protocols of concurrent administration of somatostatin and diclofenac or somatostatin with other NSAIDs to elucidate the best practice. We had some limitations. The study sample size in our study was not very large. Therefore, it is suggested to perform further clinical trials with larger sample size.

5. Conclusion

Rectal diclofenac combined with intravenous somatostatin was superior to rectal diclofenac alone to prevent PEP, but without a statistically significant difference, which is probably due to the synergic effect of somatostatin and diclofenac. So, probably, intravenous injection of somatostatin reduced pancreatic secretion and consequently duct pressure and the intensity of Oddi's sphincter contraction or inhibited proteolytic enzymes or free radical release and can be alternative therapeutic option in ERCP complications.

Key Message

Intravenous somatostatin no statistically significant effect on preventing pancreatitis.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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