INVESTIGATION ABOUT THE EFFECT OF SOMATOSTATIN SINGLE DOSE INTRAVENOUS INJECTION VERSUS RECTAL INDOMETHACIN IN PREVENTION OF POST ENDOSCOPIC RETROGRADE CHOLANGIO-PANCREATICOGRAPHY (ERCP) PANCREATITIS; A RANDOMIZED CLINICAL TRIAL

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Abstract

OBJECTIVES: Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is used to diagnose and treat of pancreatico-biliary disorders. Post ERCP pancreatitis (PEP) is one of the life threatening complications. This trial performed to assess the effect of indomethacin versus somatostatin for prevention of PEP.

METHODS: All 101 adult patients who referred for ERCP were enrolled in this trial. Patients randomly assigned in group A (N=51) who received indomethacin (100 mg) rectally immediately before ERCP beginning and group B (N=50) who received an intravenous injection of somatostatin (250 bolus injection + 500 infusion =750 mcg) during 2 hours. Demographic data, ERCP recording data/ findings, PEP rate, severity of PEP and drug adverse effects were recorded before and during the first day after ERCP.

RESULTS: Totally 90 patients (55.6% male) with the mean age of 61.64 ± 18.89 years completed the study. There was no statistically significant difference between the two treatment groups in respect of demographic characteristics, laboratory, clinical and ERCP data. The rate of PEP, severity of PEP, ICU admission rate, hospital stay and mortality rate were not significantly different between treatment groups (P= 0.830, P>0.999, P>0.999, P=0.511, P>0.999 respectively). No serious adverse effects were reported in this study.

CONCLUSION: There was no significant difference between treatment modalities regarding in the PEP rate, the severity of PEP, hospital staying, ICU admission rate, and mortality rate. Somatostatin may be a safe and tolerable substitute for patients who are not a good candidate for NSAIDs administration.

Keywords: Somatostatin; Indomethacin; ERCP; Pancreatitis.

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Introduction

Endoscopic Retrograde CholangioPancreatography (ERCP) is used to diagnose and treat pancreatico-biliary disease, such as common bile duct (CBD) stones, Oddi sphincter disorders, Periampullary tumors, and pancreatic duct (PD) disorders (1, 2). Common complications of ERCP include pancreatitis, bleeding, perforation, infection, and cardiovascular problems (1). Acute pancreatitis is still the most important complication after ERCP. Its incidence is reported in various reports ranging from 1% to 6% and is observed in more than half of the patients requiring sphincterotomy (3, 4). The risk of pancreatitis is reaching to 40% in high-risk cases (5, 6). There are various reports of death following pancreatitis (7, 8). The risk of post pancreatitis is related to some factors including, the patient`s related factor (patients physical performance/age/gender/body mass index/comorbidity), preventive medications, expertise of the operator, and the type of ERCP procedure (9, 10).

Previous studies reported that hyperamylasemia could be seen in 35-70% of cases after ERCP and clinical pancreatitis could be seen in 5% of diagnostic ERCPs, 7% of therapeutic ERCPs (11, 12). Patients with Sphinctor of Oddi dysfunction (SOD) and/or a history of recent pancreatitis could experience PEP up to 40%. (13, 14). The definitive mechanism for the development of Post ERCP Pancreatitis (PEP) is not known and a number of chemical, enzymatic, mechanical and hydrostatic factors appear to be involved (13). PEP leads to morbidity, mortality, and costs of $150 million per year in the United States (14). Early detection of PEP by measurement of amylase or lipase is possible 2 hours after ERCP. It seems that amylase above 276 U/L and lipase above 1000 U/L could almost always predict PEP (13). There is a great deal of enthusiasm for the introduction of a medication for PEP prevention, but few studies have been able to find a medication that is worth using extensively (13).

Due to the role of inflammatory process in the pancreatitis, NSAIDs have been recommended in many studies and medical guidelines, especially in high-risk PEP patients (13, 15). However, the NSAID adverse effects on the gastrointestinal tract and kidneys have been known to be justified by their low cost, availability, and ease of administration. The European Digestive Association recommended the use of rectal NSAIDs for PEP in 2010. An alternative PEP preventive medication was somatostatin (and its analogue octreotide) with the ability to reduce pancreatic secretion. Somatostatin was first used to prevent PEP in the 1980s. Recently a meta-analysis have assessed the effect of Somatostatin with different doses on PEP prevention. (15-17).

Two meta-analyses showed that a single rectal doses of Indomethacin and Diclofenac immediately before or after ERCP had the role in prevention of PEP without any serious adverse effects (18, 19). However the superiority of any medication in this purpose has been indistinct. The present study was designed as a randomized clinical trial to compare the effect of Indomethacin rectally and a single intravenous administration of Somatostatin on prevention of PEP.

Methods and materials

This study was a single-blind, randomized clinical trial. All adult patients (age>17 years) who referred for ERCP procedure at Rasoul Akram hospital were enrolled in this study. Exclusion criteria were any history of acute/chronic pancreatitis, cancer of ampulla/CBD/pancreas, previous sphincterotomy, allergy to the prescribed medications, lactation and pregnancy, unsuccessful ERCPs, need to pancreatic duct stent during ERCP, and those patients who didn't comply. We explain the protocol of study to all eligible patients and asked them to complete an informed written consent form. All the researchers of this study were believed in Helsinki –Ethical principles. The Ethics Committee of Iran university of medical sciences approved our study protocol (IUMS.Code: IR.IUMS.FMD.REC.1399.492).

Materials

Group A (N=51) patients who received (100 mg) indomethacin rectally immediately before the beginning of ERCP.

Group B (N=50) patients who received an intravenous injection of somatostatin (250 bolus injection + 500 infusion =750 mcg) during 2 hours.

Measurements

Demographic data including gender, age, smoking, alcohol usage, and ERCP indications were recorded. All of the ERCPs were done by 2 expert physicians in ERPC field. Information of procedure including sphinctor of Oddi dysfunction (SOD), precut/sphincterotomy method, minor papillary cannulation, and ERCP stiffness were recorded based on the Freeman Score (Grade 1: 1-5 attempts; Grade 2: 5-15 attempts, Grade 3: >15 attempts; Grade 4: unsuccessful).

The PEP rate was defined as the proportion of patients who suffered from a typical upper abdominal pain, nausea/vomiting and increased serum amylase level (at least 3 times higher than upper limit of normal value) at 6, 12, and 24 h after ERCP.

All patients diagnosed with PEP underwent ultrasound to check for parenchymal and/or extra-parenchymal pancreatitis and other complications. Severity of PEP was defined as hospital staying and clinical BISAP score beside the sonographic data.

Outcomes:

The primary outcome was the PEP rate. The secondary outcomes were the PEP severity, ICU admission rate, duration of hospital staying, mortality rate and drug adverse effects.

Statistical issue

Quantitative data were reported as mean and standard deviation and qualitative data as frequency and percentage. Chi-square test was used to analyze qualitative variables. Independent t-test was used to compare the two means and one-way ANOVA was used to compare more than two means. P value less than of 0.05 was considered significant. The data were analyzed through SPSS version 21.

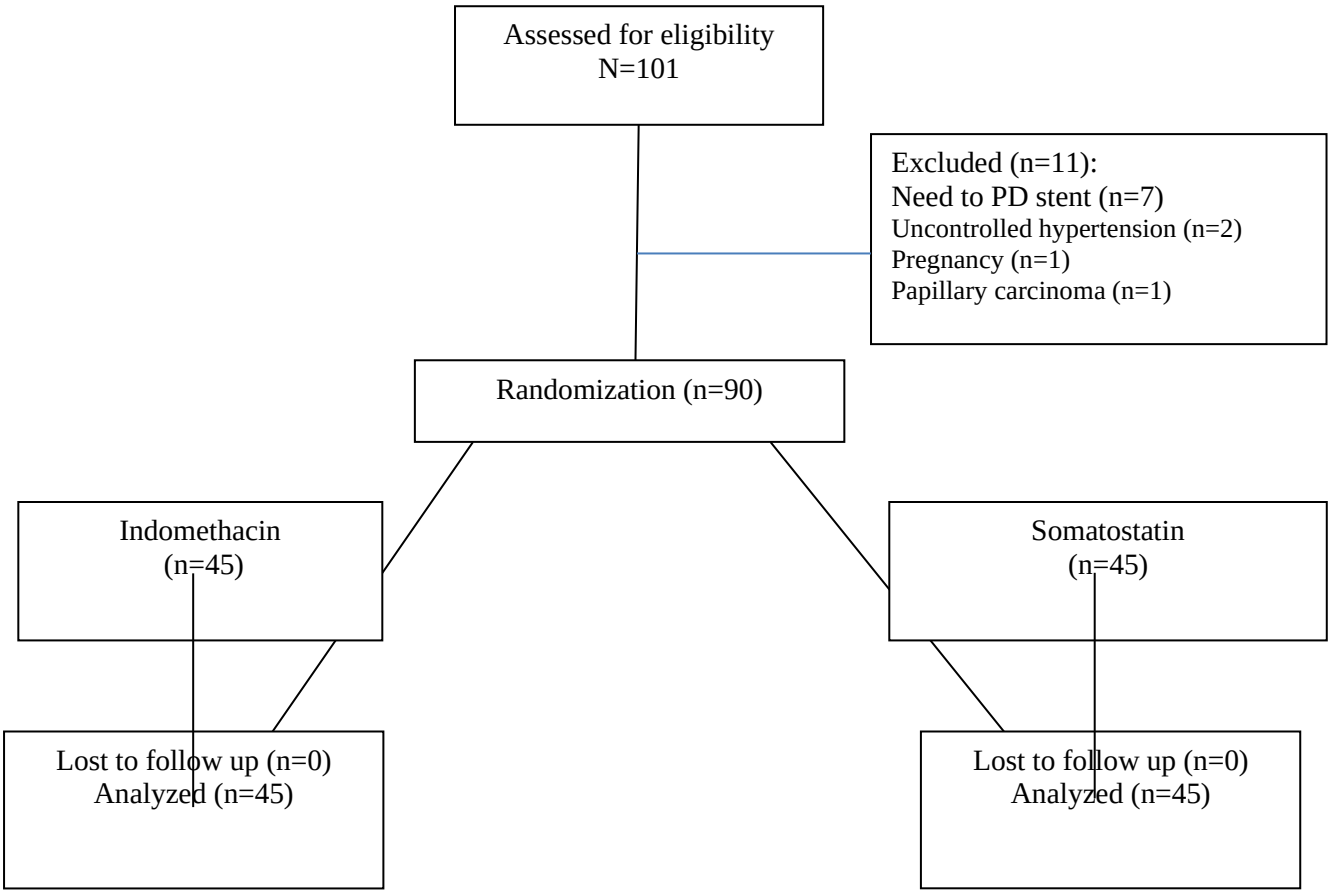

Figure.1: Participant Flow for Enrollment and Allocation to the Study Groups

Results

Totally, 90 patients completed the study. Four patients were dropped due to 1 case of pregnancy, 2 case of uncontrolled hypertension, and 1 case of papillary carcinoma (Figure.1). The mean age of the patients was 61.64 ± 18.89 years and 55.6% of them were male. The results showed that there was no statistically significant difference between treatment groups in respect of demographic characteristics (Table 1).

All laboratory and clinical findings in post-ERCP patients were compared between treatment groups. The variables were not statistically significant in both treatment groups (P> 0.05)

Table 1: Comparison of demographic characteristics between treatment groups

Variable		Group		P value
		Indomethacin	Somatostatin	
Age		62.29±19.14	61.00±18.83	0.748
Gender	Female	20(50.0)	20(50.0)	1.000
	Male	25(50.0)	25(50.0)	
Smoking	No	36(49.3)	37(50.7)	0.788
	Yes	9(52.9)	8(47.1)	
Alcohol	No	44(50.0)	44(50.0)	1.000
	Yes	1(50.0)	1(50.0)	
ERCP findings: Small stone (in CBD less than 10mm)	No	26(57.8)	22(48.9)	0.398
	Yes	19(42.2)	23(51.1)	
ERCP findings: large stone (more than 10 mm with dilated CBD more than 10 mm)	No	30(66.7)	25(55.6)	0.280
	Yes	15(33.3)	20(44.4)	
ERCP findings: Benign strictures (PSC ,immune base cholangiopathy, secondary sclerosing cholangitis)	No	39(86.7)	38(84.4)	0.292
	Yes	6(13.3)	7(15.6)	

Any ERCP events such as pancreatic duct (PD) cannulation, common bile duct (CBD) stenting, and post ERCP abdominal pain, nausea and vomiting were reported. No significant differences were seen between groups in this regard. (Table-2)

Table 2: Distribution of PD cannulation, CBD stenting, abdominal pain, nausea and vomiting after ERCP by group

Variable	Group		P Value
	Indomethacin	Somatostatin	

PD cannulation	No	34(51.5)	32(48.5)	0.634
	Yes	11(45.8)	13(54.2)	
CBD stenting	No	21(56.8)	16(43.2)	0.284
	Yes	24(45.3)	29(54.7)	
Abdominal Pain	No	32(53.3)	28(46.7)	0.371
	Yes	13(43.3)	17(56.7)	
Nausea	No	38(50.7)	37(49.3)	0.777
	Yes	7(46.7)	8(53.3)	
Vomiting	No	42(51.2)	40(48.8)	0.714
	Yes	3(37.5)	5(62.5)	

Pancreatic duct=PD, Common bile duct=CBD.

Serum amylase mean levels were measured in all patients at 6, 12 and 24 hours after ERCP. The results showed that the trend of within group changes were statistically significant (P=0.001).

Serum amylase level was not significantly different between the two treatment groups at 6, 12 and 24 hours after ERCP (P=0.383) (Table 4, Figure 1)

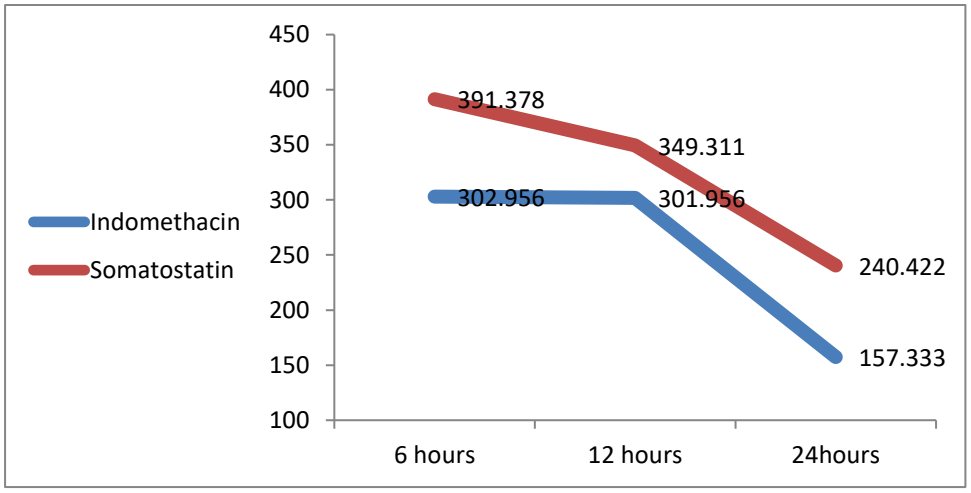

Figure 1: Mean amylase at 6, 12 and 24 hours after ERCP between Somatostatin and Indomethacin groups

Mean serum calcium level was measured among all patients at 6, 12 and 24 hours after ERCP. And its trend were compared between somatostatin and indomethacin groups in which the changes within groups were statistically non-significant (P=0.077). Serum calcium level was not significantly different between the two treatment groups at 6, 12 and 24 hours after ERCP (P=0.573) (Table 4, Figure 2).

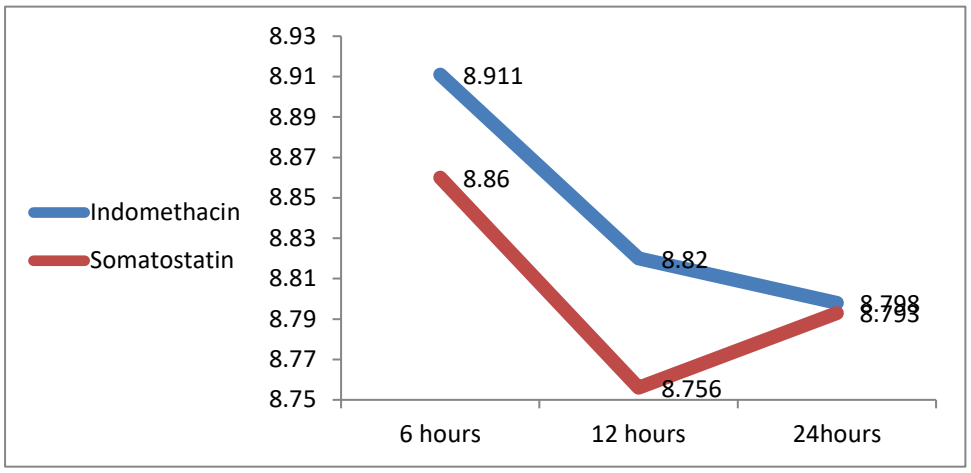

Figure 2: Mean calcium at 6, 12 and 24 hours after ERCP by groups

Mean serum glucose level was measured among all patients at 6, 12 and 24 hours after ERCP.

Serum glucose level was not significantly different between the two treatment groups at 6 and 24 hours after ERCP (p=0.599, and p=0.432, respectively). However it was significantly higher at 12 hours after ERCP in somatostatin group compared with indomethacin group (p=0.020). (Table 4, Figure 3).

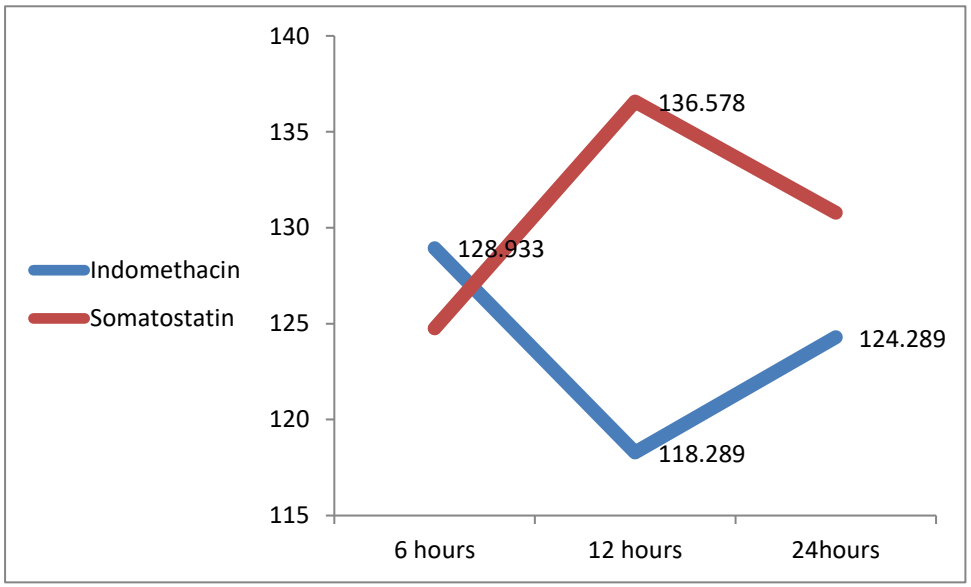

Figure 3: Mean blood sugar at 6, 12 and 24 hours after ERCP by groups

Table 4: Mean amylase, calcium and blood sugar at 6, 12 and 24 hours after ERCP between Somatostatin and Indomethacin groups

			Mean	SD	P value
Amylase	6 hours after ERCP	Indomethacin	302.956	427.7440	0.401
		Somatostatin	391.378	557.6507	

	12 hours after ERCP	Indomethacin	301.956	452.6029	0.660
		Somatostatin	349.311	559.5858	
	24 hours after ERCP	Indomethacin	157.333	215.3640	0.192
		Somatostatin	240.422	364.8246	
Calcium	6 hours after ERCP	Indomethacin	8.911	0.3944	0.590
		Somatostatin	8.860	0.4965	
	12 hours after ERCP	Indomethacin	8.820	0.3448	0.447
		Somatostatin	8.756	0.4490	
	24 hours after ERCP	Indomethacin	8.798	0.3980	0.959
		Somatostatin	8.793	0.4239	
Blood sugar	6 hours after ERCP	Indomethacin	128.933	34.0797	0.599
		Somatostatin	124.756	40.6343	
	12 hours after ERCP	Indomethacin	118.289	33.3893	0.020*
		Somatostatin	136.578	39.5598	
	24 hours after ERCP	Indomethacin	124.289	35.1242	0.432
		Somatostatin	130.778	42.5179	

*Means statistically significant.

We found no significant differences in post-ERCP pancreatitis rate, pancreatitis severity, ICU admission rate, hospital staying duration and mortality rate between the treatment groups. (P> 0.05) (Table 5, Figure 4).

Table 5: Comparison of post ERCP pancreatitis rate, pancreatitis severity, ICU admission rate, morality rate and hospital staying duration in two treatment groups

Variable		Indomethacin	Somatostatin	P value
Post ERCP pancreatitis	No	39(86.6)	40(88.8)	0.830
	Yes	6(13.3)	5(11.1)	
Pancreatitis severity	Mild	3 **(6.6)**	2(4.4)	>0.999
	Moderate	1(2.2)	2(4.4)	
	Severe	2(4.4)	1(2.2)	
ICU admission	No	43(49.4)	44(50.6)	>0.999
	Yes	2(66.7)	1(33.3)	
Mortality	No	45(100.0)	45(100.0)	>0.999
	Yes	0(0.0)	0(0.0)	
Hospital staying duration (Mean ± SD)		4.16±4.258	4.78±4.685	0.511

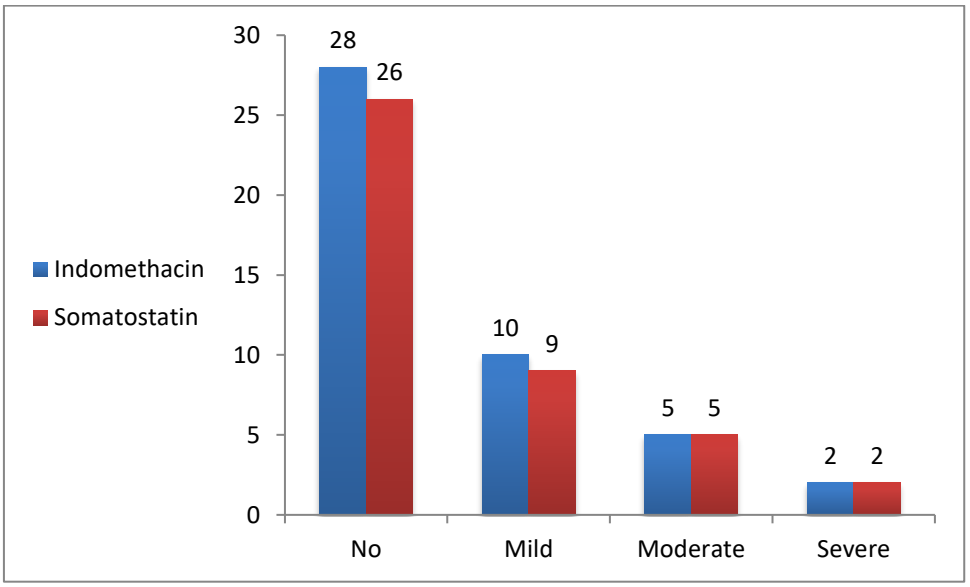

Figure 4: Comparison of pancreatitis severity by group

We did not find any serious drug adverse effects, 4 patients (2 anal irritation, 1 headache, and 1 tenesmus) in group A and 5 patients (1 flushing, 1 slow heart rate from 75 to55 beat/min, 2 diarrhea and 1 transient hypoglycemia) in group B had mild and tolerable side effects.

Discussion

Based on the results of our study, which was designed to compare the effect of indomethacin as the current preventive treatment and somatostatin as a proposed alternative method for this purpose, none of the variables of lab tests, PD cannulation, CBD stenting, abdominal pain, nausea and vomiting after ERCP were statistically significant between the two treatment groups. There were no significant differences between the groups in respect of amylase, calcium at 6, 12 and 24 hours after ERCP and serum glucose level was not significantly different between the two treatment groups at 6 and 24 hours after ERCP (p=0.599, and p=0.432, respectively) however it was significantly higher at 12 hours after ERCP in somatostatin group compared with Indomethacin group (p=0.020). It might be related to the effect of pancreatitis on increasing blood glucose and effect of somatostatin in lowering the blood sugar. No significant differences was found regarding the distribution of PEP (in somatostatin group=11.1% or 5/45 and in indomethacin group=13.3% or 6/45 patients), pancreatitis severity, ICU admission, hospital staying duration and mortality rate between the treatment groups.

Several studies have been done to find any single or combined medication to prevent PEP. Luo et al in 2019 conducted a randomized multi-center trial to compare the effects of the combination of indomethacin and epinephrine versus indomethacin plus saline in the prevention of PEP. The study concluded that the combination of rectal indomethacin with epinephrine spray increased the risk of PEP compared to indomethacin alone and the combination of these medications should not be advised for PEP prevention (20). Another meta-analysis showed topical epinephrine and rectal NSAIDs are the most effective modality in PEP prevention. The combination could act at different stages in the pathogenesis of PEP (21).

Martín et al conducted a study to evaluate the effect of somatostatin on the incidence of PEP. Finally, this study concluded that intravenous bolus administration of somatostatin following short continuous infusion was not able to reduce the PEP (22). We didn't find any superiority for somatostatin in comparison with indomethacin.

In contrast, Bai et al showed that Somatostatin is

effective and safe for the prevention of PEP and hyperamylasemia (23). The results of this study were consistent with our study.

In similar study, Elmunzer et al found that, rectal indomethacin significantly reduced the incidence of the PEP among high-risk patients (24). The result of this study was similar to our study, however, instead of high risk group, all patients were included in our study.

Two meta-analyses were designed to assess the role of somatostatin and its analog on PEP. The results were in favor and against somatostatin for solving the problem. The first study showed that PEP could be prevented with somatostatin. And so it might be able to control hyperamylasemia and abdominal pain. After seven years, the other meta-analysis with the addition of several other studies showed that somatostatin was ineffective in preventing PEP and abdominal pain (25-27). Our results compatible with the first one.

Yaghoobi et al revealed that rectal indomethacin significantly decreased the incidence of moderate and severe PEP as well as mortality, only if given before the procedure (28). Our study showed that indomethacin suppository form before the ERCP procedure had the same effect as intravenous somatostatin injection.

However, there is no general agreement on the dose and method of somatostatin consumption for example bolus injection versus infusion. A recent study showed that a combination of somatostatin plus indomethacin could be safe and could slightly reduce the hyperamylasemia and PEP rates in the intervention group compared with the control group who received just rectal indomethacin (29). One of the most useful method for PEP prevention is prophylactic pancreatic stent placement during ERCP procedure. A study showed that while indomethacin denotes an easy, cheap therapy, prophylactic pancreatic stent placement is quiet the better prevention approach for PEP (30).

Strengths of this study were head-to-head comparison of both medications and consider confounding factors in in this study via a detailed case selection. Limitations of this study were small sample size, and qualitative and subjective measurement tools for PEP severity and clinical data.

Conclusion

There were no significant differences between somatostatin and indomethacin regarding the post ERCP pancreatitis, the severity of PEP, hospitalization, ICU admission, mortality rate, and drug adverse effects. Somatostatin was safe and tolerable and could be an alternative for PEP prevention in patients who have a higher risk to develop NSAID adverse events. **Suggestion**

Further studies to assess any available modalities in the prevention of PEP as a rare fatal outcome, should be considered.

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Conflict of interest

The authors declare that there is no conflict of interest in this study.

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