

# Determination of the Effectiveness of Epinephrine Spray on the Papillae in Preventing Pancreatitis after Endoscopic Retrograde Cholangiopancreatography

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## Abstract

**Background:** As the most common complication of endoscopic retrograde cholangiopancreatography (ERCP) is acute pancreatitis, researchers have paid due attention to minimize this complication using various drugs, one of which is epinephrine. Therefore, the present study aimed at evaluating the effectiveness of epinephrine spray on the papilla in preventing post-ERCP pancreatitis (PEP).

**Materials and Methods:** The present double-blind clinical trial was performed on 164 patients undergoing ERCP. Patients in both groups received 50 mg rectal suppository as usual before ERCP. Then, during ERCP, epinephrine or normal saline was sprayed topically on the major papillae. After the intervention, patients were evaluated in terms of the incidence of PEP.

**Results:** The results of the present study revealed that the incidence of PEP in the epinephrine and control groups was 2.4% and 4.9%, respectively ( $P > 0.05$ ). There was no significant difference between the two groups in terms of the incidence of bleeding after ERCP, number of accidental pancreatic duct cannulation, the increase in vision during common bile duct cannulations, the need for precut sphincterotomy, and the number of hospitalization days ( $P > 0.05$ ). In addition, the chance of developing PEP was lower and higher in patients with higher ages (odds ratio [OR]: 0.86;  $P = 0.030$ ) and biliary sludge (OR: 4.97;  $P = 0.042$ ), respectively.

**Conclusion:** As compared with indomethacin alone (control group), it seems that the administration of epinephrine can be effective in reducing the incidence of PEP, although this relationship was not recognized to be significant in this study and only the age and the presence of sludge had a negative and positive relationship with the incidence of PEP, respectively.

**Keywords:** Cholangiopancreatography, endoscopic retrograde, epinephrine, pancreatitis

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## INTRODUCTION

Pancreatitis is still the most common complication of endoscopic retrograde cholangiopancreatography (ERCP).<sup>[1,2]</sup> Its incidence has declined slightly over the past 30 years in spite of the significant advances in endoscopic technology and ERCP ancillary equipment as well as an increased familiarity with the way of its application.<sup>[3]</sup> The incidence of post-ERCP pancreatitis (PEP) has been reported to be up to 15%–20%.<sup>[4,5]</sup>

The pathogenesis of acute pancreatitis is undecided. According to the reports, the diversion of calcium signaling pathway and reactive oxygen species may lead to the auto-digestion of the pancreas by its own proteases.<sup>[6]</sup> Although various mechanisms have been proposed with respect to PEP, papillary edema due to the manipulation during the cannulation in the endoscopic treatment has received the most attention nowadays. Papillary

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edema may temporarily block the outflow of pancreatic juice, leading to the increased pancreatic duct (PD) pressure, which eventually results in pancreatitis.<sup>[7,8]</sup>

Now, considering the proper efficiency and invigorating and promising performance of ERCP as well as its increasing application, experts put their effort into the prevention and improved management of ERCP-related complications.<sup>[6]</sup> In this regard, different approaches have been evaluated to reduce the risk and severity of PEP. For example, nonsteroidal anti-inflammatory drugs (NSAIDs), protease inhibitors, and vascular mediators such as lidocaine, nifedipine, epinephrine, and glyceryl trinitrate have also been evaluated for their preventive effects on PEP.<sup>[9-15]</sup>

A number of studies have reported that the topical administration of epinephrine has played a significant role in reducing the incidence and severity of PEP.<sup>[7,15-17]</sup> In fact, the topical administration of epinephrine causes the contraction of intestinal mucosal arterioles without affecting venules and the great reduction in the percentage of mucosal capillaries containing erythrocytes.<sup>[17]</sup> Ohashi *et al.* reported that spraying epinephrine on papillae after endoscopic balloon sphincteroplasty prevented the pancreatic damage.<sup>[18]</sup> However, some studies have not reported the significant role of epinephrine in reducing the incidence of PEP.<sup>[7]</sup> Thus, it seems that the topical administration of epinephrine in papillae may reduce papillary edema by reducing capillary permeability or loosening the sphincter of Oddi; however, further studies are required in this regard due to uncertainties in the reported findings. Therefore, the present study was performed to determine the effectiveness of epinephrine spray on the papillae in preventing the incidence of PEP.

## MATERIALS AND METHODS

The present study was a randomized, double-blind, controlled clinical trial. The study population included all patients that referred to Hajar and Ayatollah Kashani hospitals in Shahrekord, Iran for ERCP.

The sample size of 164 patients (each group consisting of 82 patients) was selected using the convenience nonprobability sampling technique at 95% confidence interval (CI) and 90% test power and considering the results of previous studies indicating the incidence of pancreatitis in the control and epinephrine groups to be equal to  $P1 = 0.15$  and  $P2 = 0.005$ , respectively.

The inclusion criteria comprised the age of 18 years or older, a healthy major papilla, the lack of deformity in papilla, and patients' consent to participate in the study. Moreover, the patients were excluded from the study and substituted with another sample in case with pancreatic stent placement, having chronic pancreatitis with an acute exacerbation, higher than normal levels of serum amylase or lipase ( $>200$  units per liter) before the intervention, bile duct cancer, previous ERCP history or papilla manipulation, and allergy to epinephrine.

After obtaining the code of ethics from Shahrekord University of Medical Sciences (IR.SKUMS.REC.1399.191), the code of clinical trial (IRCT20200825048515N35), and written consent from eligible patients, patients were randomly assigned to the intervention group (10 ml of 0.02 epinephrine spray) and the control group (10 ml of saline spray) using the random allocation software [Figure 1]. At the beginning of the study, patients' age, sex, and biliary diseases including gallstones and biliary sludge were recorded.

As usual, patients in both groups received 50 mg rectal suppository before ERCP. During ERCP, before cannulation, epinephrine (10 ml of 0.02 epinephrine spray) or normal saline was sprayed topically on the major papillae by a sprinkler catheter. The endoscopic device was completely removed from the patient after the intervention.

It should be mentioned that the ERCP operator was not aware of the contents of the syringes and the blinding conditions were observed as the solution of epinephrine and saline was colorless and odorless. In addition, all ERCPs were performed on all patients by a single operator that had sufficient skills and experience in performing ERCP considering the effect of ERCP interventions.

Then, the balloon dilation of the sphincter of Oddi, the length of hospitalization after ERCP, the incidence of bleeding and bleeding time after ERCP, the duration of common bile duct (CBD) cannulation since enface, number of accidental PD cannulation, the need for precut sphincterotomy, and the increase in vision during CBD cannulation (according to ERCP specialist' perspective) were recorded.

Moreover, both groups were evaluated for the incidence of PEP based on clinical evidence and then paraclinical findings such that the clinical manifestations of pancreatitis including new abdominal pain, exacerbation of previous abdominal pain, and prolonged length of hospital stay with at least a threefold increase in serum amylase or lipase were considered as PEP.

Finally, the collected data were entered into the SPSS software (version 26; SPSS Inc., Chicago, Ill., USA). Data were presented as frequency (percentage) or means  $\pm$  standard deviation. At the inferential statistics level, tests such as Chi-squared test and independent samples *t*-test were used to compare the findings between the two groups. Logistic regression analysis was also used to evaluate the factors affecting the incidence of PEP. The significance level of  $<0.05$  was considered in all analyses.

## RESULTS

In the present study, the epinephrine group consisted of 25 (30.5%) males and 57 (69.5%) females with a mean age of  $58.00 \pm 19.87$  years and the control group comprised 32 (39%) males and 50 (61%) females with a mean age of  $58.93 \pm 16.22$  years ( $P > 0.05$ ). In addition, biliary diseases including CBD stones and biliary sludge were identical in the two groups ( $P > 0.05$ ) [Table 1].

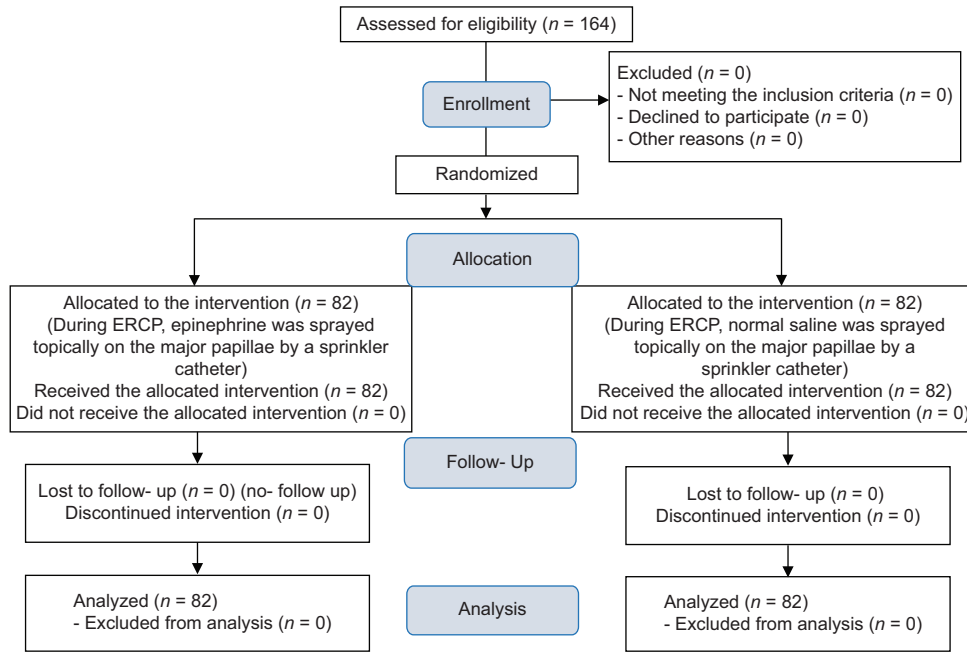


Figure 1: Consort flowchart of patients

Table 1: Demographic and clinical characteristics of patients in the two groups

Characteristics	Epinephrine group (n=82), n (%)	Control group (n=82), n (%)	P
Sex			
Male	25 (30.5)	32 (39)	0.251*
Female	57 (69.5)	50 (61)	
Age (year)	58.00±19.87	58.93±16.22	0.744**
CBD stone			
One stone	17 (20.7)	12 (14.6)	0.413*
Multiple stones	15 (18.3)	21 (25.6)	0.258*
Biliary sludge	14 (17.1)	15 (18.3)	0.838*

\*Used of Chi square test, \*\*Used of independent sample t-test. CBD: Common bile ducts

Evaluations after ERCP revealed that light and heavy bleeding was 96.3% and 3.7% in the epinephrine group and 97.5% and 2.5% in the control group, respectively ( $P > 0.05$ ). The number of accidental PD cannulation was  $<3$  times in both groups and its duration was  $105.13 \pm 20.82$  s in the epinephrine group and  $105.26 \pm 17.20$  s in the control group ( $P > 0.05$ ). In addition, 2 (2.4%) patients in the epinephrine group and 3 (3.6%) patients in the control group required precut sphincterotomy, which was not statistically significant ( $P > 0.05$ ). Moreover, although the percentage of the increase in vision during CBD cannulation in the epinephrine group was higher than that of the control group, this difference was not statistically significant (97.6% vs. 96.3%;  $P = 0.650$ ). The maximum number of hospitalization days after ERCP was 4 days for both groups ( $P > 0.05$ ) [Table 2].

The results of positive cases of amylase and lipase, the presence of clinical signs of pancreatitis, and finally, the diagnosis of PEP revealed that the percentage of the incidence of

pancreatitis was 17.1% during  $6.93 \pm 4.32$  h in the epinephrine group and was 24.4% during  $8.58 \pm 11.45$  h in the control group. Furthermore, the levels of amylase and lipase positive were, respectively, 8.5% and 6.1% in the epinephrine group and 37.3% and 11% in the control group. Finally, the percentage of the incidence of PEP was 2.4% in the epinephrine group and 4.9% in the control group and was no statistically significant different between the two groups ( $P > 0.05$ ) [Table 3].

The examination of factors affecting the incidence of PEP indicated that the control group had a higher chance of developing PEP than the epinephrine group, although this relationship was not statistically significant ( $P > 0.05$ ). In contrast, the chance of developing PEP decreased significantly with aging (OR 95% [CI]: 0.86 [0.75–0.96];  $P = 0.030$ ). In addition, patients with biliary sludge had an increased chance of PEP incidence (OR 95% [CI]: 4.97 [0.83–24.43]  $P = 0.042$ ). Although the chance of PEP incidence, the need of precut sphincterotomy, balloon dilation of the sphincter of Oddi, incidence postcannulation bleeding, and the number of accidental PD cannulation were lower and were higher in females as compared with males, statistically these factors were not significantly associated with the incidence of PEP ( $P > 0.05$ ) [Table 4].

## DISCUSSION

At present, various drugs have been administered to prevent PEP. These drugs include antisecretory agents, sphincter relaxants, anti-inflammatory agents, antioxidants, and protease inhibitors, among which indomethacin as a safe, inexpensive, available, and easy to use agent has been effective in reducing the severity of PEP.<sup>[19-21]</sup> In contrast, a number of other studies have reported that indomethacin is ineffective in preventing PEP.<sup>[22-24]</sup>

**Table 2: Evaluation of the patients' parameters and outcomes after endoscopic retrograde cholangiopancreatography in the two groups**

Variables	Epinephrine group (n=82), n (%)	Control group (n=82), n (%)	P
Length of hospitalization after ERCP (days)			
≤4	82 (100)	82 (100)	1.00*
>4	0	0	
Incidence of bleeding after ERCP			
Light	79 (96.3)	80 (97.5)	0.755*
Heavy	3 (3.7)	2 (2.5)	
Bleeding time (h after ERCP)			
≤24	3 (100)	1 (50)	0.182*
>24	0	1 (50)	
Duration of cannulation	105.13±80.82	105.26±57.20	0.992**
Number of accidental PD cannulation			
One time	1 (1.2)	0	0.405*
Two times	1 (1.2)	1 (1.2)	
Three times	2 (2.4)	1 (1.2)	
Balloon dilation of the sphincter of Oddi	8 (9.8)	15 (18.3)	0.115*
Precut sphincterotomy	2 (2.4)	3 (3.6)	0.862*
Increased vision during CBD cannulation	80 (97.6)	79 (96.3)	0.650*

\*Used of Chi square test, \*\*Used of independent sample t-test. PD: Pancreatic duct; CBD: Common bile ducts, ERCP: Endoscopic retrograde cholangiopancreatography

**Table 3: Percentage of the incidence of PEP between the two groups**

Variables	Epinephrine group (n=82), n (%)	Control group (n=82), n (%)	P
Presence of clinical signs of pancreatitis	14 (17.1)	20 (24.4)	0.248*
Duration of the incidence of signs; hours	6.93±4.32	8.58±4.45	0.201**
Amylase and lipase+	7 (8.5)	6 (7.3)	0.773*
Lipase+	5 (6.1)	9 (11)	0.264*
Incidence of PEP	2 (2.4)	4 (4.9)	0.682*

\*Used of Chi square test, \*\*Used of independent sample t-test. PEP: post-ERCP pancreatitis

**Table 4: Investigation of factors affecting the incidence of PEP**

Variables	OR	95% CI	P*
Control versus epinephrine	1.53	0.17-4.63	0.311
Age	0.86	0.75-0.96	0.030
Sex	1.98	0.06-16.60	0.694
Incidence of bleeding	0.93	0.89-1.00	0.999
Number of accidental PD cannulation	0.96	0.93-1.00	0.998
Precut sphincterotomy	0.10	0.01-11.57	0.342
Balloon dilation of the sphincter of Oddi	0.85	0.80-1.00	0.998
Biliary sludge	4.97	0.83-24.43	0.042

\*Used of logistic regression analysis, OR: Odd ratio, CI: Confidence interval, PD: Pancreatic duct, PEP: post-ERCP pancreatitis

Furthermore, according to the results of previous studies, the topical administration of epinephrine as a vasoactive mediator leads to a reduction in PEP by reducing papillary edema.<sup>[25-27]</sup>

Therefore, in the present study, all patients in both groups received 50 mg of indomethacin rectal suppository as a typical routine before ERCP. Then, during ERCP, epinephrine or normal saline was sprayed topically on the major papillae in the intervention and control groups, respectively. After the

intervention, patients were evaluated in terms of the incidence of PEP. Finally, the effectiveness of the intervention was evaluated. According to the results of the present study, the incidence of PEP was reported to be 2.4% and 4.9% in the epinephrine and control groups, respectively. In addition, it was indicated that the chance of developing PEP in the control group was higher than that of the epinephrine group; however, the observed difference was not statistically significant.

Hatami *et al.* figured out that out of 68 patients in the indomethacin group, six patients developed pancreatitis. However, only 1 (1.66%) patient developed pancreatitis in the epinephrine group. In addition, they revealed that the administration of epinephrine alone and the combination of epinephrine with indomethacin significantly reduced the risk of PEP.<sup>[6]</sup> The mentioned study was in line with our study as both studies reported the effectiveness of epinephrine on reducing the incidence of this complication, although the findings of our study were not significant.

In contrast, Kamal *et al.* indicated that there was no difference in the incidence and severity of PEP among high-risk patients receiving rectal indomethacin alone as compared with patients receiving the combination of rectal indomethacin and topical

epinephrine spray. Therefore, the use of topical epinephrine cannot be recommended to prevent PEP.<sup>[17]</sup>

The procedure of ERCP may lead to the systemic or local inflammatory response that is a precursor of PEP.<sup>[6]</sup> In addition, Phospholipases A2 (PLA2) plays a crucial role in causing this inflammatory response.<sup>[28]</sup> The mechanisms of NSAIDs in preventing PEP have been shown to involve the suppression of exogenous molecular pathways that aid in the synthesis of prostaglandins, PLA2, and the attachment of neutrophils to endothelial cells.<sup>[28]</sup> Indomethacin as an important PLA2 inhibitor has been studied in several previous studies due to its key role in preventing PEP.<sup>[19-21]</sup>

According to the observations of Matsushita *et al.*, PEP was developed in 1.1% of cases in the control group while no PEP occurred in the epinephrine group, although the mentioned results were not statistically significant.<sup>[7]</sup> One of the vital roles of epinephrine is its ability to reduce edema and PD obstruction, which is associated with the pathogenesis and progression of PEP.<sup>[4-6]</sup> In another study, Xu *et al.* reported a PEP incidence of 6.45% and 1.95% in the control and epinephrine groups, respectively.<sup>[15]</sup> Therefore, it seems that the use of epinephrine as a promising method can reduce the incidence of PEP.

In addition, the results of the present study showed that the chance of developing PEP was lower and higher in patients with older age and biliary sludge, respectively. However, other factors such as the need for precut sphincterotomy, the balloon dilation of the sphincter of Oddi, incidence postcannulation bleeding, and the number of accidental PD cannulation had nonsignificant relationship with the incidence of this complication. In contrast, females were slightly more likely to develop this complication than males.

In this regard, Kamal *et al.* reported that females under 50 years of age and difficult cannulations were the most common risk factors for PEP.<sup>[17]</sup> Another study reported that sex and age as well as amylase and lipase before ERCP were the risk factors for PEP while the procedure including PD dilation, PD cannulation, and difficult cannulation did not play a significant role in the incidence of this complication.<sup>[6]</sup>

The results of the study by Xu *et al.* also showed that female gender, bile duct diameter of <10 mm, history of cholangitis, body mass index of 24 kg/m<sup>2</sup>, and high triglycerides may be the risk factors for PEP.<sup>[15]</sup>

Regarding stents, it has been mentioned that this operation has limited generalizability due to the technical problem in placing pancreatic stents, which has made it a lower-than-optimal prevention strategy. Repeated attempts to reach the pancreas for placing the stent increased the risk of PEP (especially in cases where stent placement is unsuccessful).<sup>[29]</sup> However, in our study, patients with pancreatic stent placement were not included in the study due to increased study accuracy.

It should be noted that the patients studied in this study were all from a single center and underwent endoscopy by a single

operator using a single device, which could be regarded as the strength of the present study as some controllable factors were controlled. However, the nonevaluation of the control, epinephrine alone, and the combination of epinephrine and indomethacin groups were one of the limitations of the present study. In addition, the sample size was small. Therefore, it is essential to conduct more studies with larger sample sizes to achieve more reliable and generalizable results.

## CONCLUSION

According to the results of the present study, the incidence of PEP in the epinephrine group was lower than that of the control group, although the mentioned finding was not statistically significant. In addition, the chance of developing this complication was lower and higher in patients with older age and biliary sludge, respectively.

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### Conflicts of interest

There are no conflicts of interest.

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