The Effect of Epinephrine Sprayed on the Papilla on Prevention of Post–Endoscopic Retrograde Cholangiopancreatography Pancreatitis (PEP); a Double-Blind Randomized Control Trial

Aliasghar Alipour[1], Abbas Esmaeilzadeh[2], Omid Shadkam[3], Tahere Sarboozi-Hoseinabadi[4,5], Samaneh Kakhki[4,5]

[1] Department of Internal Medicine, 9 Dey Educational Hospital, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
[2] Department of Gastroenterology and Hepatology, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Department of Gastroenterology and Hepatology, Razavi Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[4] Department of Nursing, School of Nursing and Midwifery, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
[5] Health Sciences Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

Received: 16 Apr. 2020; Accepted: 12 Aug. 2020

Abstract- Acute pancreatitis is the most common and serious complication of Endoscopic Retrograde Cholangiopancreatography (ERCP). The use of effective medicines with low side effects should be considered in the process of RCP due to acute pancreatitis prevention. Therefore, we investigate the effects of epinephrine sprayed on the papilla in this study. This randomized clinical trial was performed on 343 patients referred to the ERCP Department of Imam Reza Hospital and Apadana Clinic, Mashhad, Iran. About 10 ml of diluted epinephrine (case group) or normal saline (control group) were sprayed on the papilla before diagnostic ERCP. Afterward, the two groups were assessed in terms of post-ERCP pancreatitis. The data were analyzed using Statistical Package for the Social Sciences (SPSS) software, version 20. The level of significance was considered to be 0.05. The overall results of this study indicated that post-ERCP pancreatitis occurred in 4.95% of the patients. Mild pancreatitis was diagnosed in five patients of the case group and three patients of the control group, respectively. Moderate pancreatitis was diagnosed in three patients of the case group and three patients of the control group. Only one patient in the case group and two patients in the control group were shown to have severe pancreatitis. Moreover, there was no significant difference between the incidence of pancreatitis between the two groups (P>0.05). With regard to the findings of this study, it appears that the topical application of epinephrine is not effective in preventing post-ERCP pancreatitis.

Acta Med Iran 2020;58(9):456-460.

Keywords: Pancreatitis; Epinephrine; Endoscopic retrograde cholangiopancreatography (ERCP)

Introduction

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a diagnostic and therapeutic method for pancreatic and biliary disorders. It can lead to several complications, such as pancreatitis, hemorrhage, gastrointestinal perforation, and cardiopulmonary events, all of which may range from mild to severe (1). Acute pancreatitis is the most common post ERCP complication, which is associated with varying rates of morbidity and mortality (2). The occurrence of post ERCP pancreatitis (PEP) depends on several factors, including the proposed method, the patient's condition, and the endoscopist's skills (3).

It is of great importance to identify the damage mechanism and clinical manifestations of PEP. Papillary edema might lead to pancreatitis due to obstruction of pancreatic juice outflow and the consequent increase in ductal pressure, which may cause serious side effects. PEP is diagnosed based on amylase and lipase serum levels being three times higher than the upper limit normal during the initial hours of admission, as well as the form of abdominal pain (4,5).

The advancements in the current decade have broadened our understanding of the ERCP treatment-related complications. Pharmacological interventions are applied to prevent pancreatitis and reduce the risk of complications (6). The prescribing medication with strong influence and a low systemic side effect can decline the possible complications after ERCP. With

Corresponding Author: S. Kakhki
Department of Nursing, School of Nursing and Midwifery, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
Tel: +98 9155186014, Fax: +98 5138591057, E-mail address: samane_ph@yahoo.com

regard to these factors, epinephrine is known as an effective agent in preventing post-ERCP pancreatitis (7). The topical application of this medication constricts the mucosal arterioles, in addition to decreasing the mucosal capillaries containing erythrocytes (8). These impacts might be attributed to the effect of epinephrine on the papillary edema by reducing the capillary permeability or loosening the sphincter of Oddi (7).

High hepatic first-pass clearance diminishes the complications of sprayed epinephrine and makes it an advisable and safe medicine (9). Recently, epinephrine is being used as an inexpensive preventive agent for post-ERCP pancreatitis and is recommended to be applied as the spray form for minimizing the incidence of this disease (10). Therefore, regarding the high risk of PEP and the importance of preventing this complication in patients undergoing ERCP, this study aimed to determine the role of epinephrine sprayed on the papilla in preventing post-ERCP pancreatitis.

Materials and Methods

This randomized, double-blind clinical trial was performed on the patients referred to the Endoscopic Retrograde Cholangiopancreatography (ERCP) Department of Imam Reza Hospital and Apadana Clinic in Mashhad, Iran. The sample study was determined by considering the means of space and hypothesis of the same study (11).

The exclusion criteria entailed the presence of 1) Renal failure, 2) Pancreatic cancer, 3) Chronic pancreatitis, 4) Cardiovascular disorders, 5) Cholangiocarcinoma, 6) bleeding disorders, 7) Peri-ampullary cancer, 8) hypertension, 9) Non-pancreatic hyperamylasemia, 10) Impaired consciousness, and 11) history of chronic alcohol consumption.

Laboratory and radiology data were recorded using a questionnaire. Firstly, a detailed history was taken from the patients referred to the ERCP Department. Afterward, they were carefully physically examined, and all the findings were recorded in the information registration form.

Immediately before ERCP, all patients received a diclofenac 100 mg suppository. At the next step, the patients were randomized in the block randomization method in two groups. The patients were not aware of randomization in case or control groups.

Patients in the case group underwent topical washing of papilla by 10 ml of diluted epinephrine solution (1/10,000), which was performed by a physician that not aware of the contains of the solution and aim of the study. In the control group, the participants received the topical washing of papilla by 10 ml normal saline.

The appearance of syringes was the same, and the syringe that contains epinephrine and normal saline were coding 1 and 2, respectively.

All the patients in both groups were analyzed prospectively for the occurrence of post-ERCP pancreatitis. The patients were monitored 24 hours after ERCP, and the serum levels of amylase and lipase were measured if the typical pancreatic abdominal pain was observed during this period. The problem was considered as post-ERCP pancreatitis in cases with the amylase and lipase serum levels three times higher than the upper limit normal (greater than 200 U/L), and the patients were followed up.

The statistical analysis was done by Statistical Package for the Social Sciences (SPSS) software, version 20. The data were analyzed by descriptive statistics method, variance analysis, t-test, and Chi-square test. The level of significance was considered to be 0.05.

The current study was performed based on the Declaration of Helsinki, and written informed consent was obtained from all the patients. All the stages were explained to the patients prior to the initiation of the study, and they were assured of the confidentiality of their personal information.

Results

Among 343 participants (164 patients were assigned to the case group and 179 patients entered the control group), the mean ages of the patients in the case group were 60.32±1.4 years, and 47.5% of them were male. Moreover, the mean age of participants in the control group was 59.45±1.32 years that most of them (45.3%) were female. There was not any significant relationship between case and control groups in terms of age (P=0.65) and gender (P=0.59).

The frequency of post-ERCP pancreatitis in the case group based on gender and age is showed in Table 1. Further, the frequency of post-ERCP pancreatitis in the control group based on gender and age is demonstrated in Table 2.

The findings also demonstrated that pancreatitis was not observed in 170 and 156 cases of the case and control groups, respectively. Five and three of the patients in the case and control groups were diagnosed with mild pancreatitis, respectively. Moderate pancreatitis was also observed in three patients in the case group and three patients in the control group. In addition, only one patient in the case group, and two patients in the control group

experienced severe pancreatitis.

It should be noted that post-ERCP pancreatitis occurred in 17 of the 343 patients (4.95%). The frequency of pancreatitis in the control group was higher compared to the case group (nine patients in the control group [5.02%] and eight patients in the case group [4.87%]). A comparison of the frequency of post-ERCP pancreatitis showed no significant differences between the two groups (*P*=0.85).

Table 1. The frequency of post-ERCP pancreatitis in the case group based on gender and age

		Post-ERCP pancreatitis					*P*
		No Pancreatitis	Mild	Moderate	Severe	Total	
Gender	**Male**	74	2	0	2	78	0.14
	Female	82	1	3	0	86	
Age	**< 30**	12	0	0	0	12	0.56
	30-59	57	1	2	2	62	
	≥ 60	87	2	1	0	90	

Table 2. The frequency of post-ERCP pancreatitis in the control group

		Post-ERCP pancreatitis					*P*
		No Pancreatitis	Mild	Moderate	Severe	Total	
Gender	**Male**	75	3	1	1	80	0.59
	Female	95	2	2	0	99	
Age	**< 30**	16	1	0	0	17	0.75
	30-59	65	2	2	1	70	
	≥ 60	89	2	1	0	92	

Discussion

The aim of this study was the evaluation of the preventive effect of epinephrine Sprayed on the Papilla compare with normal saline on Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis (PEP).

The most important finding of this study was that the epinephrine spray is not useful in preventing the incidence of pancreatitis after ERCP; however, conflicting results were reported in the literature. Some previous studies showed that the application of topical epinephrine leads to a decrease in papillary edema (12,13).

Due to the potential effect of epinephrine on reducing sphincter of Oddi pressure, it has been tested as a prophylactic agent for post-ERCP pancreatitis in different studies (9,10,12,15). According to a prospective study by Ohashi *et al*., (10), irrigation of the dilated orifice with epinephrine reduced the incidence of acute pancreatitis in patients who underwent endoscopic sphincteroplasty (ES). The influence of epinephrine on papilla was increased when ES was presented in this study; however, the level of hyperamylasemia was lower in the experiment group. Based on their findings, they suggested that epinephrine could prevent pancreatitis after ES (10). The subsequent studies (14,15), as our investigation, failed to show the efficacy of epinephrine in post-ERCP pancreatitis prevention.

In the study performed by Matsushita *et al*., (9), no significant difference was noted between the patients who received epinephrine and those of the control group regarding visualization of the bile duct and the pancreatic duct, as well as the presence of pancreatic acinarization. Their results revealed that post-ERCP pancreatitis occurred in only 1.1% of the patients, all of whom belonged to the control group. They indicated that the frequency of post-ERCP pancreatitis was not significantly lower in the patients administered epinephrine. Nonetheless, in our study, nine and eight patients in the case and control groups were diagnosed with acute post-ERCP pancreatitis, respectively.

According to Xu *et al*., (15), the frequency of post-ERCP pancreatitis was lower in the patients who applied epinephrine compared to the other patients; nevertheless, this difference was not significant. Based on this study, post-ERCP pancreatitis was observed in 4.25% of the cases. Considering the large sample size, these findings were reliable.

Kubiliun *et al*., showed that epinephrine is not useful for clinical application (16), which is similar to our findings. It was revealed in their study that rectal non-steroidal anti-inflammatory drugs (NSAIDs) are the treatment of choice, especially in patients at high risk of post-ERCP pancreatitis. Moreover, sublingual nitroglycerin, nafamostat, and somatostatin are used to prevent pancreatitis. However, all these medications require further investigations to confirm their

effectiveness. According to the latter study, topical epinephrine does not seem to be efficient for clinical usage (16).

Although the studies conducted by Matsushita (9) and Xu (15) have rejected the effectiveness of epinephrine in preventing post-ERCP pancreatitis, it should be considered that there were some limitations in their evaluations. For instance, only the patients affected with post-ERCP pancreatitis were entered into their studies. In addition, an ERCP protocol was applied in both of these studies. Also, it should be considered that the risk of post-ERCP pancreatitis is low among the patients undergoing diagnostic ERCP (17,18). However, it should be borne in mind that methodological limitations can occur in all similar clinical trials, which may lead to discrepant results.

The efficacy of pharmacological agents in preventing post-ERCP pancreatitis has been investigated in various studies; however, choosing the proper agents in clinical practice is a challenge. According to a systematic review (13), topical epinephrine has been the most efficacious agent among 16 investigated agents with an 85.9% probability of ranking. A reduction of 75% was observed in the risk of post-ERCP pancreatitis in patients who received epinephrine. Based on this study, topical epinephrine, rectal NSAIDs, and nafamostat could be considered as the top three drugs for pancreatitis prevention, followed by antibiotics, secretin, and somatostatin, respectively.

We cannot rely on the data published in the previous studies due to their limitations in assessing the effect of epinephrine on the prevention of acute pancreatitis. Pancreatic outflow obstruction caused by papillary edema plays a critical role in the incidence of post-ERCP pancreatitis; however, its pathophysiology is still inconspicuous (6,19). Some studies showed that the majority of prophylactic pancreatic stents move spontaneously in 24-48 hours (20,21); therefore, the pancreatic stents may be of limited therapeutic application. Furthermore, topical epinephrine has not been investigated in high-risk patients.

With this background, we cannot claim a definitive role for epinephrine in the prevention of post-ERCP pancreatitis, and the problem may be cured by other influential factors. Considering the contradictory results regarding the efficacy of epinephrine in post-ERCP pancreatitis prevention, topical epinephrine should be assessed in future studies.

Overall, the findings of our study demonstrated that using epinephrine after ERCP is not effective for pancreatitis prevention. Given the contradictory findings in this regard, further studies are recommended.

Acknowledgments

We would like to thank all the individuals for their cooperation in this study. This study was the result of the specialty in adult liver and gastrointestinal dissertation at Mashhad University of Medical Sciences, Mashhad, Iran.

References

1. Freeman ML. Complications of endoscopic retrograde cholangiopancreatography: avoidance and management. Gastrointest Endosc Clin N Am 2012;22:567-86.
2. Kemppainen E, Hedström J, Puolakkainen P, Halttunen J, Sainio V, Haapiainen R, et al. Increased serum trypsinogen 2 and trypsin 2-α1antitrypsin complex values identify endoscopic retrograde cholangiopancreatography-induced pancreatitis with high accuracy. Gut 1997;41:690-5.
3. Zheng M, Bai J, Yuan B, Lin F, You J, Lu M, et al. Meta-analysis of prophylactic corticosteroid use in post-ERCP pancreatitis. BMC Gastroenterol 2008;8:6.
4. Schwartz JJ, Lew RJ, Ahmad NA, Shah JN, Ginsberg GG, Kochman ML, et al. The effect of lidocaine sprayed on the major duodenal papilla on the frequency of post-ERCP pancreatitis. Gastrointest Endosc 2004;59:179-84.
5. Wehrmann T, Schmitt T, Stergiou N, Caspary W, Seifert H. Topical application of nitrates onto the papilla of Vater: manometric and clinical results. Endoscopy 2001;33:323-8.
6. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc 2004;59:845-64.
7. Igawa M, Miyaoka M, Saitoh T. Influence of topical epinephrine application on a microcirculatory disturbance in subjects with ulcerative colitis evaluated by laser Doppler flowmetry and transmission electron microscopy. Dig Endosc 2000;12:126-30.
8. Panteghini M, Pagani F, Alebardi O, Lancini G, Cestari R. Time course of changes in pancreatic enzymes, isoenzymes and, isoforms in serum after endoscopic retrograde cholangiopancreatography. Clin Chem 1991;37:1602-5.
9. Matsushita M, Takakuwa H, Shimeno N, Uchida K, Nishio A, Okazaki K. Epinephrine sprayed on the papilla for prevention of post-ERCP pancreatitis. J Gastroenterol 2009;44:71-5.
10. Ohashi A, Tamada K, Tomiyama T, Wada S, Higashizawa T, Gotoh Y, et al. Epinephrine irrigation for the prevention of pancreatic damage after endoscopic balloon sphincteroplasty. J Gastroenterol Hepatol 2001;16:568-71.

11. Edlund H. Pancreatic organogenesis--developmental mechanisms and implications for therapy. Nat Rev Genet 2002;3:524-32.
12. Nakaji K, Suzumura S, Nakae Y, Kojima K, Kumamoto M, Kozu T. Effects in the control of edema of the papilla of Vater by epinephrine saline irrigation after endoscopic retrograde cholangiopancreatography in an endoscopy center in Japan, 2003 to 2007: exploratory retrospective analysis to evaluate the characteristics of eligible patients with a focus on serum amylase levels. Intern Med 2009;48:945-52.
13. Akshintala V, Hutfless S, Colantuoni E, Kim K, Khashab M, Li T, et al. Systematic review with network meta-analysis: pharmacological prophylaxis against post-ERCP pancreatitis. Aliment Pharmacol Ther 2013;38:1325-37.
14. Dumonceau J-M, Andriulli A, Devière J, Mariani A, Rigaux J, Baron T, et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. Endoscopy 2010;42:503-15.
15. Xu LH, Qian JB, Gu LG, Qiu JW, Ge ZM, Lu F, et al. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis by epinephrine sprayed on the papilla. J Gastroenterol Hepatol 2011;26:1139-44.
16. Kubiliun NM, Adams MA, Akshintala VS, Conte ML, Cote GA, Cotton PB, et al. Evaluation of pharmacologic prevention of pancreatitis after endoscopic retrograde cholangiopancreatography: a systematic review. Clin Gastroenterol Hepatol 2015;13:1231-9.
17. Freeman M. Complications of Endoscopic Retrograde Cholangiopancreatography. Avoid Manag 2012;22:567-86.
18. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001;54:425-34.
19. Pezzilli R, Romboli E, Campana D, Corinaldesi R. Mechanisms involved in the onset of post-ERCP pancreatitis. Jop 2002;3:162-8.
20. Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. Gastrointest Endosc 2005;62:367-70.
21. Kawaguchi Y, Ogawa M, Omata F, Ito H, Shimosegawa T, Mine T. Randomized controlled trial of pancreatic stenting to prevent pancreatitis after endoscopic retrograde cholangiopancreatography. World J Gastroenterol 2012;18:1635-41.