ORIGINAL ARTICLE

The effect of prophylactic peripapillary administration of methylprednisolone in reducing the risk and severity of postendoscopic retrograde cholangiopancreatography pancreatitis: A double blind clinical trial

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Background: The most common complication of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography (ERCP) is acute pancreatitis. A number of therapeutic trials have been studied due to reduce the occurrence of postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) but many of them were unsuccessful. Periampullary corticosteroid injection was proposed to use as prophylactic agents for PEP because of its anti-inflammatory property with relative low systemic side effects. **Materials and Methods**: By conducting a double blinded clinical trial study in a single center university hospital, all patients undergoing therapeutic or diagnostic ERCP in our gastrointestinal endoscopy ward, enrolled the study. During ERCP, we randomly assigned the patients in blocks of 40 to undergo a locally injection of methylprednisolone acetate (corticosteroid group) or saline (control group) on the major papilla and prospectively evaluated the occurrence of PEP pancreatitis in each groups. Clinical and laboratory findings of acute pancreatitis were collected by means of a validated questionnaire during the procedure and before discharge. At baseline and end of the study, were compared pancreatitis prevalence and also its severity by using Chi-square and *t*-test statistics. **Results**: The frequency of moderate to severe PEP pain was not significantly between the placebo and corticosteroid receiving group (13.7% ± 3.2% vs. 9.3% ± 2.1%, respectively; $P = 0.8$). There is no significant difference in the mean concentration of lipase and amylase between corticosteroid receiving group and placebo receiving group at the first, second, and third time. In the corticosteroid receiving group, 3 patients (10.3%) while in the control group, 11 patients (11.3%) developed pancreatitis. **Conclusion:** We found no significant difference in PEP rates and also severity between the corticosteroid and placebo groups. The mean increase in serum amylase and amylase level in pancreatitis patients and the frequency of abdominal pain were not significantly higher in the placebo group. Besides, there were no cases of severe PEP pancreatitis in either group.

Key words: Corticosteroid, endoscopic retrograde cholangiopancreatography, pancreatitis, papillary edema

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INTRODUCTION

Rising of serum amylase concentration is common laboratory finding after endoscopic retrograde cholangiopancreatography (ERCP), it may occur over 75% of patients, but association of abdominal pain and hyperamylasemia termed as acute clinical pancreatitis is not so common.[1] Postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) was found to be the most frequent complication after ERCP, with an average rate of 5-7% and incidence of 3.47%.[2] In a recent systematic review of 108 randomized controlled trials, which included 13,296 patients undergoing both diagnostic and therapeutic ERCP, the overall rate of PEP was about 10%, with a mortality rate of 0.7% in the control group (placebo or no-pancreatic duct stent

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arms).[1] The exact mechanism of injury during ERCP is unknown, but they can be categorized as mechanical, chemical, enzymatic, and possibly thermal.[3] It seems that the ampullary edema may cause temporary outflow obstruction of pancreatic juice, and then increase ductal pressure, resulting in the occurrence of pancreatitis.[1,4] A number of drugs have been applied for prevention or alleviation of the PEP pancreatitis.[3,5] However, the results of these therapeutic drug interventions have been generally unsatisfactory.

A few studies referred to role of prophylactic systemic corticosteroid in the prevention of PEP because of its anti-inflammatory property and autodigestion theory of PEP pancreatitis.[6,7] On the other hand, most clinical trials did not recommend prophylactic use of corticosteroid after ERCP procedure.[7] These agents may also induce acute pancreatitis in these patients. All studies did not recommend prophylactic use of corticosteroid for ERCP.[6,7] Numerous well described side effects of corticosteroids were described either. However, we think that these side effects will be significantly diminished after a single dose and locally injection.[7] Local injection of methyl prednisolone around the papilla may reduce papillary edema. Based on this hypothesis, in a hospital-based, prospectively randomized clinical trial study we evaluated if prophylactic local injection corticosteroids around the papilla decrease the incidence of PEP pancreatitis.

MATERIALS AND METHODS

Trial registrations and organization

This clinical trial study is registered by the Iranian Clinical Trial registration Center at Iranian ministry of health and education (Trial Number: Irct-21342). This trial was conducted as a single center trial at Al-Zahra university hospital in Isfahan, Iran. The study is financially supported by the vice chancellor of research at Isfahan University of medical sciences (research proposal number at faculty of medicine: 393937).

Objectives of our study

In our study, the main objective was to determine whether locally injection of methyl prednisolone administrated after the ERCP procedure could decrease the occurrence and severity of PEP pancreatitis. Secondary aims included the assessment of the severity of PEP pancreatitis, the duration of the hospital stay, the amylase and lipase levels measured 6 and 24 h PEP, and the in hospital mortality after ERCP.

Study design and patients

This double-blind, randomized, placebo-controlled clinical trial was done between September 2014 and February 2015. All patients, undergoing therapeutic or diagnostic ERCP in the gastrointestinal endoscopy ward of Al-Zahra Hospital, Isfahan, Iran, enrolled the study. This department is one of the recognized ERCP centers in the central part of Iran. Contributing endoscopists were highly skilled operators who had been performing ERCPs for at least 5 years.

In our study, the population of the study consisted of serially enrolled patients above 18 years scheduled to undergo ERCP. Exclusion criteria's were age lower than 18, active (<2 weeks before ERCP) or chronic pancreatitis, history of previous sphincterotomy, acute renal failure, pregnancy or refusal to give informed consent. Then, all eligible patients were invited to take part in the study and had to give written informed consent before study entry.

During ERCP, we randomly assigned the patients in blocks of 40 to undergo a locally injection of methylprednisolone acetate (prednisolone group) or a block of 91 to saline (control group) (in a 1:2 drug/placebo group ratio) around the major papilla and prospectively evaluated the occurrence of PEP pancreatitis in each groups. Deciding as using of either placebo or prednisolone was performed in the ERCP Unit, whereas gastrointestinal ward physician caring for PEP patients was unaware of assigned treatments.

All patients had fasted over night before doing ERCP. The procedures were done under local and light anesthesia with a combination of meperidine, hyoscine, midazolam, and propofol as premedications and during the procedure.

Primarily, a TRUEtome Cannulating Sphincterotome (M00545150; Autotome RX 49 Cannulating Sphincterotome; Boston, Massachusetts, USA) was used for cannulation and when this failed, a tapered catheter (M00530960; Fluoro Tip ERCP Cannula Standard Tip; Boston, Massachusetts, USA) was subsequently used with a guide wire. Placebo (1 mL of 0.9% saline solution) or methylprednisolone acetate (40 mg/1 mL Depocortin®, injection, Iran-hormone, Tehran, Iran), were injected periampullary using after the endoscopic session around the papilla in the second part of duodenum. Using of sedatives, analgesics, and antibiotics were permitted as needed. Finally, some independent variables such as: Total number of trials for pancreatic duct injections, length of sphincterotomy, number of cannulations, common bile duct morphological appearance, diameter of the bile duct; using needle-knife sphincterotomy, possibility of pancreatic acinarization during contrast injection, and the presence of choledocolithiasis were recorded by endoscopist in the questionnaires. Then, the technical difficulty level of the procedure was applied according to the scores Schutz and Abbott.

Data were collected by means of a validated questionnaire during the procedure and before discharge.

Definition of postendoscopic retrograde cholangiopancreatography pancreatitis

In this study, we defined PEP as a combination of elevated serum amylase or lipase levels (more than a threefold increase of the normal upper limit) associated with at least two clinical symptoms (new or increased abdominal pain or tenderness, backache, nausea, and vomiting) after the procedure for 6-24 h or requiring hospital admission or prolongation of a planned admission.

The normal upper limit of serum amylase and lipase is 180 IU/L and 90 IU/L, respectively. The severity of pancreatitis was graded according to Cotton et al. classification and it was categorized according to the duration of therapeutic intervention for PEP.[8] Usually mild PEP needs hospitalization not for more than 2-3 days; moderate PEP required 4-10 days; and severe PEP necessitated more than 10 days, and probably more needed to surgical or intensive care unit treatment, or contributed to death. Serum amylase and lipase levels were measured before ERCP and at 6 h and 24 h after ERCP.

Statistical analysis

We used the Student's *t*-test for continuous variables and the Chi-square test for category data. Statistical significance of differences was determined by $P < 0.05$. Statistical analysis was performed by using SPSS software (version 19.0; SPS Inc., Chicago IL, USA).

Ethical considerations

All patients had been given a detailed session on the nature, choices, and probable consequences of the trial by a responsible physician and then before entry to this trial, give written informed consent from patient and one of his/her relatives.

RESULTS

Between August 2014 and February 2015, 149 ERCP procedures were performed in Al-Zahra hospital. A total of 126 patients were eligible for this study; 29 patients received local methylprednisolone injection at the end of ERCP procedure. The flowchart by which patients were enrolled and treated is illustrated in Figure 1. Table 1 shows demographic data of our patients. Two groups were similar with regard to indications for ERCP and also risk factors that might increase the possibility of PEP [Table 2]. No patients underwent precut sphincterotomy, pancreatic stent placement or using suppository nonsteroidal anti-inflammatory drugs (NSAID) at the end of the procedure.

Serum concentration of amylase and lipase were determined at baseline, 6 and 24 h after doing ERCP. Table 3 shows the mean concentration of amylases and lipase at different times. After ERCP, hyperamylasemia was observed in 7 patients (24.4%) in the corticosteroid receiving group and 40 patients (41.1%) in the control group, although the difference was not statistically significant ($P = 0.07$). Increase

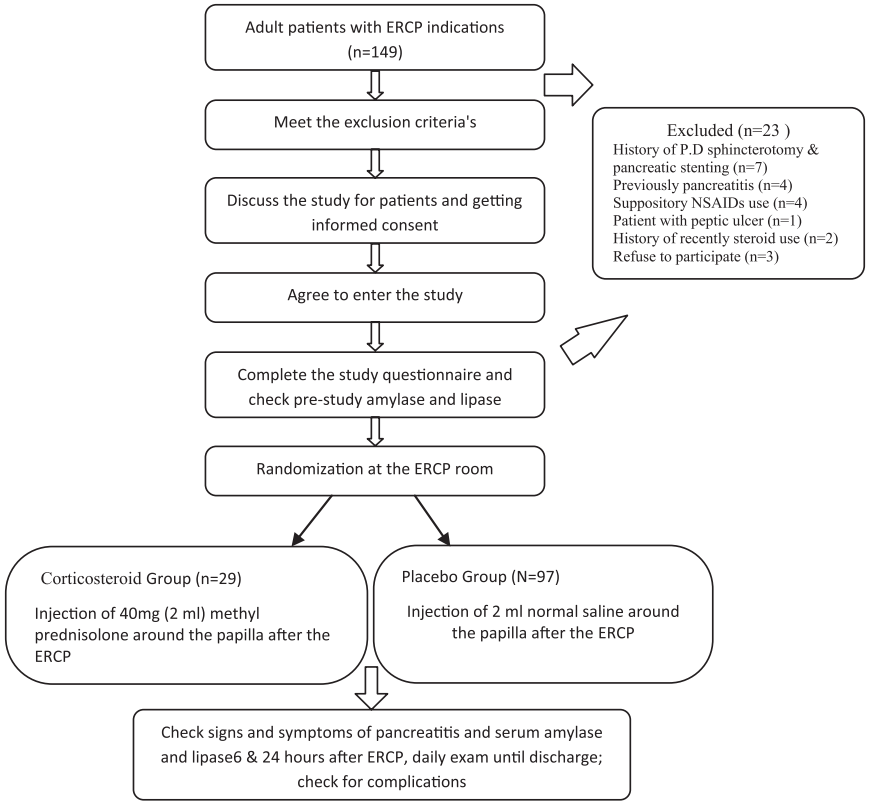

Figure 1: Treatment flow diagram in this study

in serum lipase concentration after ERCP was seen in 6 in the corticosteroid receiving group (20.7%) and 38 patients in the control group (39%) with no statistically significant difference ($P = 0.08$). Besides, there is no significant difference in the mean concentration of lipase and amylase between corticosteroid receiving group and placebo receiving group at the first, second, and third time [Table 3]. The frequency of moderate to severe PEP pain was not significantly between the placebo and corticosteroid receiving group (13.7% vs. 9.3%, respectively; $P = 0.8$).

The occurrence of PEP pancreatitis is summarized Table 4. In the corticosteroid receiving group, 3 patients (10.3%) developed pancreatitis; on the other hand, among Control Group, 11 patients (11.3%) developed pancreatitis. There was no significant difference ($P = 0.4$) in the overall incidence of PEP pancreatitis in the corticosteroid treated group when compared with control group.

DISCUSSION

The most common complication of diagnostic and therapeutic ERCP is acute pancreatitis, which occurring in 1-15% of patients.[1] During ERCP and endoscopic sphincterotomy, the pancreas is subjected to many types of potential damage including of enzymatic, infectious, allergic, mechanical, thermal, chemical, and finally hydrostatically. All above mentioned types of injury may act separately or work together to induce postprocedure pancreatitis.[3,9]

The number of ERCP performed annually in the world has increased dramatically over the past 25 years, and PEP pancreatitis occurs commonly.[9] A number of therapeutic trials have been studied due to reduce the occurrence of PEP. Several drugs were tried to find effective in the prevention of PEP pancreatitis including NSAIDS, allopurinol, glucagon, somatostatin, calcitonin, gabexate mesilate, and corticosteroid[3-6,8] but most have been disappointing.[2,9] Since the year of 1994, corticosteroids was proposed to use as prophylactic agents for PEP because of its anti-inflammatory property.[6]

Hypothetically, local injection of corticosteroid may decrease the severity of inflammation in the papillary area so it may diminish edema and subsequently lower the pancreatic ductal outflow obstruction. Our study was performed to assess the effect of locally periampullary injection of methylprednisolone after the ERCP procedure could decrease the incidence and severity of PEP pancreatitis. However, we found no significant difference in PEP rates and also severity between the corticosteroid and placebo groups. The mean increase in serum amylase and amylase level in pancreatitis patients and the frequency of abdominal pain were not significantly higher in the placebo group.

Table 1: Patient risk factors for pancreatitis by each treatment group ($n = 126$)

Risk factor	Corticosteroid group = 29	Placebo group	*P*
Number of patients	29	97	0.4
Mean age (SD)	63.7 (18.3)	62.5 (18)	0.7
Sex (male/female)	15/14	47/50	0.7
Age >60 years (%)	18 (62)	58 (60)	0.5

SD = Standard deviation

Table 2: Procedure risk factors for pancreatitis by each treatment group ($n = 126$)

Risk factors	Corticosteroid group = 29	Placebo group = 97	*P*
Moderate – difficult cannulation (%)	9 (31)	31 (32)	0.5
Mean number of pancreatic injection (SD)	1.7 (1.3)	1.8 (1.4)	0.5
Number of pancreatic injections >2 (%)	17 (58)	41 (42)	0.09
Biliary sphincterotomy (%)	25 (86)	86 (88)	0.4
Precut sphincterotomy (%)	3 (10)	18 (18.8)	0.2
Acinarization (%)	4 (14)	7 (7)	0.2
Mean CBD diameter (mm) (SD)	10.6 (2.5)	9.7 (1.6)	0.06
Mean duration time (min) (SD)	25.3 (6.5)	28.1 (7.1)	0.07

SD = Standard deviation; CBD = Common bile duct

Table 3: Amylase, lipase concentration in two groups (preexam and postexam) (mean ± SE) (IU/mL)

Amylase level	Corticosteroid group	Placebo group	*P*
Amylase serum level at baseline	161±60	248±65	0.32
Lipase serum level at baseline	83±31	116±19	0.37
Amylase serum level at 6 h after ERCP	261±92	443±72	0.12
Lipase serum level at 6 h after ERCP	171±70	207±28	0.63
Amylase serum level at 24 h after ERCP	335±42	478±69	0.45
Lipase serum level at 24 h after ERCP	231±67	288±97	0.76

SE = Standard error; ERCP = Endoscopic retrograde cholangiopancreatography

Table 4: Frequency of post-ERCP pancreatitis by each treatment group

Treatment group	Number of patients	Post-ERCP pancreatitis				*P*
		n (%)	If yes			
			Mild	Moderate	Severe	
Corticosteroid group	29	3 (10.3)	1	2	0	0.4
Placebo group	97	11 (11.3)	7	3	1	
Total	126	14 (11.1)	8	5	1	

ERCP = Endoscopic retrograde cholangiopancreatography

Besides, there were no cases of severe PEP pancreatitis in either group. To our knowledge, in spite of negative results, our study represents the first to evaluate the prophylactic role of local injection of corticosteroid in prevention of patients after ERCP. Several explanations are possible for this nonsignificant relation. First, the dose of corticosteroid is not sufficient for PEP prevention and the second is the noninflammatory cause of PEP.

However, there are several limitations to the present article. Small number of cases included the study was the main, so we could able to analyzed the role of ERCP indications separately. It is also important to emphasize that there is currently no method to quantify the risk of developing PEP based on known demographic, clinical, and procedural risk factors.[9]

CONCLUSION

In conclusion, the present study did not show any statistically significant benefit of prophylactic corticosteroid use for prevention of PEP. Therefore, the use of corticosteroids in the prophylaxis of PEP is not recommended.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

AS: contributed in the conception of the work,conducting the study including acquisition, approval of the final version of the manuscript, and agreed for all aspects of the work. MK: contributed in approval of the final version of the manuscript including acquisition. BT: contributed in the conception of the work, conducting the study including acquisition, analysis, and interpretation of data for the work, revising the draft , approval of the final version of the manuscript, and agreed for all aspects of the work.

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