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Original article

A comparative study of combination octreotide plus methylprednisolone with octreotide and placebo on prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis

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SUMMARY

This study compares the effect of the combination of octreotide plus methylprednisolone with octreotide and placebo on biochemical and clinical parameters of endoscopic retrograde cholangiopancreatograpy (ERCP) induced pancreatitis. Two hundred and twenty two patients were randomised to receive either octreotide plus methylprednisolone, octreotide or placebo. There was no difference in the median serum amylase at 2 to 24 hours after ERCP in the three groups. Clinical pancreatitis, developed in 11 patients -one in the octretode plus methylprednisolone, four in the octretode and six in the placebo groups, although there was no statistically significant difference between the three groups. This study suggests a tendency that octreotide plus methylprednisolone may protect against ERCP- induced pancreatitis.

Key words: Octreotide, Methylprednisolone, Hyperamylasemia, Pancreatitis, Endoscopic Retrograde Cholangiopancreatography.

Abbreviations: Endoscopic Retrograde Cholangiopancreatography (ERCP), Endoscopic Sphincterotomy (ES)

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INTRODUCTION

Pancreatitis is one of the major complications of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST).[1]

The reported incidence of pancreatitis following ERCP or ES ranges from 0% to as high as 39,5%.[1-3]

This variable incidence is reflective of the diverse definitions of pancreatitis used in these series and the method of data collection, i.e., prospective with frequent enzyme determinations or retrospective. It is recognized that amylase and lipase elevations are common after ERCP and ES, but concomitant clinical findings are often absent, suggesting active pancreatic inflammation.[1-4] Mild pancreatitis, probably has little significance other than the financial considerations of the short hospitalization. Although infrequent, severe pancreatitis with secondary complication of phlegmon, pseudocyst, or abscess, requiring prolonged hospitalization may occur.[1]

Octreotide has been found to have many effects on the gastrointestinal tract, including potent inhibitory effects on pancreatic exocrine secretion.[5,6] Most of the studies dealing with the prophylactic administration of octreotide to prevent post-ERCP pancreatitis, showed neither an advantage nor a disadvantage in octreotide administration.[7-21] Corticosteroids may be protective in the prevention of acute pancreatitis, altering the events in the cascade of autodigestion to pancreatitis.[22-26]

Based on the hypothesis that a combination of pro-

phylactic administration octreotide plus corticosteroids may have a synergical action on prevention of post-ERCP pancreatitis, we decided to embark on a pilot-study to examine this effect on post-ERCP pancreatitis.

METHODS

This study was designed as a controlled clinical trial, incorporating a placebo control. All patients undergoing ERCP were considered for evaluation and entry. Patients were excluded if they were under 18 or above 85 years of age, or receiving octreotide for another indication; brittle diabetes, evidence of clinical pancreatitis, pregnancy, acute myocardial infarction in the three months before the study, were also considered grounds for exclusion.

Amylase and glucose were measured and clinical asessment was performed prior to and 2 and 24h after ERCP. All procedures were performed by two experienced gastroenterologists (KP, EN), assisted by senior gastroenterologists fellows.

Octreotide 100mg and methylprednisolone 250mg was given 30 min and one hour respectively before and after ERCP as an intravenous bolus injection. Before ERCP, all patients received premedication consisting of hyoscin-n-butyl bromide (Buscopan) with midazolam and/or pethidine intravenously titrated to age and tolerance. Antibiotics (ciprofiroxacin or piperacillin) were given before and after ERCP in patients with cholangitis. All patients were hospitalised and confined to bed for at least 24 after ERCP. Fasting was maintained for a minimum of twelve hours.

Contrast medium (50% urographine in normal saline) was injected mannually in a controlled, titrated fashion under fluoroscopic control. When indicated sphincterotomy was performed. Endoprosthesis placement was performed in the conventional manner using a plastic prosthesis for the bile ducts.

The findings of the ERCP, the number of cannulations of the pancreatic duct with and without contrast, the total volume of contrast used, the degree of duct injection (primary, secondary, tertiary or acinarization), the extent of injection (head, head and body or head, body and tail), the presence of a nephrogram and sphincterotomy, if one was performed, were recorded.

In this study, post-ERCP pancreatitis was defined as severe epigastric pain and abdominal tenderness requiring narcotic analgesics and associated with serum amylase levels greater than thrice the normal upper limit, requiring hospitalization for a period longer than 24 hours after the endoscopic procedure. The white blood cell count was determined immediately before and after the study; leukocytosis was defined as a white cell count greater than 10.000 cells/mm^3.

STATISTICAL ANALYSIS

Comparison between the three groups was performed using chi-square test with Yates' correction for nominal variables and unpaired t-test for continuous variables. All analyses were performed using the Statview IIΣ+ statistcal package program in an Apple computer (Macintosh). A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Two hundred and twenty two patients were randomized to octreotide plus methylprednisolone (75), octreotide (73) and placebo (74) groups. Duodenal intubation failed in 3 patients, previous Billroth II gastrectomy (2) or severe respiratory distress during endoscopy (1) to these patients being excluded from the analysis, leaving 217 patients for the study. There was no significant difference in the gender, age (Table 1) and indications for ERCP between the three groups (Table 2). The details of the ERCP procedures are given in T able 3. The three groups were similar in terms of difficulty of bile duct cannulation, frequencies of pancreatic injection, acinarization of pancreas and therapeutic procedures, (Table 4). None of the patients had undergone sphincter of Oddi manometry, pancreatic duct sphincterotomy or other pancreatic duct manipulations. Before ERCP the baseline amylase was within the normal

Table 1. Clinical data of treatment groups

	Placebo	Octreotide	Methylprednisolone plus octreotide
Number of patients	74	73	75
Sex: Male	38	40	39
Female	36	33	36
Age (± SD) years	67.1±16	62.6±16.7	65.4±15.1

Table 2. Indication for ERCP

	Placebo	Octreotide	Octreotide plus methylprednisolone
Suspicion of pancreatic carcinoma	11	17	14
Previous acute pancreatitis	9	5	12
Biliary pain with abnormal LFTs	36	36	31
Recurrent pancreatitis	4	4	5
Epigastric pain	2	3	5

Table 3. ERCP findings

	Placebo	Octreotide	Octreotide plus methylprednisolone
Normal ducts	20	17	18
Choledocholithiasis	25	24	22
Pancreatic carcinoma	8	9	11
Benign bile duct stenosis	1	2	2
Malignant bile duct stricture	7	5	7
Sump syndrome	-	-	1
Dilated common bile duct	4	4	3
Pancreas divisum	3	4	4
Chronic pancreatitis	2	4	2
Neoplasm of papilla Vater	3	2	3
Unsuccesfull ERCP	1	2	2

Table 4. ERCP results

	Placebo	Octreotide	Octreotide plus methylprednisolone
ERCP	42	39	44
ERP only	13	13	6
ERC only	18	16	21
Main pancreatic duct only	24	25	28
Secondary pancreatic ducts	23	21	17
Acinarization	8	11	9
Papillary precut	1	1	3
Sphincterotomy	23	26	25
Biliary endoprosthesis placement	4	3	7

limit in all patients.

The frequency of hyperamylasemia at 2 and 24 hours after ERCP was equal in the three groups (Fig. 1).

Despite the fact that fewer patients in the octreotide plus methylprednisolone (1) group developed clinical pancreatitis than those in the octreotide (4) and placebo (6) group, the difference between the groups was not statistically significant (Fig. 2). Post-ERCP pancratitis was clinically mild with uncomplicated recovery in all 11 patients, although analgesia was required by all patients.

Statistical analysis was not performed for the association of post-ERCP pancreatitis with different endoscopic procedures because of the small number of patients with pancreatitis.

There were no deaths in the whole study group. Apart from a post sphincterotomy moderate bleeding there was no other complication resulting from ERCP. No serious adverse effects attributable to octreotide or methylpred-

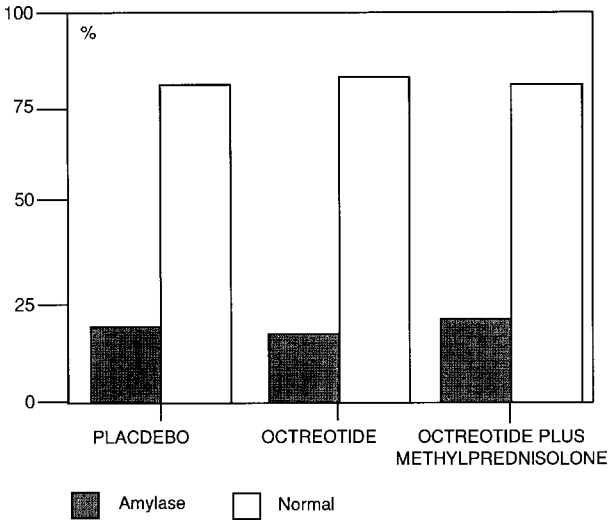

Figure 1. Median serum amylase activity at two and 24 hours after ERCP in the three groups.

Figure 2. This figure demonstrate the lower frequency, but not statistically significant (<p=0.05), of post-ERCP pancreatitis in octreotide plus methylprednisolone group (p=0.0622 VS p=0.1772 VS p=0.5543).

nisolone were observed.

DISCUSSION

Somatostatin and its long-acting cyclic analogue octreotide exert a potent inhibition of both basal and stimulated exocrine pancreatic secretion.[5,6] In a study of experimentally induced pancreatitis in rats, somatostatin and octreotide have been shown to reduce the increase of serum pancreatic enzymes.[7] Both somatostatin and octreotide have been evaluated in several clinical studies for the prevention of acute pancreatitis and elevation of serum pancreatic enzymes after ERCP.[8-21]

Considering the results of all studies dealing with the prophylactic administration of octreotide or somatostatin to prevent post-ERCP pancreatitis, it becomes clear that only a few studies, including few patients, suggest a positive effect of the drug. Most of the studies showed neither advantage nor disadvantage in octreotide or somatostatin administration. The largest study of Tulassay et al[18] showed that the prophylactic use of long acting somatostatin, does not alter the frequency of post-ERCP pancreatic injury, but it may diminish the rate of increased serum amylase levels in patients with chronic obstructive pancreatitis and also in those with an endoscopic sphincterotomy.

Corticosteroids affect a number of factors involved in the process of tissue inflammation. Corticosteroids elevated functional C_1 esterase inhibitor levels, which have shown to suppress trypsin activation within the pancreas. Once trypsin is activated it is able to activate many other enzymes such a kallikrein, thrombin, elastase and phospholipase A_2.[25]

Phospholipase A_2 itself is inhibited by a protein called lipomodulin; synthesis of which protein is induced by corticosteroids. Since corticosteroids have been shown to increase the activity of selected protease inhibitors, especially C_1 esterase inhibitor,[26] they are able, indirectly, to inhibit phospholipase A_2 activity.[25] This mechanism could, after the cascade of autodigestion, leading to pancreatitis.

The role of corticosteroids as a pancreatitis-preventing drug was evaluated in two retrospective studies and in another prospective study.

Kulkarni A, et al[22] studied 36 patients retrospectively. In his study a standard dose of 50mg hydrocortisone as an IV bolus and 100mg as an IV infusion, before and after ERCP respectively, was administered and compared to controls matched for age and sex distribution. Numbers of diagnostic and therapeutic ERCP were similar in both groups. This study showed no positive effect of a preprocedure application of corticosteroids in decreasing the incidence of pancreatitis.

A further study[24] evaluated the intrapancreatic instilation of dexamethasone in preventing sphincterotomy-induced pancreatitis in a canine model. However, this invasive method did not show a positive effect on the incidence of pancreatitis.

Weiner et al[23] evaluated the effect of corticosteroids in preventing post-ERCP pancreatitis in a retrospective study. There was a total of 824 patients with a history of iodine with oral steroids and 173 with IV steroids just before ERCP to prevent allergic reactions. These patients were studied retrospectivelly and compared with two control groups. The control groups consisted of 1000 patients undergoing ERCP during the same period (1984 to 1993).

There was no significant difference among the groups undergoing diagnostic ERCP in the incidence of pancreatitis. Comparing the patients groups who underwent therapeutic ERCP with or without sphicterotomy, the incidence of pancreatitis was significantly lower in the corticosteroid group.

An explanation for this may be that corticosteroids reduce the oedema of the papilla. This retrospective study was not controlled for the number of cannulations, the amount of injected contrast media and the radiological incidence of acinarization, which are known to be predisposing factors for post-ERCP pancreatitis.

Our study of 222 patients randomised to receive octreotide plus methylprednisolone, octreotide or placebo failed to show a statistically significant effect of octreotide plus methylprednisolone on the biochemical and clinical parameters of ERCP induced pancreatitis, although the occurrence of clinical pancreatitis was lower in the octreotide plus methylprednisolone group (Fig. 2).

Post-ERCP pancreatitis was mild with uncomplicated recovery of all patients in our study, the main sequel being a longer hospital stay. Despite the large number of patients recuited for this study, from a purely statistical standpoint, a significantly larger number of subjects would be required to eliminate a type II error in a negative study due to the low incidence of ERCP-induced clinical pancreatitis.

Overall, our study population could be considered a relatively low risk group as there was a low proportion of patients with previous acute pancreatitis and none of our patients required pancreatic duct manipulations. Post-ERCP pancreatitis is multifactorial, involving both patient and technical factors. During diagnostic ERCP and endoscopic sphincterotomy, the pancreas is subjected to many types of potential injury -mechanical[27-30] chemical,[31-35] hydrostatic,[36-40] enzymatic,[41-44] microbiological,[45-47] allergic[48-51] and thermal.[52-52]

These factors act independently or in concert to induce post-procedure pancreatitis. The potential role of each etiologic factor in the development of ERCP and endoscopic sphincterotomy induced pancreatitis is unclear. Procedure-related risk factors that have been described as important in previous retrospective studies are better identified in prospective multicenter studies. The recent study by Freeman et al,[54] including 2347 concecutive patients submitted to endoscopic sphincterotomy in multivariate analysis, identified five risk factors significantly related to pancreatitis. Two of these factors were linked to characteristics of the patients (suspected sphincter of Oddi dysfunction and younger age), and three were related to the endoscopic technique (difficult cannulation, a higher number of injections of contrast medium into the pancreatic ducts and use of precutting techniques).

Possible dysfunction of the sphincter of Oddi represented the strongest risk factor in this study: pancreatitis occurred in 19.1% of these patients, compred with 3.6% in all other indications for endoscopic sphincterotomy. The endoscopist's technical skill and training (more than one endoscopic sphincterotomy procedure per week), although allowing a less traumatic procedure was not associated with a lower incidence of pancreatitis (5.5% vs 5.3%). This seems to confirm that post-ERCP/ES pancreatitis is an unforesen event, even if it is partially explained by the higher numbers of patients with suspected sphincter of Oddi dysfunction undergoing ES at the more experienced centers. In a prospective study, Tarnasky et al[55] described a high rate of post-ERCP pancreatitis (57%) in patients with both pancreatic sphincter of Oddi hypertension and small-diameter bile duct (<5mm), supporting previous data.

The lack of the usual clinical and technical risk factors in most patients developing post ERCP/ES pancreatitis indicates how unpredictable post-procedural pancreatitis is.

In summary, our prospective study has demonstrated that administration of octreotide plus methylprednisolone prior to therapeutic or diagnostic ERCP procedure results in a decreased, but not statistically significant, incidence of post-ERCP pancreatitis. A study with a higher number of patients is necessary to assess the tendency of octreotide plus methylprednisolone to prevent pancreatic damage due to endoscopic and therapeutic maneuvers involving the papilla of Vater.

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