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Single dose of intravenous hydrocortison for preventing hyperamylasemia after Endoscopic retrograde cholangiopancreatography

Masoud Shirmohammadi, Mohammad H Somi, Morteza Ghojazadeh and Amin Sadrazar*

Department of Gastroenterology, Liver and Gastrointestinal Disease Research Center, Tabriz University of Medical Sciences, Iran

Corresponding author

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A B S T R A C T

Acute pancreatitis and Hyperamylasemia is still an important complications after Endoscopic retrograde cholangiopancreatography (ERCP). Some studies have focused on the effect of nonsteroidal anti-inflammatory drugs versus other studies dispute. The aim of this study was determine effect of intravenous hydrocortison for preventing post-ERCP hyperamylasemia. This double blind clinical traial was conducted in Imam Reza hospital, Tabriz University of medical sciences. Patients were randomly assigned to receive either intravenous hydrocirtiosone or normal saline 30 minutes before ERCP. Level of post-ERCP hyperamylasemia was assessed and compared between the two groups. From the total of 125, 100 patients were eligible and participated (66% females). Mean age was 59.06 ± 16.03 for experimental group and 57.98 ± 16.67 for controls (P=0.724). Mean CBD diameter was 11.98 ± 5.14 mm in the experimental group and 11.43 ± 5.14 in controls (P=0.561). mean amylase level increased from 58.66 ± 34.78 to 65.62 ± 41.16 (P=0.363) in patients receiving hydrocortisone and from 145.34 ± 282.25 to 288.94 ± 594.12(P=0.127) in controls. Post ERCP hyperamylasemia (amylase > 200) was found in 7 patients of case group and 10 case control group (P=0.424). A single dose of hydrocortisone 30 minutes before ERCP was ineffective in reducing hypramylasemia.

Introduction

Clinical symptoms of acute pancreatitis may range form mild attacks of abdominal pain to severe illness along with hypotension, metabolic disorders, sepsis, fluid accumulation in the third space, organ failure and death. Pancreatitis and hyperamylasemia are still known as the most important complications after Endoscopic retrograde cholangiopancreatography (ERCP). The occurrence of is reported to be

between 1 to 6% by different studies and occurs in more than half the patients when sphincterotomy is required. The rate of post-ERCP pancreatitis reaches 40% in high-risk individuals (1-2). Post-ERCP pancreatitis may be associated with technical issues or patient related factors (3) with the trauma caused by canalization as the most important (4-5). Blood pressure drop during ERCP and obesity are also among the effective but not determining factors (7-8).

Pharmaceutical methods for preventing post-ERCP pancreatitis and hyperamylasemia have been the subject of numerous studies but most of them were disappointed. A large number of studies have evaluated somatostatin and octreotide, which reduce pancreas secretions and urethral pressure (9-11). The only effective prophylactic pharmacologic treatment to date, seem to be the rectal indomethacin or diclofenac. The meta-analysis by Sotoudemanesh et al. and Elmunzer et al. report that indomethacin and rectal diclofenac may reduce the incidence and severity of acute pancreatitis after ERCP (12-13). Conversly oral diclofenac has been ineffective in high risk patients for post-ERCP pancreatitis (15).

Results of studies on Nifedipine and Alluporinol were not satisfactory (16-17). A single dose of IL-10 as an anti-inflammatory agent which could inhibit pancreas exocrine secretions reduced the occurrence of pancreatitis and hyperamylasemia when administered thirty minutes before surgery (17).

Unsuccessful efforts has been made by Semapimod which is another a cytokine inhibitor (18-19). Corticosteroid may reduce inflammatory response during initial steps of acute pancreatitis which is a process of autodigestion. After promising early results for corticosteroids, some controlled trials did not replicate their effectiveness and studies could not reach a clear conclusion (20).

Differences of trials may be a result of subtle methodologial differences as well. The standard threshold level of serum amylase within the 24 hours after ERCP (three times the upper limit of normal) has been introduced as the fudametal factor for diagnosing post_ERCP pnacreatitis by European society of Gastrointestinal endoscopy (21). As physical examination and the reported pain may be biased, this will be the only objective measure. Based on feasibility of using corticosteroids and the contradictory reports anout its usefulness, the aim of present study was to evalute prophylastic effect of a single dose of hydrocortisone on post-ERCP hyperamylasemia as the most important factor in detecting pancreatitis.

Materials and Methods

This double blind randomized clinical trial was carried out in Imam Reza hospital, Tabriz University of medical sciences. The protocol was in accordance with the principles of the Declaration of Helsinki and approved by the institutional review board of Tabriz University of medical sciences. This trial is registered with the Iranian Clinical Trials Registry (IRCT201410236388N6). The whole procedure was explained to selected patients as well as the current standard of care and potential risks and benefits of the intervention and a written consent was obtained from all. Eligible patienst were then randomly assigned to two group by a non-investigator staff using a schedule generated by RandList.

The study population included all of the patients referred to the endoscopy unit of

Imam Reza Hospital who were subjected to ERCP based on the relevant indications. These indications included choledocholithiasis, biliary obstruction and dilated common bile duct (CBD). Patients with gallstone pancreatitis and active cholangitis were not included because of the required particular care. Other exclusion criteria included diabetes mellitus, pregnancy, corticosteroid use within two weeks before the study and chronic pancreatitis.

Each patient in the experimental group received one intravenous dose of 100 mg hydrocortisone 30 minutes before ERCP while patients in the control group received normal saline. The level of amylase in both groups was measured initially and two hours after ERCP. The patients were observed for 24 hours after ERCP and examined for development or intensification of epigastric pain as the standard care of the hospital.

Considering the prevalence of post-ERCP hyperamylasemia (P=12%) the minimum size of each group was calculated to be 40.5 patients with a confidence interval of 95% and power of 90%. Allowing for drop outs, 50 participants were selected for each group. Data was analyzed by SPSS-17 statistical software. Results are expressed as percentage and mean ± SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤0.05 was considered statistically significant.

Results and Discussion

From the total of 125, 100 patients were eligible and participated. The baseline characteristics of two groups are presented in table 1. The two groups were matched in terms of age, gender and level of amylase prior to ERCP.

The mean level of amylase after ERCP was not different between groups. It was 145.34±282.25 in patients receiving hydrocirtisone and 288.94±594.12 in the controls (P=0.127). Incidence of Post-ERCP hyperamylasemia (amylase over 200) was not different between group either. It was detected in 7 patients (14.0%) receiving hydrocortisone and 10 controls(20.0%) (P=0.424). There was a direct significant linear relationship between the patients' primary amylase and the secondary amylase value (r=0.257 and P=0.010) and post-ERCP amylase level was higher in patients who had a higher initial amylase level.

Level of amylase was higher in younger patients and there was a reverse significant linear relationship between the patients' age and the primary amylase value (r=-0.241 and P=0.016), the secondary amylase (r=-0.302 and P=0.002), and the amount of amylase change (r=-0.287 and P=0.004).

Described factors are also compared between males and females. As described in table 2, serum level of amylase after ERCP was higher in females as was the degree of increase in amylase level.

This study aimed to evaluated preventive effect of a single dose of hydrocintirsone on reducing the incidence of post-ERCP hyperamilasemia in a double blind setting. The results added to the evidence that a single dose of hydrocintirsone given 30 minutes before ERCP is ineffective for preventing post-ERCP. Even though the incidence of hyperamylasemia in patients receiving hydrocortisone was lower than controls, the difference was not statistically significant. This was the first study in our population.

Table.1 Baseline characteristics of enrolled patients

	Hydricortisone (n=50)	Control (n=50)	p
Male/Female	19/31	15/35	0.398
Age (mean ±SD)	59.06±16.03	57.98±16.67	P=0.724
CBD* diameter (millimeter)	11.98±5.14	11.43±4.28	0.561
Indication:			
Choleducolithiasis	36	32	0.391
Dilated CBD	14	18	
ERCP for the second time	8	11	0.444
Level of amylase	58.66±34.78	65.62±41.16	0.363

*: common bile duct.

Table.2 Gender differences

	Male	Female	P
Age	60.74 ± 13.92	57.38 ± 17.37	0.231
CBD diameter	11.36 ± 4.85	11.88 ± 4.67	0.603
Primary Amylase	61.06 ± 41.37	62.70 ± 36.58	0.840
Secondary Amylase	109.50 ± 114.78	272.59 ± 564.10	0.027
Amylase Changes	48.44 ± 101.09	209.89 ± 555.13	0.025

While ERCP is one of the foundations of diagnosing and the treatment of hepatobiliary and pancreatic diseases, patients may face higher rate of major complications from which pancreatitis is the most important one. An effective method to prevent this complication is still a challenge for researchers. Practicability of administration of corticosteroids leaded to several researches based on this approach but results are inconclusive. As prolonged administration in the post-procedure period would not be required and the medication is economical, corticosteriods seem as an ideal pharmacological prevention of post-ERCP pancreatitis.

Weiner et al. (1999) reported that administration of corticosteroids prior to ERCP results in a decreased incidence of post-ERCP pancreatiti (22). These results were obtained from 824 patients who received hydrocortisone because of a history of iodine sensitivity. Additionally, Kwannzonn and colleagues conducted a randomized clinical trial and had a similar experience on 120 patients. They reported that corticosteroid before ERCP causes a decrease in the incidence of pancreatitis and hyperamylasemia in patients undergoing ERCP (6.67% as opposed to 11.86%, P=0.031) (23).

However these results were not replicated in other trials (24-27) and in a meta-analysis by Bai et al. , 2008, it was stated that use of systemic corticosteroid before ERCP does not decrease the incidence of hyperamylasemia and pancreatitis after ERCP (24). In accordance with these reports, the incidence of hyperamylasemia was 14% in the patients receiving

corticosteroid in our study, and 20% in the placebo group, but there was not a significant difference between these two groups.

Patient related factors could also affect occurrence of post ERCP pancreatitis. In a study conducted by Perney and colleagues on patients undergoing ERCP, they stated that the female gender is a risk factor that increases the incidence of hyperamylasemia and pancreatitis after ERCP (28). In our study, as described above, the incidence of hyperamylasemia was 8% in the female patients receiving corticosteroid and 14% in female controls, which suggests the high incidence of hyperamylasemia in female patients as compared with that in males. But as the two groups were matched in terms of gender, as well as number of young females this could not bias the results. Technique related factors might also affect the results. This trial included patients undergoing theraputic procedures (mostly biliary diseases) and results should not be generalized on other conditions.

In conclusion a single dose of hydrocortisone given 30 minutes before ERCP could not make a significant decrease in incidence of hyperamylasemia (amylase over 200) in patients.

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