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Original Research Article

A study on ulinastatin in preventing post ERCP pancreatitis

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ABSTRACT

Background: Pancreatitis remains the major complication of endoscopic retrograde cholangiopancreatography (ERCP), and hyperenzymemia after ERCP is common. Ulinastatin, a protease inhibitor, has proved effective in the treatment of acute pancreatitis. The aim of this study was to assess the efficacy of ulinastatin, compare to placebo study to assess the incidence of complication due to ERCPP procedure.
Methods: In this study a randomized placebo controlled trial, patients undergoing the first ERCP was randomizing to receive ulinastatin one lakh units (or) placebo by intravenous infusion one hour before ERCP for ten minutes duration. Clinical evaluation, serum amylase, ware analysed before the procedure 4 hours and 24 hours after the procedure.
Results: Total of 46 patients were enrolled (23 in ulinastatin and 23 in placebo group). The incidence of Hyper enzymemia is lower in ulinastatin group (13 %) than in placebo group (30.4%).
Conclusions: Prophylactic short-term administration of ulinastatin one lakh units intravenously, one hour before ERCP procedure is effective when compared to placebo infusion.

Keywords: Enzymemia, ERCP, Pancreatitis, Ulinastatin

INTRODUCTION

ERCP is widely performed for the diagnosis and management of various pancreaticobiliary diseases. Early complications after ERCP include acute pancreatitis, bleeding, perforation, and infection (cholangitis and cholecystitis) Of these ERCP related complications, pancreatitis remain the most common with a reported incidence of 2 to 15% in multicenter prospective studies.[1-5] Most cases of post ERCP pancreatitis are mild, showing complete recovery in a few days. After severe ERCP related Pancreatitis however., secondary consequences (e.g. pancreatic pseudocyst and abscess) and multiorgan failure frequently develop: surgical intervention and prolonged hospital stay are usually required, and eventually the patient dies. In a reported series of 7,869 patients undergoing diagnostic or therapeutic ERCP, 3 patients (0.04%) died from severe post-ERCP Pancreatitis. The prevention of post ERCP pancreatitis has been a never-ending challenge ever since ERCP was introduced in clinical settings in the 1970s. The exact pathogenesis of post-ERCP pancreatitis has remained unclear but diverse factors, which include mechanical injury, hydrostatic injury, chemical and allergic injury. enzymatic Injury, infection and thermal injury have been postulated as causes of post ERCP pancreatitis.[6-8] Many pharmacologic agents of different types he been used to prevent post ERCP pancreatitis on the assumption that they Pharmacologically inhibit one or more of the aforementioned factors associated with pancreatic damage. Irrespective of the etiology of acute pancreatitis, the activation of proteases enzymes starting with trypsinogen activation to trypsin in pancreatic acinar cells, has been considered to play an Initial role in the

pathogenesis of pancreatitis. Trypsin would subsequently trigger the activation of other enzymes and the inflammatory cascade. Based on this pathogenesis, antiproteases, which have been used to manage acute pancreatitis in routine clinical settings in some countries, may be theoretically useful for preventing pancreatitis after ERCP. Since we know the timing for the development of pancreatitis after ERCP adequate doses of antiproteases could be administered prophylactically. Currently, three anti proteases aprotinin gabexate, and ulinastatin, have been evaluated for their prophylactic efficacy against post ERCP pancreatitis in prospective randomized controlled trials (RCTs).[9] Since aprotinin was found to be ineffective in 1977 and no further RCTS of aprotinin have been conducted, this review will focus on the efficacy of gabexate and ulinastatin regarding the prevention of post ERCP pancreatitis.

Ulinastatin is an intrinsic trypsin inhibitor extracted and purified from human urine which inhibits various enzymes such as α-chymotrypsin lipase, amylase, elastase, and carboxylase. Ulinastatin has been used clinically to treat acute Pancreatitis.[10] Furthermore, this agent has been given routinely in many Japanese institutions as a prophylactic to prevent post-ERCP pancreatitis. The main advantages of Ulinastatin over gabexate are as follows: a) The Inhibitory effect of Ulinastatin on pancreatic enzymes is stronger than that of gabexate, b) In various experimental models of Pancreatitis, suppression of the development and progression of pancreatitis is more potent in the Ulinastatin group than in the gabexate group,[11,12] C) And since its serum half-life is relatively long (35 minutes), Ulinastatin can be administered by bolus injection in contrast to gabexate. Ulinastatin would be superior to gabexate with regard to clinical use if a short-term administration of Ulinastatin reduced the incidence and severity of pancreatitis after ERCP. In 1990, a Japanese non-randomized study revealed that a bolus injection of Ulinastatin prevented pancreatitis damage after ERCP more effectively than continuous injection.

METHODS

This study was conducted in SREE Balaji medical college and hospital, chromepet from June 2014 to June 2015. Pancreatitis over 18yrs of age undergoing ERCP were enrolled in this study. Patients with acute pancreatitis, hypersensitivity to ulinastatin, pregnant females and severe chronic pancreatitis were excluded from the study. Written informed consent were obtained from the patients.

In this single center randomized double placebo controlled trial, patients undergoing ERCP were randomized to receive Ulinastatin, 1 lakh units dissolved in 100ml normal saline or placebo infusions 100 ml of normal saline were administrated intravenously 1 hour before ERCP for 10 mins. Serum amylase were analyzed before 4 and 24 hrs. after the procedure.

After the procedure., the difficulty in cannulation, whether precut was done or not, whether pancreatic duct cannulation was done was noted.

Hyperenzymemia was defined as lipase or amylase elevation of more than 3 times of normal. Acute pancreatitis was defined as abdominal pain with more than 3 times rise in amylase or lipase.

RESULTS

A total of 46 patients were enrolled (23 in Ulinastatin in and 23 in placebo group).

The most common indication for ERCP is choledcolithiasis in both the groups. The second common indication is periampullary cancer. Out of the 46 patients, 32 patients were males. Out of 32 males, 16 were in Ulinastatin group and 16 were in placebo group.

Out of 46 patients, Precut papillotomy was done in 6 patients. Out of the 6 patients 4 were in Ulinastatin group.

Pancreatic duct cannulation was done in 10 patients. Out of 10 patients, 6 were in placebo group_ One patient in Ulinastatin group had repeated PD cannulation more than 3 times.

Table 1: There were no severe pancreatitis in both groups. there was no side effect in ulinastatin group.

	Ulinastatin group (n = 23)	Placebo group (n=23)
Male	16	16
Precut papillotomy	4	2
PD cannulation	4	6
Pancreatitis	1 (4.3%)	4 (17.3%)
Hyperlipasemia	(25.5%)	(37.6%)

There were no failed ERCPs. The overall incidence of pancreatitis is 10.8%. The incidence of pancreatitis is significantly lower in Ulinastatin group (4.3%) than placebo group (17.3%) which is statistically significant ($p<.05$). The incldence of hyperenzymemia is lower in Ulinastatin group (13%) than placebo group (30.4%).

DISCUSSION

We show that ulinastatin administered immediately before ERCP decreases the incidence of pancreatitis and hyperenzymemia after ERCP. The incidence of post-ERCP Pancreatitis varies depending on the definition of Pancreatitis, study population, indication for the procedure, and intervention performed. This study was conducted in consecutive patients who underwent diagnostic or therapeutic ERCP, and the overall rate of Pancreatitis was 4.3% (17.3% in the placebo group). Pancreatitis is still the most common and potentially fatal complication of ERCP. Activation of proteolytic enzymes

starting with the intra-acinar activation of trypsin seems to play a key role in the pathogenesis of pancreatitis. Trypsin subsequently activates other enzymes including kallikrein, phospholipase A, and elastase, which are far more cytotoxic than trypsin, resulting in acinar-cell injury and autodigestion. Considering this pathogenesis enzyme inhibitors theoretically may be use full for the prevention of post ERCP Pancreatitis. However, aprotinin, a trypsin-kallikrein inhibitor failed to prevent pancreatic injury after ERCP.

Cavallini et al conducted a multicenter, randomized placebo-controlled trial on the efficacy of gabexate, a synthetic protease inhibitor, in preventing post-ERCP pancreatitis.[13] The incidence of post-ERCP pancreatitis was significantly lower in the gabexate group than in the placebo group (2% vs. 8%, P=.03) Patients with Pancreatitis in the gabexate group had mild pancreatitis, whereas one third of patients with pancreatitis in the placebo group developed necrotizing pancreatitis. Despite such an excellent result, gabexate administration has not become widely used. The primary reason may be the inconvenience of a continuous 12-hour infusion after ERCP, which may necessitate additional costs of hospitalization. Ulinastatin is used to prevent pancreatic damage after ERCP.[14,15]

Therefore, they also conducted a comparative study of gabexate administered for 13 hours and 6.5 hours; the incidence of post-ERCP pancreatitis was similar in the 2 gabexate treated groups. On the other hand, Andriulli et al studied the efficacy of a 2.5 hours and 6-5-hour treatment with gabexate in multicenter placebo-controlled trials and recognized no significant difference in the incidence of pancreatitis between the gabexate group and the placebo group. In addition, a meta-analysis of the preventive effect of gabexate on post-ERCP pancreatitis also revealed that a short-term infusion (<4h) of gabexate did not significantly decrease the rate of Pancreatitis. These diverse effects may be related to the short half-life of gabexate (55s), which has to be administered for a long period of time to prevent pancreatitis.

Ulinastatin is a glycoprotein with a molecular weight of about 24000 daltons, and is extracted and purified from human urine. It consists of 143 amino acid residues, 2 tandemly arranged kunitz-type protease-inhibitor domains, and represents the light chain of inter-α- trypsin inhibitor existing in blood. It is produced when inter-α-trypsin inhibitor is treated with neutrophil elastase. Ulinastatin is a potent inhibitor of neutrophil elastase and of trypsin. This endogenous trypsin inhibitor extensively inhibits other pancreatic enzymes such as α chymotrypsin, lipase, amylase, elastase, and carboxylase, and it may inhibit proteolytic enzymes, including elastase and cathepsin B and G, released by stimulation of trypsin or phospholipase A_2. The inhibitory effect of ulinastatin on pancreatic enzymes is stronger than that of gabexate and aprotinin. In addition, Ulinastatin suppresses the production of inflammatory mediators such as tumor necrosis factor-α and interleukin-6, which are associated with the severity of pancreatitis. In various experimental models of pancreatitis, Ulinastatin suppressed the development, and the progression of pancreatitis and its therapeutic effect in patients with pancreatitis was more potent than that of gabexate and aprotinin. Ulinastatin is used clinically to treat pancreatitis and to prevent pancreatic damage after ERCP. We tried to clarify the effect of Ulinastatin regarding the prevention of post-ERCP pancreatitis.

Besides the extensive and potent inhibitory effect on pancreatic enzymes, the relatively long half-life in serum (35 min) is an advantage of ulinastatin over other pancreatic enzyme inhibitors. Ulinastatin can be given by intravenous bolus injection because its safety has been confirmed in an acute toxicity test at a higher dose.

In our study, a short-term (10 min) administration of ulinastatin significantly decreased the incidence of post-ERCP pancreatitis and hyperenzymemia, and no adverse reaction related to ulinastatin was observed. When patients undergoing abdominal surgery were given the same dose of ulinastatin by bolus injection or continuous infusion, serum ulinastatin concentration 30 minutes after the administration was higher in the bolus injection group than in continuous infusion group, but serum ulinastatin concentration 30 minutes after the administration was higher in the bolus injection group than in the continuous infusion group. But the serum ulinastatin concentrations at 3.5 and 6.5 hours were similar in the 2 group, although the exact time of onset of post-ERCP pancreatitis is hard to determine, the initial damage to acinar cells may occur during or immediately after the procedure because serum pancreatic enzymes in patients with post-ERCP pancreatitis were increased immediately after ERCP. Thus, ulinastatin administered for a short time immediately before ERCP may contribute to prevent pancreatic injury.

The selective use of ulinastatin in patients at high risk for post-ERCP pancreatitis is likely to be cost effective. In our multivariate analysis, significant risk factors for post-ERCP pancreatitis were identified as no administration of ulinastatin and therapeutic ERCP. The incidence of post therapeutic ERCP pancreatitis in the placebo group was 17.3% which was comparable with the results of recent trials conducted in patients undergoing therapeutic procedures. As for the subgroup analysis, the difference in the incidence of postherapeutic ERCP pancreatitis between the Ulinastatin group and the placebo group was statistically significant.

Multicenter prospective studies have identified various risk factors for post-ERCP pancreatitis younger age, female sex, suspected sphincter of Oddi dysfunction, history of previous post-ERCP pancreatitis, difficult cannulation, precut sphincterotomy, and pancreatography. Because ulinastatin can be given for a short term, patients at risk for developing pancreatitis

identified before ERCP should be treated before the examination as shown in this study and those who are found to be at risk during the procedure should be administered ulinastatin during the procedure. This may be a more cost-effective use of ulinastatin but further studies are required to confirm this.

CONCLUSION

In conclusion, a short-term administration of ulinastatin immediately before ERCP can decrease the incidence of post-ERCP Pancreatitis and hyperenzymemia. Further studies on the efficacy in patients with a risk factor for pancreatitis and studies on the dosage and the timing of administration are needed to determine cost effectiveness.

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REFERENCES

1. Loperfido S, Angelini G, Benedetti G. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc. 1998;48:1-10.
2. Masci E, Toti G, Mariani A. Complications of diagnostic and therapeutic ERCP: a prospective, multicenter study. Am J Gast. 2001;96:417-23.
3. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gast Endos. 2001;54(4):425-34.
4. Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. Am J Gast. 2006;101:139-47.
5. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gast Endos. 1998;48(1):1-0.
6. Williams EJ, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. Endos. 2007;39(09):793-801.
7. Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, et al. Risk factors for ERCP-related complications: a prospective multicenter study. Ame J Gastroenterol. 2009;104(1):31-40.
8. Testoni PA, Bagnolo F, Natale C, Primignani M. Incidence of post-endoscopic retrograde-cholangiopancreatography/sphincterotomy pancreatitis depends upon definition criteria. Digestive and Liver Dis. 2000;32(5):412-8.
9. Cavallini G, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatetography. Gabexate in digestive endoscopy. N Engl J Med. 1996;335:919-23.
10. Tsujino T, Komatsu Y, Isayama H, Hirano K, Sasahira N, Yamamoto N, et al. Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized controlled trial. Clin Gastroenterol Hepatol. 2005;3:376-83.
11. Ohara H, Goto K, Noguchi Y, Shiraki S, Kamiya Y, Nakayama Y, et al. The usefulness of Ulinastatin for post-ERCP pancreatitis and hyperpancreto-enzymemia-comparative examination between one-shot injection and drip infusion of ulinastatin. Gastroenterol. 1990;12:361-8.
12. Fujishiro H, Adachi K, Imaoka T, Hashimoto T, Kohge N, Moriyama N, et al. Ulinastatin shows preventive effect on post endoscopic retrograde cholangiopancreatography pancreatitis in a multicenter prospective randomized study. J Gastroenterol Hepatol. 2006;21:1065-9.
13. Cavallini G, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. Gabexate in digestive endoscopy. Italian Group. N Engl J Med. 1996;335:919-23.
14. Ohara H, Goto K, Noguchi Y, Shiraki S, Kamiya Y, Nakayama Y. The usefulness of ulinastatin for post-ERCP pancreatitis and hyperpancreatoenzymemia-comparative examination between one-shot injection and drip infusion of ulinastatin. Gastroenterol. 1990;12:361-8.
15. Fujishiro H, Adachi K, Imaoka T, Hashimoto T, Kohge N, Moriyama N, et al. Ulinastatin shows preventive effect on post-endoscopic retrograde cholangiopancreatography pancreatitis in a multicentre prospective randomized study. J Gastroenterol Hepatol. 2006;21:1065-9.

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