ORIGINAL RESEARCH PAPER

Volume-7 | Issue-7 | July-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A PROSPECTIVE STUDY OF THE EFFICACY OF INTRAVENOUS ULINASTATIN IN THE TREATMENT OF ACUTE PANCREATITIS

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ABSTRACT

Background: Acute pancreatitis is a major cause of acute abdominal pain. The morbidity and mortality of acute pancreatitis are largely determined by the degree of inflammatory response mediated by a variety of cytokines.

Aim: To study the effect of addition of ulinastatin to standard care on mortality and morbidity in Indian subjects with acute pancreatitis.

Methods: This prospective, randomized, placebo controlled, double blind study was conducted at Victoria Hospital, Bangalore medical college and Research Institute, Bangalore. Fifty adult subjects, aged 18 to 60 years, with acute pancreatitis and elevated serum C-reactive protein (CRP) levels, were included in the study. APACHE II scoring system was employed to classify the subjects into mild (score <8) and severe pancreatitis (score > or = 8). Standard care was given to all subjects as per the treating physician's protocol. Eligible subjects were randomized to receive intravenous infusion of 200,000 IU ulinastatin or placebo in 100 mL of 0.9% saline given over one hour every 12 hours for 5 days.

Results: Pancreatitis was due to alcohol intake in a majority of subjects. Baseline characteristics were similar between the ulinastatin and placebo groups. Efficacy was evaluated in subjects who had received at least 3 days (6 doses) of ulinastatin / placebo. A total of nine deaths were observed in the severe pancreatitis group, two in the Ulinastatin group and seven in the placebo group, the difference was found to be statistically significant. The number of organ dysfunctions were also considerably higher in the placebo group and was also found to be statistically significant. The mean hospital stay was marginally more in the placebo group and the difference was not statistically significant.

Conclusions: The use of intravenous Ulinastatin in cases of severe pancreatitis was found to significantly reduce mortality and new onset organ dysfunction.

KEYWORDS

INTRODUCTION

The clinical presentation of the acute pancreatitis is variable. Most of these patients recover without specific complications. Some patients however display severe complications and these patients show high morbidity and mortality. The morbidity and mortality of acute pancreatitis are largely determined by the degree of inflammatory response mediated by a variety of cytokines like tumour necrosis factor (TNF-α), interleukin 6 and 8. Severe pancreatitis is associated with high morbidity and mortality – approximately 32% in the initial few days, mainly from organ failure and necrotic tissue becoming infected, 19% in the third week and 37% in the fourth(1) .

Many scoring systems have been developed to grade severity and serve as early prognostic signs.(2-4) The APACHE (Acute Physiology and Chronic Health Evaluation) II score is commonly used as it correlates with the mortality risk in acute pancreatitis; death rates vary between 4% to 16% depending upon the APACHE II severity score.(5)

The treatment of severe acute pancreatitis can become complex, particularly in situations wherein multiple organ systems are involved or if there are local complications like necrosis or pseudocyst formation. Thus it is safe to assume that, the suppression of these pro inflammatory cytokines responsible for myriad sequels of severe pancreatitis is the key to reducing the mortality or morbidity associated with the condition. Ulinastatin is a glycoprotein and a serine protease inhibitor found in human urine and blood. It is secreted when inter-α-trypsin inhibitors are degraded by neutrophilic elastase. Trypsin inhibitors act to suppress the proteolytic action of trypsin on a variety of tissues and exert a localized anti-inflammatory effect. Ulinastatin attenuates the elevation of neutrophil elastase release, thereby blunting the rise of pro-inflammatory cytokines and also inhibits secretion of pro-inflammatory cytokines IL-6 and IL-8.(6)

In this study, the efficacy of Ulinastatin in the treatment of severe pancreatitis and its role in the prevention of the onset of new end organ dysfunctions, local and systemic complications and lowering the morbidity and mortality associated with the pancreatitis are studied.

METHODS

This prospective, randomized, placebo controlled, double blind study was conducted at Victoria Hospital, Bangalore medical college and Research Institute, Bangalore. Valid written informed consent was taken from all the subjects. 50 subjects with pancreatitis were included in the study and segregated into 2 groups, Group A were subjected to Ulinastatin and Group B were subjected to placebo. Adult subjects, aged 18 to 60 years, with acute pancreatitis and elevated serum C-reactive protein (CRP) levels, were eligible for the study. Presence of at least two of the following three criteria was essential for diagnosis of pancreatitis: suggestive abdominal pain, serum amylase and/or lipase >3 times upper limit of normal (ULN), and imaging findings of acute pancreatitis. APACHE II scoring system was employed to classify the subjects into mild (score <8) and severe pancreatitis (score > or = 8).

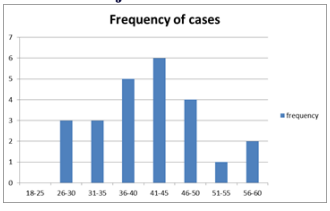
Subjects in each group were randomized using 1:1 block randomization to receive intravenous infusion of either 200,000 IU ulinastatin or placebo in 100 mL of 0.9% saline, administered over one hour every 12 hours for 5 days. Subjects completing atleast 3 continuous days of infusions were considered in this study. Subjects receiving Ocreotide or somatostatin were excluded from the study. Baseline laboratory parameters, demographic information, pre-existing co-morbid conditions, presence of any organ dysfunction at the time of presentation were assessed. Serum CRP levels were assessed on day 3 and 7. Liver and renal parameters were periodically assessed. All the subjects were followed up till discharge from hospital. Efficacy amongst the subjects was evaluated in those who received at least 3 continuous days of ulinastatin. The efficacy end points were set at the reduction ofserum CRP levels compared to baseline values, reduction in hospital stay, prevention of new end organ dysfunction and associated mortality including infusion related reactions or any other adverse event.

All the data was statistically analysed and results interpreted. P value of less than 0.05 was considered to be statistically significant.

RESULTS

A majority of the fifty subjects enrolled in the study were found to be in the 3rd or 4th decade of life, as demonstrated in the graph below.

Fig 1: Age distribution of subjects



As many as 94% of the subjects were male, as opposed to only 6% of females. The major cause of pancreatitis in our study was alcohol related (Table 1)

Table 1: Etiology of pancreatitis

	Alcohol induced	Biliary	Idiopathic	Total
Group A	22(88%)	2(8%)	1(4%)	25(100%)
Group B	21(84%)	1(4%)	3(12%)	25(100%)

The baseline APACHE II scores, number of organ dysfunctions, and visual analogue scale (VAS) scores for pain were similar in both the groups.

Table 2: Efficacy results in acute mild pancreatitis

	GROUP A	GROUP B	P value
New onset organ dysfunction	0	1	.317
Deaths	0	1	.317
Days of hospital stay	7 days	6 days	.085

In patients with mild pancreatitis (APACHE <8), one patient developed new onset organ dysfunction in the placebo group, and one patient died in the same group. The mean hospital stay was found to be one day lesser in the placebo group. However, none of these were found to be statistically significant.

Table 3: Efficacy results in severe pancreatitis

	GROUP A	GROUP B	P value
New onset organ dysfunction	5	10	.047
Deaths	2	7	.025
Days of hospital stay	12	13.4	.218

A total of nine deaths were observed in the severe pancreatitis group, two in the Ulinastatin group and seven in the placebo group, the difference was found to be statistically significant. The number of organ dysfunctions were also considerably higher in the placebo group and was also found to be statistically significant. The mean hospital stay was marginally more in the placebo group and the difference was not statistically significant.

DISCUSSION

Mild acute pancreatitis (MAP) was defined according to the Atlanta classification (7) as con- firmed acute pancreatitis without development of one or more major local or systemic complications caused by pancreatitis. Severe acute pancreatitis (SAP) was defined as AP associated with one or more major local or systemic complications caused by pancreatitis. Local complications include pancreatic necrosis, acute pancreatic fluid collection, pancreatic pseudo-cyst, or pancreatic abscess. Systemic complications include respiratory failure (pO2>2 mg% in the absence of prior renal insufficiency), or the presence of gastrointestinal haemorrhage.

Morbidity and mortality in acute pancreatitis is largely determined by distant organ failure in severe attacks. These systemic manifestations of a disease initially limited to the pancreas are thought to be mediated by a variety of pro- and anti-inflammatory mediators released from the pancreas and various other sources during the course of the disease[8]. Studies on AP have demonstrated that these mediators are produced in a variety of tissues in a predictable sequence, initiated by local release of pro inflammatory mediators such as interleukin (IL)-1â, IL-6, and IL-8, which induce a systemic inflammatory response. This results in inflammatory infiltration of distant organs with multi organ failure and death.[8] The systemic inflammatory response is kept at bay by local and systemic release of anti inflammatory mediators such as interleukin 1â receptor antagonist (IL-1RA) and IL-10 which were shown to reduce the severity of pancreatitis and pancreatitis associated organ failure.[9-11] These observations demonstrate the potential of immunomodulation in preventing pancreatitis associated organ failure.

Ulinastatin is an acid-resistant protease inhibitor found in human urine and released from the high-molecular-weight precursor I alpha T1. Ulinastatin protein has been found in the brain, liver, kidney, gastrointestinal tract, cartilage, plasma, ovarian follicular fluid, amniotic fluid, and urine. It's secretion is up regulated by pro-inflammatory cytokines, including IL-6, IL-1beta, and TNF-alpha. Ulinastatin also suppresses neutrophil accumulation and activity. The genes and proteins regulated by ulinastatin are implicated in the inflammatory process. Therefore, ulinastatin is not just a protease inhibitor, but can also prevent inflammation and cytokine-dependent signalling pathways hence playing a key role in the reduction of new end organ dysfunctions in subjects with severe pancreatitis.[12-15]

In our study we observed that subjects with mild pancreatitis did not significantly benefit with the intravenous aministration of Ulinastatin, whereas those subjects with severe pancreatitis showed significant decrease in mortality after administration of the drug as compared to those who received placebo.

Studies in Japan have documented reduction in the incidence of ERCP-induced pancreatitis with the use of ulinastatin. In one study, the incidence of hyperenzymemia and pancreatitis was significantly lower in the ulinastatin group than in the placebo group[16].

In a study conducted by Uemura K et al[17], Ulinastatin reduced the levels of serum and drain amylase and the incidence of postoperative pancreatitis following pancreaticoduodenectomy.

CONCLUSION

The use of intravenous Ulinastatin in cases of severe pancreatitis was found to significantly reduce mortality and new onset organ dysfunction. However, additional benefit was not found in the use of the drug in cases of mild pancreatitis.

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