Effect of Somatostatin, Ulinastatin and Gabexate on the Treatment of Severe Acute Pancreatitis

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ABSTRACT

Objective: The objective of this study is to evaluate the efficacy of somatostatin, ulinastatin and gabexate for the treatment of severe acute pancreatitis.

Materials and Methods: A total of 492 patients with severe acute pancreatitis were assigned randomly into the following 4 groups: (1) somatostatin; (2) somatostatin + ulinastatin; (3) somatostatin + gabexate and (4) somatostatin + ulinastatin + gabexate. Acute physiology and chronic health evaluation II scores; clinical parameters including time of abdominal pain and distention extinct; recovering to normality of heart rate and respiration rate; amylase and blood glucose; ratios of efficacy; multiple organ dysfunction syndrome (MODS); mortality; complication; levels of endotoxin; tumor necrosis factor alpha; interleukin-6 (IL-6), IL-8 and IL-10 and side effects were analyzed.

Results: Acute physiology and chronic health evaluation II scores, time of abdominal pain extinct and distention extinct, time of recovering to normality of heart rate, time of recovering to normality of respiration rate and time of recovering to normality of amylase and blood glucose were significantly decreased in the somatostatin + ulinastatin, the somatostatin + gabexate and the somatostatin + ulinastatin + gabexate subgroups compared with the somatostatin subgroup. Ratios of efficacy were significantly improved, whereas ratios of MODS, mortality and complication were significantly decreased in the somatostatin + ulinastatin and the somatostatin + ulinastatin + gabexate subgroups compared with the somatostatin subgroup. Tumor necrosis factor alpha, IL-6 and IL-8 levels on the fourth day after treatment showed significant decrease in the somatostatin + ulinastatin, the somatostatin + gabexate and the somatostatin + ulinastatin + gabexate subgroups compared with the somatostatin subgroup. The IL-10 levels on the fourth day were significantly improved in the somatostatin + ulinastatin, the somatostatin + gabexate and the somatostatin + ulinastatin + gabexate subgroups compared with the somatostatin subgroup.

Conclusions: Somatostatin is effective for the treatment of acute pancreatitis, ulinastatin demonstrates improvement in therapeutic benefits and gabexate can relieve the clinical symptoms and shorten the course of disease but cannot improve the effective ratio or decrease MODS, mortality and complication.

Key Indexing Terms: Severe acute pancreatitis; Somatostatin; Ulinastatin; Gabexate; Cytokine. **[Am J Med Sci 2016;351 (5):506–512.]**

INTRODUCTION

Severe acute pancreatitis (SAP) with severe complications such as multiple organ failure, necrosis, abscess and formation of pancreatic pseudocysts often gives rise to a high mortality (30-40%) despite intensive treatment.[1,2] Current strategy of treatment in acute pancreatitis is mainly based on supportive measures, adequate analgesia, elimination (if possible) of any underlying cause and prevention of complications. Over the last few years, lessons from experimental animal models helped us to better understand many important pathways involved in the pathogenesis of necrotizing acute pancreatitis and associated systemic complications. Both the risk of multiple organ failure and infectious complications appear to be related to the degree of pancreatic necrosis. The morbidity and mortality of SAP are determined largely by the extent of the related inflammatory response[3,4] that is mediated by a variety of cytokines, including proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and IL-8 and anti-inflammatory cytokines such as IL-10. To inhibit the activity of pancreatic enzyme is the key to the treatment for SAP. Somatostatin, ulinastatin and gabexate are all inhibitors of pancreatic enzyme. Combination of drugs directed against several different pathways involved in the pathophysiologic events in severe experimental pancreatitis is superior to monotherapies.[5] Somatostatin has been proven worldwide to be used absolutely necessarily for the treatment of SAP. Ulinastatin is also used frequently because it has been proven to be able to improve the therapeutic effects on treatment of SAP.[6] The efficacy of gabexate mesilate treatment remains controversial because several studies suggested that it can reduce mortality,[7] whereas other studies indicated that it had no significant effect on mortality or difference in cost-effectiveness compared

with control groups.[8] The objective of this study is to compare the efficacy of somatostatin, somatostatin + ulinastatin, somatostatin + gabexate and somatostatin + ulinastatin + gabexate for the treatment of SAP.

MATERIALS AND METHODS

Patients

This was a prospective and double-blind study. The option corresponding to each patient was placed in sealed envelopes that were opened immediately before inclusion. According to a computerized random number generation, 492 consecutive patients who were diagnosed with SAP and admitted to the intensive care unit of our hospital between January 2000 and December 2014 were randomly assigned into the following 4 groups: (1) somatostatin; (2) somatostatin + ulinastatin; (3) somatostatin + gabexate and (4) somatostatin + ulinastatin + gabexate. Individual patients were diagnosed according to the diagnosis criteria. The SAP was diagnosed using criteria based on the Consensus of the International Symposium on Acute Pancreatitis (Atlanta definition)[9]: (1) systemic inflammatory response syndrome; (2) persistent organ failure (defined by the Modified Marshall Scoring System) (>48 hours); (3) computed tomography scores of pancrease ≥6 and (4) Acute physiology and chronic health evaluation II (APACHE II) scores ≥8. Exclusion criteria included (1) evidence or a known history of renal dysfunction (creatinine > 1.5 mg/dL); (2) pregnancy, malignancy or immunodeficiency and (3) pre-existing chronic kidney diseases requiring regular hemodialysis. A total of 20 healthy volunteers who did not receive any treatment were enrolled as the control group. This prospective, randomized clinical study protocol was approved by the Ethics Committee, and informed consent was obtained from all subjects. Patient demographics are shown in Tables 1 and 2. Demographic data, serum level of amylase, computed tomography severity index, APACHE II scores, abdominal compartment syndrome rate and severity grade ratio were not statistically different between the 4 subgroups.

Basic Treatment

All patients underwent a rigorous clinical treatment protocol consisting of adequate central venous fluid replacement, hemodynamic monitoring via central venous pressure, analgesia, proton pump inhibitors, a nasogastric tube, prophylaxis, antibiotics, parenteral or enteral nutritional support and respiratory and renal support as needed. The patients diagnosed with severe biliary pancreatitis accepted the endoscopic treatments that included endoscopic retrograde choledochopancreatography, endoscopic sphincterotomy, endoscopic lithotripsy basket, endoscopic retrograde biliary drainage or removal of the stones with an extraction balloon.

Somatostatin Subgroup

In addition to basic treatment, 3.0 mg of somatostatin (Laboratoires Serono S. A. Aubonne, Switzerland) was added to 100 mL 0.9% sodium chloride and was delivered intravenously 250 μg/hour for 10 days.

Somatostatin + Ulinastatin Subgroup

In addition to the basic treatment, 3.0 mg somatostatin (Laboratoires Serono S. A. Aubonne, Switzerland) was added to 100 mL 0.9% sodium chloride and was delivered intravenously 250 μg/hour for 10 days. A 1.0×10^5 U ulinastatin (Guangzhou Tianpu Biochemical Pharmaceutical Company Limited, Guangzhou, China) was added to 250 mL 5% glucose infusion and was delivered intravenously twice a day for 10 days.

Somatostatin + Gabexate Subgroup

In addition to basic treatment, 3.0 mg somatostatin (Laboratoires Serono S. A. Aubonne, Switzerland) was added to 100 mL 0.9% sodium chloride and was delivered intravenously 250 μg/hour for 10 days. A 0.1 g gabexate (Chengdu Tiantaishan Pharmaceutical Company Limited, Chengdu, China) was added to 250 mL 5% glucose and was delivered intravenously thrice a day for 10 days.

Somatostatin + Ulinastatin + Gabexate Subgroup

In addition to the basic treatment, 3.0 mg somatostatin (Laboratoires Serono S. A. Aubonne, Switzerland) was added to 100 mL 0.9% sodium chloride and was delivered intravenously 250 μg/hour for 10 days. A 1.0×10^5 U ulinastatin (Guangzhou Tianpu Biochemical Pharmaceutical Company Limited, Guangzhou, China) was added to 250 mL 5% glucose infusion and was delivered intravenously twice a day for 10 days. A 0.1 g gabexate (Chengdu Tiantaishan Pharmaceutical

TABLE 1. Comparisons of etiology of SAP and sex ratio in the 4 subgroups.

		Etiology				Sex	
Groups	***n***	**Gallstone**	**Hyperlipidemia**	**Alcohol**	**Unknown**	**Male**	**Female**
Somatostatin	122	46	22	36	18	63	59
Somatostatin + ulinastatin	124	48	24	22	30	63	61
Somatostatin + gabexate	130	61	24	24	21	72	58
Somatostatin + ulinastatin + gabexate	116	42	24	20	30	56	60
χ^2 Values		0.788	0.693	0.584	0.692	0.586	0.903
P Values		0.629	0.526	0.626	0.596	0.626	0.484