Impact of alanyl-glutamine dipeptide on severe acute pancreatitis in early stage

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Abstract

AIM: To evaluate the therapeutic effect of alanyl-glutamine dipeptide (AGD) in the treatment of severe acute pancreatitis (SAP) in early and advanced stage.

METHODS: Eighty patients with SAP were randomized and received 100 mL/d of 20% AGD intravenously for 10 d starting either on the day of (early treatment group) or 5 d after (late treatment group) admission. Groups had similar demographics, underlying diseases, Ranson score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Balthazar’s computed tomography (CT) score at the beginning of the study and underwent similar other medical and nutritional management.

RESULTS: The duration of acute respiratory distress syndrome (2.7 ± 3.3 d vs 12.7 ± 21.0 d, P < 0.01), renal failure (1.3 ± 0.5 d vs 5.3 ± 7.3 d, P < 0.01), acute hepatitis (3.2 ± 2.3 d vs 7.0 ± 7.1 d, P < 0.01), shock (1.7 ± 0.4 d vs 4.8 ± 3.1 d, P < 0.05), encephalopathy (2.3 ± 1.9 d vs 9.5 ± 11.0 d, P < 0.01) and enteroparalysis (2.2 ± 1.4 d vs 3.5 ± 2.2 d, P < 0.01) and hospital stay (28.8 ± 9.4 d vs 45.2 ± 27.1 d, P < 0.01) were shorter in the early treatment group than in the late treatment group. The 15-d APACHE II score was lower in the early treatment group than in the late treatment group (5.0 ± 2.4 d vs 8.6 ± 3.6 d, P < 0.01). The infection rate (7.9% vs 26.3%, P < 0.05), operation rate (13.2% vs 34.2%, P < 0.05) and mortality (5.3% vs 21.1%, P < 0.05) in the early treatment group were lower than in the late treatment group.

CONCLUSION: Early treatment with AGD achieved a better clinical outcome in SAP patients.

Key words: Severe acute pancreatitis; Alanyl-glutamine dipeptide; Clinical study

INTRODUCTION

Acute pancreatitis (AP) contributes to thousands of annual hospital admissions, of which severe acute pancreatitis (SAP) accounts for 10%-20%[1, 3]. Despite considerable improvement in the treatment, the mortality of SAP still ranges between 10%-15%[6].

The course of SAP tends to be prolonged and the patients usually are hypermetabolic and high protein catabolic due to systemic inflammatory response syndrome (SIRS) induced by acute local inflammatory process and subsequent vital-organ dysfunction[6]. Thus, if nutritive support is not appropriately administrated to match rapidly increased demand in the treatment of SAP, the patients consequently come down with metabolic disorder and nutrition deficiency, which is considered to increase mortality due to impaired immune function, increased risk of infections and intractable vital-organ failure.

In recent years, research showed a conditional deficiency of glutamine would be an independent predictive factor for a poor outcome and its correction improved survival by restoring cellular protective mechanisms, improving immune function and resistance of the gut barrier to hypoperfusion, metabolic stress and subsequent bacterial translocation, and decreasing the risk of infection in critical illness[5, 10]. Since free glutamine is unstable in solution, intravenous administration is limited[3]. Alanyl-glutamine...
peptide (AGD), however, can be taken via vein and hydrolyzed into alanine and glutamine in circulation as a substitute[3]. Presently AGD supplement in parenteral nutrition is a worth-trying approach and an evidence-based recommendation in the management of SAP[11], but there has been no study describing an optimal protocol of AGD administration. Our study aims to evaluate the favorable effects of early supplement with AGD in the treatment of SAP.

MATERIALS AND METHODS

Patient selection
In this study, the diagnostic criteria[12] formulated for SAP at the Bangkok World Congress of Gastroenterology 2002 in Thailand was employed. All of the patients, who had been diagnosed with SAP and admitted to our hospital within 72 h after onset of symptoms, were included. The patients who had histories of trauma, operation or prior treatment with AGD were excluded, and the patients who died within 5 d after admission were also rejected.

Methods
In this study, 80 identified SAP patients who were admitted to West China Hospital of Sichuan University from May 2004 to March 2005 were randomized and treated with 100 mL/d of 20% AGD intravenous infusion for 10 d (SSPC No. SF1505) starting either on the day of (early treatment group) or 5 d after (late treatment group) admission.

Upon admission, all of the patients were treated with intensive care, oxygen inhalation, intermittent gastrointestinal decompression, and fluid infusion. Prophylactic antibiotics were used for 7-14 d. H2 receptor antagonist or proton pump inhibitor agent was given for 7 d; the acid-base balance and the electrolyte balance were maintained. When patients developed respiratory failure, the respirator was employed to assist respiration. When hypoalbuminaemia occurred, 20% human serum albumin 50 mL was used daily until the serum albumin was recovered to normal, and fat emulsion was also given for 14 d.

The following parameters were measured: 24-h APACHE II score and initial Balthazar’s CT score, 15-d APACHE II score, incidence and duration of complications including acute respiratory distress syndrome (ARDS), renal failure, acute hepatitis, encephalopathy and enteroparalysis, infection rate, hospital stay, operation rate and mortality.

Hospital stay: Hospital stay was defined as the duration from hospital admission to discharge. The duration of hospital rehabilitation due to cholecystectomy was not taken into account in this study, although cholecystectomy was regarded as a promising treatment to prevent recurrent pancreatitis.

Operation rate: Surgical intervention was performed if infected pancreatic necrosis, or pancreatic abscess, or (per)pancreatic hemorrhage or (per)pancreatic pseudocyst was identified or if the patient did not respond to intensive care treatment.

Table 1 Baseline in the two groups

| Baseline | Late treatment group (n = 38) | Early treatment group (n = 38) |
|----------|-------------------------------|-------------------------------|
| Sex (Male/Female) | 21/17 | 22/16 |
| Age (mean ± SD, yr) | 47.5 ± 12.6 (22-76) | 46.9 ± 12.8 (27-74) |
| Etiology, n (%) | Gallstones | 20 (52.6) | 16 (42.1) |
| Alcohol abuse | 2 (5.3) | 7 (18.7) |
| Hyperlipidemia | 7 (18.4) | 9 (23.7) |
| Idiopathic | 9 (23.7) | 6 (15.8) |
| 48-h Ranson score (mean ± SD) | 4.5 ± 1.7 | 4.8 ± 1.6 |
| 24-h APACHE II score (mean ± SD) | 10.8 ± 3.5 | 10.2 ± 3.1 |
| CT score (mean ± SD) | 5.8 ± 2.3 | 5.9 ± 2.4 |

APACHE II: Acute Physiology and Chronic Health Evaluation II; CT: Computed Tomography.

Statistical analysis
Data were expressed as mean ± SD or percentage. Data in normal distribution was analyzed using t test; data in non-normal distribution was analyzed using Wilcoxon rank sum test. Categorical data was analyzed using Chi-square test. P < 0.05 was considered statistically significant.

The medical ethics committee of West China Hospital at Sichuan University approved this study. All patients gave their informed consent, and the study was conducted according to the recent principles of the Declaration of Helsinki (World Medical Association, 2000).

RESULTS

Four patients including 1 death within 24 h after admission and 1 death on the 5th day after admission in the early treatment group and 2 deaths within 24 h in the late treatment group withdrew from the study, which were not included in any of the analyses. Therefore, there were 38 patients in the early treatment group and 38 in the late treatment group.

Baseline
There were no statistical differences between the two groups in sex, age and etiology (P > 0.05, Table 1), and in the 48-h Ranson score, 24-h APACHE II score and CT score in the initial stage of hospitalization (P > 0.05, Table 1).

Complications
There were no statistical differences between the two groups in the incidences of ARDS, renal failure, shock, acute hepatitis, encephalopathy and enteroparalysis (P > 0.05), but the duration of ARDS, renal failure, acute hepatitis, encephalopathy and enteroparalysis was shorter in the early treatment group than in the late treatment group (P < 0.01), and the duration of shock was also shorter in the early treatment group (P < 0.05) (Table 2).

Prognosis
The 15-d APACHE II score was lower in the early treatment group than in the late treatment group (P < 0.01).
**DISCUSSION**

In the early stage of SAP, the patients tend to be hypermetabolic due to occurrence of SIRS and subsequent multiple organ dysfunction syndromes (MODS), resulting in the greatly increased demand for nutrition[13-15]. In the late stage, the demand for nutrition increases continuously due to infection, resulting from intestinal bacterial translocation and immunosuppression. Thus, insufficient nutritive support inevitably leads to nutrition deficiency in SAP patients[16].

When a nutritional deficiency arises in critical illness including SAP, glutamine, which is very abundant and readily synthesized under most situations, tends to be a factor for a poor outcome in critical illness[16].

AGD was shown to improve clinical outcome of SAP[11,16]. In this study, we treated SAP patients with 100 mL/d of 20% AGD infusions intravenously for 10 d to compare the effects of AGD between the two groups and study its optimal protocol. The baseline data showed no significant difference between the two groups (P > 0.05). APACHE II score, the parameter for predicting and monitoring the development of local and systemic complications of SAP, was evaluated on the 15th day after admission, which was lower in the early treatment group than in the late treatment group (P < 0.01). The duration of ARDS, renal failure, acute hepatitis, shock, encephalopathy and enteroparalysis were also shorter in the early treatment group than in the late treatment group, as was lower mortality (P < 0.05). These might result from a possible consequence of early suppression of inflammatory response and restoring cellular protective mechanisms by early AGD supplementation, which is associated with mediating anti-inflammatory/immunologic factors[17] and antioxidant/inducible nitric oxide synthase (iNOS)[20], decreasing the level of TNF-alpha and interleukin-8 in mononuclear cell[22,23] and C-reactive protein in serum[23]. In this study, the hospital stay was also shorter in the early treatment group (P < 0.05), which might be correlated to the shorter duration of complications.

**COMMENTS**

**Background**

Severe acute pancreatitis (SAP) is a hypermetabolic disease. Appropriate nutrition support is essential to the management of SAP. In recent years, the supplement of glutamine has been shown to improve survival rate. Presently, the supplement of alanyl-glutamine dipeptide, as a substitute of glutamate which is stable in circulation, is a promising and worth-trying approach.

**Research frontiers**

Besides nutritional management of SAP, restoring an optimized immune system plays a role in improving survival rate. Previous pilot studies of alanyl-glutamine dipeptide (AGD) supplementation in nutritive support have revealed good outcome by restoring cellular protective mechanisms, improving the immune function and lowering the infection rate. Although this treatment was recommended by evidence-based studies, this treatment principle has not yet been systematically applied and further study is still needed in this field.

**Innovations and breakthroughs**

The optimal protocol for the AGD treatment is not yet available in published
studies. Early AGD treatment in SAP is a breakthrough in this study, which reveals for the first time that early AGD treatment achieved a better clinical outcome in SAP patients.

**Applications**

As free glutamine is instable in solution, intravenous administration is limited. AGD, however, can be given via vein and hydrolyzed to alanine and glutamine in circulation as a substitute. This study showed that early treatment with AGD achieved a better clinical outcome in SAP patients. This treatment can be applied in the management of SAP patients.

**Terminology**

Severe acute pancreatitis is a common acute abdominal disorder, characterized by various degrees of necrosis of pancreatic parenchyma together with local and systemic complications, such as SIRS and multiple organ dysfunction syndromes. Alanyl-glutamine dipeptide is an important component of parenteral nutrition ingredients with its molecular formula ingredient as N(2)-L-alanyl-L-glutamine. SIRS is a clinical response to one of the nonspecific insults caused by ischemia, inflammation, trauma, infection, or a combination of several insults, which was defined by a journal in 1992 and described as occurrence of two or more clinical symptoms of fever or hypothermia, tachypnea, tachycardia, and leukocytosis.

**Peer review**

AGD supplementation has been shown to be effective by previous studies. In this pilot study, the authors focused on the clinical effects of early treatment with AGD comparing with late treatment, which shows early AGD treatment indicates a better clinical outcome. Further researches are needed to explore its mechanism.

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