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Effects of imipenem combined with glutamine in the treatment of severe acute pancreatitis with abdominal infection in mainland China: a meta-analysis

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SUMMARY

OBJECTIVE: The aim of this study was to explore the efficacy of imipenem combined with glutamine in the treatment of severe acute pancreatitis with abdominal infection in mainland China using meta-analysis.

METHODS: We searched China National Knowledge Network, Wanfang Medical Network, Chinese Science Citation Database, PubMed, and Embase Databases for publications of imipenem combined with glutamine in the treatment of severe acute pancreatitis abdominal infection. The search time limit was from the establishment of the database to April 10, 2021. Stata software version 12.0 was used for statistical analysis; the combined effect size odds ratio and standardized mean difference values were calculated for the count data and measurement data, respectively; and the heterogeneity test was performed in this study.

RESULTS: A total of five randomized controlled trials were included. A total of 499 cases were included, with 251 in the observation group and 248 in the control group. Meta-analysis results showed that the efficacy of imipenem combined with glutamine in the treatment of severe acute pancreatitis with abdominal infection was significantly better than that of imipenem alone (odds ratio=0.78, 95%CI 0.71–0.86, p=0.040).

CONCLUSION: Imipenem combined with glutamine can significantly improve the efficacy in the treatment of severe acute pancreatitis with abdominal cavity infection.

KEYWORDS: Pancreatitis. Imipenem. Glutamine. Intraabdominal infection. Meta-analysis.

INTRODUCTION

Pancreatitis is a disease of the pancreas caused by the self-digesting effect of trypsin. The patient with pancreatitis has edema, congestion, or bleeding or necrosis. Acute pancreatitis is an inflammatory reaction that causes pancreatic enzymes to digest, edema, hemorrhage, and even necrosis after the activation of pancreatic enzymes in the pancreas. Clinical patients are characterized by acute upper abdominal pain, nausea, vomiting, fever, and increased blood pancreatin. The severity of the disease varies. Severe acute pancreatitis (SAP) is a special type of acute pancreatitis. SAP is an acute and severe disease in which the activation of pancreatic enzymes in the human body causes local inflammation of the pancreas and damages the functions of many organs. This disease is accompanied by systemic and local complications, accounting for 10–20% of the entire acute pancreatitis. In the 1980s, most cases died in the early stages of the disease. Until the past 10 years, with the advancement of SAP treatment technology, the cure rate has increased, but the overall mortality rate is still as high as 17%. According to relevant data, more than 80% of SAP patients are clinically affected by overeating, long-term alcohol abuse, and biliary diseases. This disease has the characteristics of rapid onset, rapid development, dangerous condition, complications, and high mortality rate, which seriously threatens the lives and health of people[1].

Effective clinical treatment to delay the progression of the patient's condition has become a key research topic for medical workers. The number of SPA patients who died of acute respiratory distress syndrome and shock decreased year by year, while the number of patients who died of an abdominal infection that could not be controlled earlier increased year by year. The patient's abdominal infection is closely related to the necrosis of the pancreas and surrounding tissues. The larger the range of necrosis, the higher the probability of infection. Therefore, it is necessary to take effective treatment methods in time to control the abdominal cavity infection of patients in order to improve the clinical efficacy of the treatment of SAP[2].

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A single clinical trial is difficult to confirm certain effects that may be important to clinicians because of the small sample. Meta-analysis is a systematic evaluation method that synthesizes various published research data and analyzes the combined effect of the extracted data. This method can increase statistical power and conforms to objective laws. It is a huge advancement, which is completely consistent with the idea of evidence-based medicine[3].

This study aims to systematically evaluate the therapeutic effect of imipenem combined with glutamine on SAP with abdominal cavity infection through the method of evidence-based medicine, so as to provide a reference for future clinical medication plans.

METHODS

Search strategy for publications

We used the terms "imipenem," "glutamine," "pancreatitis," "acute pancreatitis," "severe acute pancreatitis," "abdominal infection," "China," and "mainland" to search publications in the Chinese databases of China National Knowledge Network (CNKI), Wanfang Medical Network, and China Science Citation and the English databases of PubMed and Embase. The search date was from the establishment of the database to April 10, 2021.

Participants

The inclusion criteria were as follows: ① those who met the diagnostic criteria for SAP[4]; ② those who had clinical symptoms of abdominal infection, such as abdominal pain, abdominal muscle tension, abdominal wall tenderness and rebound pain, and abdominal effusion; ③ those who underwent diagnosis by serum enzymology, imaging, and abdominal puncture; and ④ those who had not taken glutamine or imipenem 1 month before treatment. The research design is a clinical randomized controlled trial (RCT). The observation group comprises patients who received combined imipenem and glutamine, and the control group comprises those who received imipenem only. The exclusion criteria were as follows: ① non-RCTs, ② unclear number of effective cases, ③ unclear efficacy indicators or criteria; and ④ animal experiments, reviews, or case reports.

Efficacy evaluation

The efficacy of the cases was classified in three ways: ① significantly effective: Clinical symptoms and signs of the patients have basically disappeared; the abdominal infection symptoms have been significantly relieved; the serum inflammatory factor levels and blood biochemical index levels have returned to normal; and imaging examinations show that the pancreas has returned to normal; ② effective: Clinical symptoms and signs of the patients have been reduced, the symptoms of abdominal infection have been improved, the levels of serum inflammatory factors and blood biochemical indicators have been significantly improved, and the results of imaging examinations have shown that the pancreatic images have been significantly improved; and ③ invalid: There is no change in clinical symptoms and abdominal infection, and there is even a tendency to worsen. The total number of effective cases is the sum of significantly effective and effective cases.

Data extraction and literature quality evaluation

The screening of literature and data extraction were carried out independently by two researchers. The main content of data extraction included ① basic information of the literature; ② evaluation index of literature quality; and ③ clinical efficacy result index.

The third researcher resolved the differences that had arisen.

The quality of the literature was assessed using the Jadad quality scoring criteria, including whether randomization (2 points), blinding (2 points), and withdrawal (1 point) were described.

Statistical analysis

Stata software version 12.0 was used in this study. The forest diagram and the funnel diagram were drawn. When the curative effect index was countable data, the odds ratio (OR) value was used as the comprehensive effect. For continuous data, the standardized mean difference (SMD) value was used as the comprehensive effect, and the 95% confidence interval (95%CI) was used for interval estimation. The Q-test was used to analyze the heterogeneity of the included studies. I^2>50% and p<0.05 were considered heterogeneous, and the random-effects model was used to merge the effect size in the meta-analysis. Otherwise, the fixed-effects model was used. The funnel plot and Egger's test were used to analyze the publication offset. A p<0.05 was considered statistically significant.

RESULTS

Basic information of the included publications

A total of 5 RCTs and 499 patients, with 251 in the observation group and 248 in the control group, were finally included. In the process of document screening, 25 publications were initially retrieved. Then, we excluded 16 reviews and non-RCTs after reading the title and abstract, and further excluded 4 articles (those with incomplete data and co-administration of other drugs) after reading the full text. Finally, five publications were

included in this study. The basic information of the included literature is provided in Table 1.

Meta-analysis results of efficacy

The result of the heterogeneity test showed that there was no heterogeneity (I^2=16.5%, p=0.309) and, therefore, the fixed-effects model was selected. Meta-analysis results showed that the efficacy of imipenem combined with glutamine was significantly better than that of imipenem alone (OR=0.21, 95%CI 0.15–0.30, p<0.001) in the treatment of SAP with abdominal infection. The forest plot is shown in Figure 1.

Table 1. Basic information of the included publications.

First author	Year	Country	Area	Interventions		Number of cases (observation group/control group)	Duration (day)	Jadad score
				Observation group	Control group			
Wang XT	2019	China	Beijing/ Haerbin	Imipenem (1 g bid)+glutamine (1.5–2.0 mL/kg qd)	Imipenem (1 g bid)	53/50	14	3
Jin ZQ	2018	China	Hubei	Imipenem (1 g bid)+glutamine (2.0 mL/kg qd)	Imipenem (1 g bid)	46/46	14	4
Jiang DQ	2017	China	Hebei	Imipenem (1 g bid)+glutamine (1.5–2.0 mL/kg qd)	Imipenem (1 g bid)	51/51	14	3
Hong L	2017	China	Jiangsu	Imipenem (1 g bid)+glutamine (20 g qd)	Imipenem (1 g bid)	58/58	14	4
Xu B	2019	China	Heilongjiang	Imipenem (1 g bid)+glutamine (2.0 mL/kg qd)	Imipenem (1 g bid)	43/43	14	3

bid: two times daily; qd: once a day.

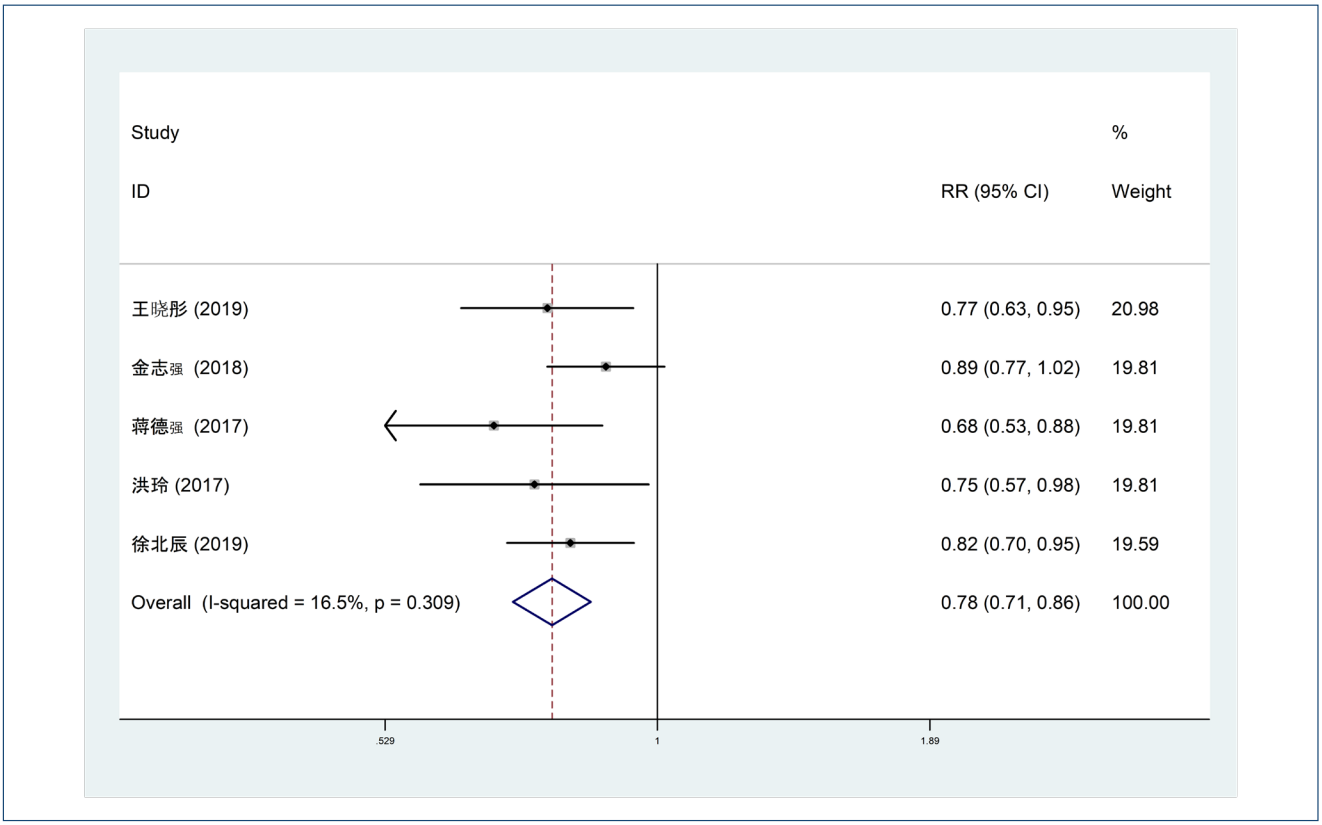

Figure 1. Forest plot of the efficacy of imipenem combined with glutamine.

Adverse reactions

Since only one of the included literature involved adverse reactions, the effect size was not combined. These adverse reactions include acute respiratory distress syndrome (0 vs. 1), renal insufficiency (1 vs. 2), shock (1 vs. 1), coagulation dysfunction (2 vs. 1), and intestinal paralysis (2 vs. 0) between the two treatment groups (observation group vs. control group).

Publication bias

Egger's test results showed that the hypothesis test results of publication bias were statistically significant (t=3.48, p=0.040). Publication bias can be considered to exist. The funnel plot is shown in Figure 2.

DISCUSSION

This study is the first to conduct a meta-analysis of imipenem combined with glutamine in the treatment of SAP with abdominal infection from the perspective of evidence-based medicine in mainland China. The included literature covers Beijing, Harbin, Hubei, Hebei, Jiangsu, Heilongjiang, and other regions of China. The results showed that imipenem combined with glutamine is significantly better than imipenem alone in the treatment of SAP with abdominal infection, which will provide great help to clinicians in medication.

SAP is a special type of acute abdomen characterized by persistent organ failure, which lasted for more than 48 h. A large-scale, multi-center, retrospective study showed that the fatality rate of SAP within 1 week of the course of disease was even as high as 67%[5,6]. SAP is usually treated by routine internal medicine combined with β-lactam antibiotics. This treatment method has a significant positive effect on alleviating the clinical symptoms of patients and achieving a cure effect. However, the long-term practice has confirmed that this treatment method only focuses on symptomatic treatment and lacks targeted treatment for the causes of abdominal infection. Therefore, the biochemical indicators of SAP patients with abdominal infection and the recovery of abdominal infection symptoms are slow, and the clinical treatment effect is not good[7,8].

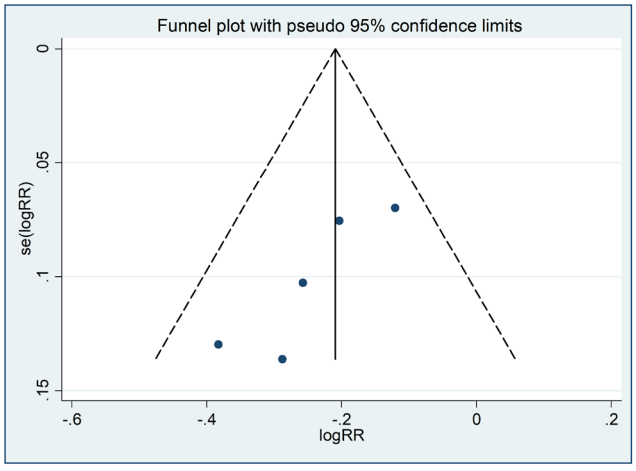

Figure 2. Funnel plot of the efficacy of imipenem combined with glutamine.

Abdominal infection and tissue damage in SAP patients are closely related to the abnormal expression of serum inflammatory factors. Tumor necrosis factor α (TNF-α) is not only the first typical cytokine to cause an increase in the onset of SAP but can also effectively induce the production of interleukin-6 (IL-6), IL-8, and other inflammatory factors, causing the release of inflammatory mediators, thereby aggravating the symptoms of abdominal infection in SAP patients[9]. Moreover, abdominal cavity infections are mostly caused by the lack of amino acids in the human body due to fasting during the treatment of SAP patients. Due to increased intestinal wall permeability, intestinal mucosal atrophy, and villi loss, the resident flora in the intestine invades the abdominal cavity[10].

The early-stage infection in SAP patients is usually caused by single bacteria. With the gradual development of the disease, infections caused by the joint action of multiple bacteria are more likely to appear in the later stage. Gram-negative bacteria are the main infection bacteria of patients, such as *Enterococcus*, *Escherichia coli*, and *Klebsiella*[11]. The severity of the disease is directly related to the complexity of the infection. It may be a bacterial or fungal infection, and there is also the possibility of double infection[12]. Imipenem is a kind of β-lactam antibiotics, with very strong effect, especially for Gram-positive bacteria and anaerobic bacteria. Therefore, imipenem is mainly appropriate for treating abdominal infection symptoms caused by a variety of pathogens[13].

Glutamine is a non-essential amino acid secreted by skeletal muscle. It is one of the components of parenteral nutrition support, which can effectively repair the digestive tract. The mechanism is to inhibit the atrophy of the intestinal mucosa, reduce the permeability of the intestinal mucosa and the release of endotoxin, improve the intestinal microenvironment, and maintain the immune function of the intestine[14].

After the diagnosis of co-infection in patients, even if the pathogen culture and drug sensitivity test results have not been obtained, antibacterial drugs should be given in time, and the data obtained in this study have certain reference value for empirical medication. In fact, the key to improving the

treatment effect of patients with SAP lies in the early diagnosis of the disease and the timely adoption of appropriate treatments to prevent abdominal infections[15,16]. After all, prevention is better than cure.

There were several limitations in this study, including a small number of included literature and cases and inconsistent medication time. In addition, there are differences in the physiological mechanisms of Asian and European populations, while the cases included in this article were only from China. RCTs with larger sample sizes are suggested in the future studies. However, our results have enriched the SAP treatment research system.

CONCLUSION

Imipenem combined with glutamine can significantly improve the efficacy in the treatment of SAP with abdominal cavity infection.

AUTHORS' CONTRIBUTIONS

SZ, LRJ, CH: All authors contributed equally to this work. Their contributions include Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, and Writing – review & editing.

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