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Original Research Article

Efficacy of combined use of octreotide and sodium tanshinone IIA sulfonate in patients with cirrhosis complicated with severe acute pancreatitis

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Abstract

Purpose: *To assess the prognosis of liver cirrhosis complicated with severe acute pancreatitis (SAP) after treatment with octreotide in combination with sodium tanshinone IIA sulfonate.*
Methods: *A total of 164 patients with cirrhosis complicated with SAP were randomly assigned to two groups, each with 82 patients. Serum levels of inflammatory factors, as well as vascular endothelial function and liver function indices were determined. Treatment outcomes in the patients were recorded in terms of abdominal pain relief time, gastrointestinal function recovery time, hospital stay duration, and incidence of complications.*
Results: *Relative to the control group, there were decreases in concentrations of inflammatory indices in the study cohort. Endothelial function index levels increased in the two groups, but the levels of endothelin (ET) and von Willebrand Factor (vWF) decreased more in the study group of patients, when compared to the control group, while nitric oxide (NO) level was raised ($p < 0.05$). Liver function improved in both groups. There were marked reductions in serum ALT, AST and total bilirubin (TBIL) in study cohort, relative to the control cohort ($p < 0.05$). However, albumin (ALB) levels were comparable in the two groups. Abdominal pain relief time, duration of hospitalization and time taken for normal digestive system function were shorter in the study cohort ($p < 005$). Receiver operating characteristic (ROC) curve analysis revealed that after treatment with octreotide and sodium tanshinone IIA sulfonate, values of area under the curve (AUC) for abdominal pain relief time, gastrointestinal function recovery time and hospital stay were 0.886, 0.918 and 0.794, respectively.*
Conclusion: *The combined use of octreotide and sodium tanshinone IIA sulfonate inhibits the release of inflammatory factors in cirrhotic patients with SAP, and improves vascular endothelial and liver functions, thereby improving disease prognosis. These data constitute a good scientific basis for the use of octreotide and sodium tanshinone IIA sulfonate in the treatment of liver cirrhosis complicated with SAP.*

Keywords: *Octreotide, Sodium tanshinone IIA sulfonate, Severe acute pancreatitis, Liver cirrhosis*

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INTRODUCTION

Acute pancreatitis (AP) is caused by diverse factors which abnormally activate pancreatic enzymes, causing pancreatic inflammatory reaction, pancreatic tissue digestion, edema, bleeding, and even necrosis [1]. The severity of the disease varies. Severe acute pancreatitis

(SAP) patients frequently exhibit organ dysfunction, and its morality may be as high as about 30 % [2]. There are several causes of SAP, amongst which is excessive alcohol intake [3,4]. Changes in dietary habits have resulted in an annual growth in alcohol intake among Chinese adults, leading to increased incidence of alcohol-induced SAP. Abnormalities in pancreatic function and structure are frequently seen in alcoholic cirrhosis patients. When pancreatitis becomes a complicating factor, the clinical manifestations may not be consistent with the typical presentation [5]. However, the patient's condition is more likely to worsen, with a propensity for recurrent episodes. Without timely and efficient treatment, disease prognosis worsens, thereby posing a grave threat to the life and well-being of the patient. Clinical treatment is still used for patients with cirrhosis complicated with SAP.

Octreotide, an octapeptide derivative of natural somatostatin, inhibits pancreatic enzyme release [6]. It reduces pancreatic tissue damage, thereby reducing tissue edema. However, although it is a frequently prescribed medication for SAP therapy, the single use of octreotide does not easily produce rapid and stable clinical efficacy in patients with cirrhosis complicated with SAP. Tanshinone IIA is a component of *Salvia miltiorrhiza* which has diverse pharmacological activities such as antioxidant and anti-tumor effects, and it is used for the treatment of cardiovascular diseases [7]. In addition, tanshinone IIA exerts anti-inflammatory and hepatoprotective effects [8, 9]. However, its specific effect on patients with cirrhosis complicated with SAP is not yet clear. Therefore, the purpose of this research was to ascertain the effectiveness of combined use of octreotide and sodium tanshinone IIA sulfonate in the treatment of patients with cirrhosis complicated with SAP, so as to provide a scientific basis for managing cirrhosis in the presence of SAP.

METHODS

General information on patients

Patients with alcoholic cirrhosis complicated with SAP who were treated in Qingdao Central Hospital from January 2017 to December 2018, served as subjects. In all, 164 patients were randomly selected and assigned to two groups: study group (n = 82) and control group (n = 82). The diagnosis of alcoholic cirrhosis was in conformity with the *Diagnosis and Treatment Guidelines for Alcoholic Liver Disease* developed by the Hepatology Branch of the Chinese Medical Association in 2010. All patients received a diagnosis of SAP with an APACHEII score of ≥ 20 points based on the classification criteria for AP in Atlanta [10]. The study group comprised 50 males and 32 females with a mean age of 56.19 ± 6.44 years, whereas the control cohort had 56 men and 26 women (mean age, 55.72 ± 4.76 years).

Inclusion criteria

The included patients were those who came to the hospital in time (not exceeding 72 h) after the onset of SAP, and patients who were confirmed as SAP after comprehensive judgment based on clinical manifestations such as persistent abdominal pain, abdominal distension, blood sample tests (blood amylase raised 3 times or more above normal), and imaging tests.

Exclusion criteria

The excluded subjects were patients who were uncooperative; those with incomplete clinical data; patients who were allergic to octreotide or sodium tanshinone IIA sulfonate, and patients with severe cardiovascular, cerebrovascular and renal conditions. In addition, patients who died within one week of admission were delisted.

Ethical approval

All patients submitted signed informed consent. The research was approved by the ethics committee at Qingdao Central Hospital (approval No. 20161120S), and it was implemented in accordance with the criteria in the Helsinki Declaration [11].

Treatment protocols

The two groups of patients were asked to fast after admission, and they were given conventional treatments such as oxygen inhalation, gastrointestinal decompression, antibiotic prophylaxis, antibiotics for prevention of infection, as well as correction of acid-base imbalance and nutritional support. The control group was given octreotide (Beijing Biot, China) twice a day, in addition to the routine treatment. The octreotide (0.3 mg) was dissolved in 24 mL of normal saline and administered as intravenous injection with micropump. The dose of administration was adjusted in line with body weight. Patients in study group were administered octreotide in combination with sodium tanshinone IIA sulfonate. The dose of octreotide was the same as that in the control group. Sodium tanshinone IIA sulfonate (40 mg; Coffeepine, Jiangsu, China) was dissolved in 250 ml physiological saline or glucose and

intravenous infusion, and was administered four times a day. The drug treatments lasted for 7 days which was regarded as one course of treatment, after which the treatment efficacy was assessed.

Evaluation of parameters/indices

The serum levels of inflammatory factors, vascular endothelial function indices as well as liver function indices before and after treatment were determined and compared between the 2 cohorts. Improvements in patients were recorded in terms of abdominal pain relief time, gastrointestinal function recovery time, hospital stay duration, and incidence of complications. The serum inflammatory factors measured were IL-6, IL-8, and TNF-α. The indices of vascular endothelial function measured were endothelin (ET), NO and von Willebrand Factor (vWF), while liver function indices comprised albumin (ALB), ALT, AST and total bilirubin (TBIL).

Venous blood sample was taken on day 2 after admission and on day 10 after treatment. Blood sample was taken from each patient in two 5-mL sample vials after an overnight fast. One of the vials contained an anticoagulant, while the other vial had no anticoagulant. The blood samples were allowed to stand at 4 °C for 30 min before centrifugation at 3000 g for 10 min. Then, the supernatant was carefully collected as serum or plasma which was kept at -80 °C prior to analysis. The levels of the various indices were measured using ELISA kit in strict compliance with the kit instructions. The levels of AST and ALT were determined using the AU400 chemical analyzer (Olympus Corporation, Japan), and the values are presented in international units per liter (U/L).

Statistical analysis

Statistical analysis was carried out using the SPSS 20.0 software, while GraphPad Prism 6.0 software was employed for plotting graphs. Data are expressed as mean ± standard deviation. Non-parametric tests were used for inter-group comparison. Enumeration data are presented as percent (%), and chi-square test analysis was utilized for comparison of both groups. Statistical significance was assumed at $p < 0.05$.

RESULTS

General clinical profile of patients

The 2 cohorts (164 subjects) were comparable in age, gender distribution, composition ratio, BMI, cirrhosis duration, and APACHEII score *(p* > 0.05; Table 1).

Levels of IL-8, TNF-α and IL-6

Prior to treatment with octreotide and sodium tanshinone IIA sulfonate, the 2 cohorts were comparable with respect to blood concentrations of inflammatory factors, i.e., IL-6, TNF-α and IL-8 *(p* > 0.05). However, after treatment, serum levels of IL-6, IL-8 and TNF-α in the study group were significantly reduced, relative to control cohort ($p < 0.05$; Table 2).

Table 1: General clinical profiles of subjects

Variable	Study group (n=82)	Control group (n=82)	*P*-value
Age (years)	56.19 ± 6.44	55.72 ± 4.76	0.618
Gender (n)			
Male	50	56	0.414
Female	32	26	
BMI (kg/m^2)	22.67 ± 1.28	22.57 ± 1.09	0.611
Cirrhosis duration (years)	8.57 ± 3.74	8.21 ± 3.61	0.427
APACHEII score	22.20 ± 0.68	21.96 ± 1.15	0.273

BMI: body mass index; APACHEII: Acute Physiological Function and Chronic Health Status Scoring System II

Table 2: Serum levels of inflammatory factors

Group	Time point	TNF-α (pg/mL)	IL-8 (pg/mL)	IL-6(pg/mL)
Study	Pre-treatment	401.62 ± 35.01	381.33 ± 21.76	100.58 ± 13.82
	Post-treatment	147.85 ± 20.70 [a]	131.01 ± 15.09 [a]	55.37 ± 4.77 [a]
Control	Pre-treatment	405.03 ± 32.26	384.40 ± 20.43	98.93 ± 14.54
	Post-treatment	213.66 ± 23.78	147.08 ± 17.64	75.01 ± 6.62

[a]$P < 0.05$, *vs* control cohort after treatment

Table 3: Effect of treatments on the levels of vascular endothelial function indices

Group	Time-point	ET (pg/mL)	NO (U/mL)	vWF (%)
Study	Before treatment	138.99 ± 7.94	4.04 ± 0.44	188.78 ± 27.74
	After treatment	105.30 ± 4.46 [a]	9.23 ± 0.66 [a]	100.34 ± 13.76 [a]
Control	Before treatment	140.16 ± 9.08	3.95 ± 0.56	192.67 ± 31.32
	After treatment	120.80 ± 7.95	6.34 ± 0.85	128.50 ± 16.40

[a]*P* < 0.05, *vs* control post-treatment

Table 4: Comparison of liver function indices

Index	Study group		Control group	
	Pre-treatment	***Post-treatment***	***Pre-treatment***	***Post-treatment***
ALT (U/L)	82.61 ± 7.98	24.06 ± 4.52[a]	81.63 ± 8.72	45.87 ± 4.23
AST (U/L)	94.03 ± 6.79	21.60 ± 2.57[a]	92.70 ± 6.59	41.07 ± 5.91
TBIL (μmol/L)	35.01 ± 6.14	16.63 ± 3.23[a]	36.67 ± 6.99	21.40 ± 4.39
ALB (g/L)	31.67 ± 3.53	38.55 ± 5.48	31.73 ± 3.78	37.78 ± 4.73

[a]*P* < 0.05 *vs* control cohort post-treatment

Table 5: Levels of selected clinical indicators in the two cohorts

Indicator	Study group	Control group
Abdominal pain relief time (days)	3.18 ± 1.18[a]	5.28 ± 1.25
Gastrointestinal function recovery time (days)	2.85 ± 0.77[a]	4.63 ± 0.99
Occurrence of complications [(n (%)]	28(34.15%)	36(43.90%)
Hospital stay (days)	14.12 ± 3.87[a]	19.36 ± 5.00

[a]*P* < 0.05, compared to control group

Levels of ET, NO and vWF

Prior to treatment, there were similar levels of vascular endothelial function indices (ET, NO and vWF) in both cohorts *(p* > 0.05). However, treatment enhanced endothelial function in patients in the study group, in contrast to the control group where values of ET and vWF were markedly decreased, whereas the NO level was increased *(p* < 0.05; Table 3).

Impact of treatment on levels of AST, ALT, ALB and TBIL

Before treatment, the levels of liver function indices (ALT, AST and TBIL) were comparable in both cohorts. However, treatment improved liver function in the patients. Moreover, the serum levels ALT, AST and TBIL of the study group were markedly decreased, when compared to those in control group *(p* < 0.05). However, ALB levels in both groups were comparable *(p* > 0.05; Table 4).

Effect of treatment on disease condition

Improvements in patients were recorded after therapy. Abdominal pain relief time, digestive system normalization time, and duration of hospitalisation were significantly shortened in the study group of patients, when compared with the control group of patients *(p* < 0.05). Moreover, the incidence of complications was decreased, although with no statistical significance (*p* < 0.05), as shown in Table 5.

Correlation of efficacy of the combined treatment using ROC

A ROC was used to analyze the effectiveness of sodium tanshinone IIA sulfonate on patients with cirrhosis complicated with SAP. Based on the ROC curve analysis, after treatment, the area under the curve of the patient's abdominal pain relief time was 0.886; the critical value was 4.31 days, and the Youden index was 0.622. The area under the curve of gastrointestinal function recovery time was 0.918, with critical value of 3.54 days, and Youden index of 0.732. The area under the curve of the hospital stay was 0.794; the critical value was 15.92 days, and Youden index was 0.524. These data are shown in Table 6.

DISCUSSION

Cirrhosis, a progressive liver disorder, is caused by multiple factors which repeatedly damage the liver parenchyma over a long period. The pathological features of cirrhosis are hepatocyte necrosis, nodular regeneration of residual hepatocytes into hepatic lobules, connective tissue hyperplasia, and fibrosis. These lesions result in gradual deformation and hardening of the liver tissue, eventually resulting in cirrhosis.

Table 6: Correlation between improvement in patients and sodium tanshinone IIA sulfonate

Parameter	AUC	Critical value	Sensitivity	Specificity	Youden Index
Abdominal pain relief time (days)	0.886	4.31	0.866	0.756	0.622
Gastrointestinal function recovery time (days)	0.918	3.54	0.866	0.866	0.732
Hospital stay (days)	0.794	15.92	0.756	0.768	0.524

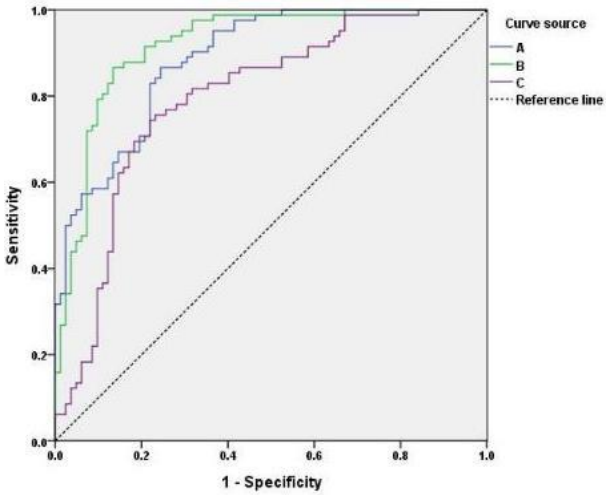

Figure 1: ROCs of improvements in patients and sodium tanshinone IIA sulfonate. A: abdominal pain relief time; B: gastrointestinal function recovery time; C: hospital stay

At the initial phase of onset of cirrhosis, patients with compensated liver show no obvious symptoms. However, as the disease progresses, liver decompensation leads to a decline in liver function, and various severe complications also occur, e.g., SAP. The clinical features of cirrhosis accompanied by SAP are not conspicuous in the affected patients. Nonetheless, the condition of the patient usually becomes aggravated, and the condition is prone to recurrence. For these patients, there is need for attention be paid to the use of different intervention strategies, with a view to achieving enhanced treatment effectiveness. Research on the pathogenesis of SAP has revealed that inflammatory response and pancreatic microcirculation disorder are important features. When pancreatic tissue is damaged, it acts as an antigen and activates macrophages which release considerable amounts of inflammatory factors. This leads to inflammation, increased vascular permeability, decreased blood volume, and in serious cases, systemic inflammatory syndrome and multi-organ disease. The inflammatory factors implicated in SAP development are IL-6, TNF-α and IL-8, with TNF-α as the initiating factor which mediates the delivery of many inflammatory cytokines from pancreatic tissues or other tissues [12]. Pancreatic microcirculation disorder refers to the three interacting factors that aggravate SAP: abnormal hemodynamics, microvascular dysfunction and cytokine secretion disorders [13].

When liver cirrhosis is complicated with SAP, care should be taken when selecting therapeutic drugs, and attention should be paid to protecting the liver. Therefore, the best option is to choose drugs with hepatoprotective potential. The isolation and screening effective ingredients from medicinal plants is a major approach to developing new drugs. In clinical practice in China, *Salvia miltiorrhiza* Bunge is often utilized for treating AP. In addition, *Salvia miltiorrhiza* Bunge is applied for treating cirrhosis and kidney diseases [14]. Tanshinone IIA is a prominent phytochemical compound isolated from *Salvia miltiorrhiza* Bunge, and it has many pharmacological properties. The present study focused on determination of the protective effect of tanshinone IIA on the liver when used as first aid for SAP.

Studies have revealed that treatment of cirrhotic rat models with tanshinone IIA resulted in decreases in serum AST and ALT, with reduction in liver fibrosis [9]. In addition, tanshinone IIA pre-treatment of an animal model of ischemia-reperfusion injury model led to protection of the liver as a result of reductions in inflammation and liver damage [15]. Moreover, a study has reported the protective impact of tanshinone IIA against cholic acid-induced liver cholestasis in a mouse model, suggesting that tanshinone IIA may likely be a novel drug for treating liver cirrhosis [16].

Currently, there is a limited number of studies focused on the treatment of SAP with tanshinone IIA. This study has demonstrated that treatment of SAP patients with *Salvia miltiorrhiza* for 7 days reduced blood concentrations of IL-6, TNF-α and IL-8 in the SAP patients [17]. The development of SAP may lead to intricate and multiple organ damage. A study in which *Salvia miltiorrhiza* was used as intervention in a SAP rat model demonstrated that *Salvia miltiorrhiza* reduced inflammatory response and apoptosis in the rats, thereby protecting the animals from diverse organ damage [18].

There are many bioactive compounds in *Salvia miltiorrhiza*. Thus, it is not clear as to which of these compounds produced the aforementioned effects. Current research on tanshinone IIA focuses mainly on its use in the treatment of cardiovascular and cerebrovascular diseases. Studies have demonstrated that tanshinone IIA mitigates vascular stiffness and resolves problems of blood pressure in healthy smokers [19]. Moreover, tanshinone IIA produced beneficial effects on blood rheology indicators in patients with acute cerebral infarction [20]. Research on rat model of SAP showed that tanshinone IIA protected rats from aortic endothelial injury through reduction in infiltration of inflammatory cells [21].

In present study, 164 subjects with cirrhosis and SAP were assigned to a control cohort treated only with octreotide, and a study group treated with combination of octreotide and tanshinone IIA. The two groups were compared with respect to serum inflammatory factors, vascular endothelial function indices and liver function indices, before and after treatment. Moreover, records were kept on improvements in patients after the course of treatment, and analysis was made to determine which treatment was more effective between octreotide alone and tanshinone IIA + octreotide. The conditions of patients were improved in the two groups, as was manifested in reduction in inflammatory response, recovery of gastrointestinal tract function and vascular endothelial function. Post-treatment assays showed significant reductions in levels of IL-6, TNF-α and IL-8 in the study group. In addition, ET and vWF were decreased, whereas the NO level was increased. There were marked decreases in serum AST, ALT and TBIL, whereas there were no noticeable changes in ALB levels. The effect of treatment on prognosis of the disease showed that the time taken for abdominal pain relief was reduced in the study group patients, relative to the control cohort. Based on ROC curve analysis, after treatment, the AUC values for abdominal pain relief time, gastrointestinal function recovery time and hospital stay were 0.886, 0.918, and 0.794, respectively, with high degree of correlation. These results provide evidence that the use of octreotide in combination with tanshinone IIA in treating patients with cirrhosis complicated with SAP protected the liver, and also improved treatment effect and patients' prognosis.

CONCLUSION

This research has shown that the administration of octreotide and sodium tanshinone IIA sulfonate protects the liver tissues of patients with cirrhosis complicated with SAP, inhibits the release of inflammatory factors, and improves endothelial liver function, thereby enhancing treatment efficacy and improving the prognosis of the disease.

DECLARATIONS

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None provided.

Ethical approval

The ethics committee at Qingdao Central Hospital, China approved this study (20161120S).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Juanzhi Hao, Peijuan Zhang conceived and designed the study, and drafted the manuscript. Juanzhi Hao, Liqing Fan and Shunshun Jiang collected, analyzed and interpreted the experimental data, while Juanzhi Hao, Peijuan Zhang and Shunshun Jiang revised the manuscript for important intellectual contents. All authors read and approved the final draft of the manuscript for publication.

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