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Journal of Gastroenterology Research and Practice

Research Article

Open Access, Volume 3

Clinical efficacy of low-molecular-weight heparin combined with insulin in the treatment of hypertriglyceridemic acute pancreatitis

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Received: Dec 04, 2023

Accepted: Dec 22, 2023

Published: Dec 29, 2023

Archived: www.jjgastro.com

Keywords: Low-molecular-weight heparin; Insulin; Hypertriglyceridemia; Acute pancreatitis.

Abstract

Background: To investigate the clinical effect of low-molecular-weight heparin combined with insulin in the treatment of hypertriglyceridemic acute pancreatitis (HTG-AP).

Methods: A total of 106 HTG-AP patients who were admitted to the Department of Gastroenterology, Huaibei People's Hospital from May 2022 to July 2023 were selected as the research subjects and divided into low-molecular-weight heparin group, insulin group, and the combination treatment group according to the random number table. Based on routine treatment, the patients in the three groups were given low-molecular-weight heparin, insulin, and a combination of low-molecular-weight heparin and insulin. The levels of serum triglyceride (TG), inflammatory factors (CRP, IL-6), and blood amylase of the patients in the three groups were monitored before treatment, and on the 1st, 2^{nd,} and 6th day of treatment. The MCTSI score and APACHE II score changes were observed before treatment and on the 6th day of treatment. The hospital stay and treatment costs of all patients were counted.

Results: On the 2nd day of treatment, the serum TG levels of patients in the combination treatment group and insulin group were significantly lower than those in the low-molecular-weight heparin group ($P<0.05$), but there was no significant difference between the combined treatment group and insulin group. On the 6th day of treatment, the levels of serum TG, blood amylase, CRP and IL-6, MCTSI score, and APACHEII score of patients in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and insulin group ($P<0.05$). The hospital stay and treatment cost in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and the insulin group ($P<0.05$).

Conclusion: Compared with the low-molecular-weight heparin group and the combined treatment group could significantly reduce serum TG, reduce serum levels of inflammatory factors, decrease the severity of the disease, shorten the course of the disease, and lower the cost of treatment, which is worthy of clinical application.

Introduction

Acute pancreatitis (AP) is a common critical severe disease of the digestive system with various etiologies, with cholelithiasis, alcohol, and hyperlipidemia as the main causes in China. Among them, AP caused by hyperlipidemia is closely related to the significantly elevated triglyceride (TG) [1], so it is also called hypertriglyceridemic acute pancreatitis (HTG-AP). With the increasing improvement of people's living standards and changes in dietary structure, the incidence of AR has been increasing year by year [2]. Studies have shown that hyperlipidemia has become the main cause of AP, second only to cholelithiasis [3]. HGT-AP progresses rapidly and has the following clinical characteristics:

(1) It primarily affects young male individuals, often accompanied by overweight or obesity;

(2) The severity rate, recurrence rate, and mortality are significantly higher than those of AP caused by other causes [4,5];

(3) Serum TG level is higher, often exceeding 1000 mg/dl;

(4) It may cause chylomicronemia syndrome [6];

(5) Clinical symptoms are atypical and amylase elevation is not prominent [7]. Therefore, rapid reduction of serum TG and improvement of microcirculation have become the key to the treatment of HGT-AP. Studies have shown that both low-molecular-weight heparin and insulin have lipid-lowering effects, and low-molecular-weight heparin can also improve pancreatic microcirculation and patient prognosis [8]. This study aimed to observe the clinical efficacy of low-molecular-weight heparin combined with insulin in the treatment of HGT-AP, and the results are reported as follows.

Information and methods

General information: A total of 106 patients with HGT-AP who were admitted to Huaibei People's Hospital from May 2022 to July 2023 were randomly divided into low-molecular-weight heparin group, insulin group, and the group treatment with low-molecular-weight heparin and insulin (the combined treatment group). Patients were graded for the severity of the disease, with 35 cases in the low-molecular-weight heparin group [29 males, 6 females, mean age of (39.6±9.5) years], including 28 mild to moderate cases and 7 severe cases. In the insulin group, there were 35 cases [29 males, 6 females, mean age of (40.0±8.2) years], with 27 mild to moderate cases and 8 severe cases. The combined treatment group comprised 36 cases [28 males, 8 females, mean age of (38.2±7.7) years], including 28 mild to moderate cases and 8 severe cases. There were no significant differences in clinical data among the groups mentioned above (P>0.05). Patients should meet the diagnostic criteria in the Guidelines for Diagnosis and Treatment of AP (2019) [9], with serum TG above 11.30 mmol/L or between 5.65 and 11.30 mmol/L, but serum manifestations of chylous changes. This study was approved by the Hospital Ethics Committee

Exclusion criteria

(1) Patients caused by alcohol, cholelithiasis, infection, and other causes;

(2) Those combined with severe organ dysfunction;

(3) Those with a history of relevant drug allergies or contraindications;

(4) Participants unwilling to engage in the study;

(5) Individuals requiring surgical intervention.

Treatment: After admission, patients in the three groups were given medical treatments such as monitoring, organ support, protection of pancreatic function, control of inflammation, pain management, prevention, and control of infection. The low-molecular-weight heparin group was treated with a subcutaneous injection of 5000U of low-molecular-weight heparin calcium (Sparin, Shenzhen Salubris Pharmaceutical Co., Ltd.) once a day for six consecutive days. Coagulation functions were monitored during the treatment. The insulin group received treatment with insulin: (1) Intravenous infusion of insulin (Jiangsu Wanbang Biochemical Pharmaceutical Group Co., Ltd.) at a rate of 2 U/h; During the insulin infusion process, random blood glucose levels were monitored to prevent hypoglycemia. Simultaneous administration of 5% glucose (glucose: insulin ratio of 4-6g:1U) was given to prevent hypoglycemia, and blood glucose levels were maintained between 6.1-8.3 mmol/L. In the event of persistent hypoglycemia, insulin administration was discontinued. (2) If serum TG levels were ≤5.65 mmol/L, insulin administration was discontinued. The combination treatment group received both low-molecular-weight heparin and insulin, following the same treatment methods as the low-molecular-weight heparin group and the insulin group.

Observed indexes: (1) The levels of serum TG, serum cholesterol, blood amylase, CRP, IL-6, calcium ion, and creatinine before treatment and on the 1st, 2nd, and 6th days of treatment in the three groups were detected and compared. (2) The changes in MCTSI and APACHE II scores before and after treatment were compared. (3) The statistics on the hospital stay and treatment cost for all patients were compiled.

Statistical analysis: Statistical analysis was conducted using SPSS 26.0 statistical software. The measurement data conforming to the normal distribution after testing were expressed as x±s, and the analysis of variance (ANOVA) was adopted. For non-normally distributed data, the data was represented as median (P25, P75), and the Mann-Whitney U test was employed. A significance level of P<0.05 was considered indicative of statistical significance.

Results

Comparison of serum TG, serum total cholesterol, blood amylase, CRP, IL-6, calcium ion, and creatinine levels among the three groups upon admission and after treatment: The serum total cholesterol levels in the low-molecular-weight heparin group were 9.9±3.5 mmol/L before treatment and 7.0±2.1 mmol/L, 6.6±1.8 mmol/L, and 6.2±1.7 mmol/L on days 1, 2, and 6 of treatment, respectively. The values in the insulin group were 9.3 3.7, 6.7 2.6, 6.2 2.6, and 6.1 1.8 mmol/L, respectively. In the insulin group, the corresponding levels were 9.3±3.7, 6.7±2.6, 6.2±2.6, and 6.1±1.8 mmol/L. For the combined treatment group, the levels were 9.2±3.9, 7.2±1.9, 6.0±1.5, and 5.7±1.2 mmol/L. Significant reductions were observed in all three groups after treatment compared to before treatment (P<0.05). However, there were no statistically significant differ-

ences in the comparisons among the three groups (P>0.05).

The calcium ion levels in the low-molecular-weight heparin group before treatment and on days 1,2, and 6 of treatment were 2.1±0.3, 2.0±0.2, 2.1±0.2, and 2.2±0.1 mmol/L, respectively. In the insulin group, the corresponding values were 2.2±0.2, 1.9±0.1, 2.1±0.2, and 2.2±0.8 mmol/L, and in the combined treatment group, they were 2.1±0.2, 1.9±0.2, 2.1±0.2, and 2.2±0.1 mmol/L. There were no statistically significant differences in calcium ion levels among the three groups after treatment compared to before treatment (P>0.05).

The creatinine levels in the low-molecular-weight heparin group before treatment and on days 1,2, and 6 of treatment were 73.7±28.2, 73.9±19.1, 61.9±14.9, and 55.7±11.9 mg/L, respectively. In the insulin group, the corresponding values were 67.9±17.9, 77.1±44.2, 63.4±26.4, and 53.9±12.1 mg/L. For the combination treatment group, the levels were 70.3±32.4, 79.0±25.1, 71.9±48.8, and 54.8±6.6 mg/L. After treatment, the creatinine levels significantly decreased compared to before treatment in all three groups (P<0.05), but there were no statistically significant differences among the three groups (P>0.05).

On the 2nd day of treatment, the serum TG levels of patients in the combined treatment group and insulin group were significantly lower than those in the low-molecular-weight heparin group (P<0.05), but there was no significant difference between the combined treatment group and insulin group. On the 6th day of treatment, the serum TG, blood amylase, CRP and IL-6 levels of patients in the three groups were significantly lower than those before treatment (P<0.05). Besides, the serum TG, blood amylase, CRP and IL-6 levels of patients in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and the insulin group (P<0.05), as shown in Table 1.

Table 1: Blood biochemistry indexes of three groups of patients.

Project	Low-molecular-weight heparin group (35 cases)	Insulin group (35 cases)	Combined treatment group (36 cases)	F/χ^2value	P value
TG (mmol/L, x±s)					
Pre-treatment	19.5±11.2	20.6±9.9	19.7±10.3	0.117	0.890
Day 1 of treatment	7.4±2.8[a]	6.8±2.4[a]	7.1±3.0[a]	0.425	0.655
Day 2 of treatment	5.6±2.0[a]	4.4±1.8[a*]	4.6±1.7[a*]	4.141	0.019
Day 6 of treatment	5.0±2.2[a]	4.3±1.9[a]	2.8±1.9[a*#]	15.267	0.000
P value	0.000	0.000	0.000		
Amylase [U/L, M (P_{25}, P_{75})]					
Pre-treatment	191.0 (95.0, 405.0)	136.0 (80.0, 364.0)	196.0 (76.5, 598.0)	0.177	0.915
Day 1 of treatment	186.0 (95.0, 414.0)[a]	205.0 (93.0, 359.6)[a]	233.8 (86.5, 520.4)[a]	0.430	0.807
Day 2 of treatment	89.0 (65.0, 104.0)[a]	105.0 (81.0, 208.0)[a]	112.8 (58.5, 136.9)[a]	1.484	0.476
Day 6 of treatment	52.0 (45.0, 64.0)[a]	59.0 (43.0, 71.0)[a]	36.0 (32.0, 45.0)[a*#]	30.293	0.000
P value	0.000	0.000	0.000		
CRP [mg/L, M (P_{25}, P_{75})]					
Pre-treatment	46.5 (9.5, 89.1)	23.5 (9.0, 109.0)	21.7 (6.7, 109.5)	0.028	0.986
Day 1 of treatment	140.3 (78.9, 264.9)[a]	142.1 (95.3, 222.3)[a]	97.9 (65.1, 186.9)[a]	1.415	0.493
Day 2 of treatment	144.7 (89.9, 211.5)[a]	156.5 (76.4, 242.9)[a]	118.8 (49.8, 168.7)[a]	2.306	0.316
Day 6 of treatment	31.4 (23.0, 45.1)[a]	35.3 (21.7, 50.3)[a]	12.9 (8.8, 29.7)[a*#]	12.752	0.002
P value	0.000	0.000	0.000		
IL-6 [pg/ml, M (P_{25}, P_{75})]					
Pre-treatment	56.1 (27.9, 112.5)	55.81 (38.2, 120.5)	53.5 (30.1, 120.4)	0.028	0.986
Day 1 of treatment	51.3 (923.4, 93.8)	49.6 (36.1, 108.2)	32.8 (24.4, 56.4)[a]	1.415	0.493
Day 2 of treatment	42.7 (17.8, 73.8)[a]	41.3 (30.4, 87.2)[a]	21.9 (14.8, 40.0)[a]	3.137	0.208
Day 6 of treatment	32.9 (914.7, 41.4)[a]	25.6 (16.4, 51.5)[a]	15.4 (9.8, 23.5)[a*#]	16.044	0.000
P value	0.000	0.000	0.000		

Comparison of MCTSI scores and APACHE II scores on the 6th day of treatment, as well as the comparison of the hospital stay and treatment cost among the three groups of patients before and after treatment: There was no significant difference in MCTSI and APACHEII scores before treatment (P>0.05). On the 6th day of treatment, the APACHEII scores of patients in the three groups, and the MCTSI scores of the insulin group and the combined treatment group were all lower than those before treatment (P<0.05). Besides, the MCTSI scores and APACHEII scores of patients in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and the insulin group (P<0.05). The hospital stay and treatment cost in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and the insulin group (P<0.05), as shown in Table 2.

Discussion

The exact pathogenesis of HGT-AP remains uncertain [10], with the cytotoxic effect of free fatty acids being a widely ac-

Table 2: Clinical data of patients in three groups.

Project	Low-molecular-weight heparin group (35 cases)	Insulin group (35 cases)	Combined treatment group (36 cases)	F/χ^2 value	P value
MCTSI score (Points, x±s)					
Pre-treatment	3.5±1.9	3.3±1.7	3.6±1.9	0.185	0.831
Day 6 of treatment	3.2±1.5	2.9±1.3[a]	2.3±0.7[a*#]	7.211	0.001
P value	0.000	0.000	0.000		
APACHEII score (Points, x±s)					
Pre-treatment	6.1±2.7	6.5±3.4	6.3±3.7	0.280	0.757
Day 6 of treatment	4.3±1.7[a]	4.5±2.2[a]	2.8±1.9[a*#]	10.020	0.000
P value	0.000	0.000	0.000		
Hospital stays (d, x±s)	8.8±3.4	8.5±2.8	6.9±1.6[ab]	4.762	0.011
Treatment cost [Yuan, M (P_{25}, P_{75})]	6696.4 (5791.5, 11026.2)	6918.5 (6087.9, 10080.8)	6040.5 (5239.4, 7105.9)[*#]	7.180	0.028

Note: compared with pre-treatment, [a]P<0.05; Compared with the low-molecular-weight heparin group, [*]P<0.05; Compared with insulin, [#]P<0.05.

knowledged mechanism [11,12]. Elevated levels of serum TG are hydrolyzed by pancreatic enzymes, generating a significant amount of free fatty acids. This process directly damages pancreatic cells, potentially triggering acidosis and activating trypsinogen, resulting in self-digestion of the pancreas. Serum TG can also increase blood viscosity and activate platelets to produce thromboxane A2, thereby leading to the formation of microthrombus and exacerbating pancreatic microcirculation dysfunction. Given the etiology, pathogenesis, and clinical characteristics of HGT-AP, etiology removal is the key to treatment [13], and rapid reduction of serum TG levels in patients can significantly improve their symptoms [14].

At present, low-molecular-weight heparin has been clinically applied to the treatment of HGT-AP [15]. Low-molecular-weight heparin can promote the hydrolysis of chylomicron and inhibit the release of 5- hydroxytryptamine and other substances from platelets, to reduce serum TG levels and exert anti-inflammatory effects [16]. Single and long-term use of low-molecular-weight heparin may lead to a re-elevation of serum TG after an initial decrease. However, considering the synergistic effects of low-molecular-weight heparin and insulin, the combined application could be considered [13,16]. Insulin can promote gene expression of lipase and increase the content of lipase to reduce serum TG levels [17,18]. Studies have shown that the application of insulin can effectively reduce serum TG levels [15].

This study showed that there were no statistically significant differences in serum total cholesterol and creatinine levels among the low-molecular-weight heparin group, insulin group, and combined treatment group before treatment and on days 1,2, and 6 of treatment (P>0.05). However, all three groups exhibited a significant reduction in these levels after treatment compared to pre-treatment (P<0.05). This suggests that all three treatment modes can effectively lower serum total cholesterol and creatinine, but no additional benefits were observed with combined treatment in terms of reducing serum total cholesterol and creatinine.

The calcium ion levels of the three patient groups showed no statistically significant differences in intra-group and inter-group comparisons on days 1, 2, and 6 of treatment compared to pre-treatment levels (P>0.05). This suggests that the three treatment modes may have no impact on the recovery of calcium ion levels in patients, and it could also be related to the limited number of cases included in this study.

We found that on the 2nd day of treatment, the serum TG levels of patients in the combined treatment group and the insulin group were significantly lower than those in the low-molecular-weight heparin group (P<0.05). On the 6th day of treatment, the serum TG, blood amylase, CRP and IL-6 levels of patients in the three groups were significantly lower than those before treatment (P<0.05). Besides, the serum TG, blood amylase, CRP and IL-6 levels of patients in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and the insulin group (P<0.05). These findings indicated that both low-molecular-weight heparin and insulin could reduce serum TG levels and exert anti-inflammatory effects, while the combination of low-molecular-weight heparin and insulin treatment could exert synergistic effects and improve efficacy.

APACHEII is currently an AP scoring system with extensive application, which can quickly predict the severity of the disease, evaluate the change of the condition and assist in clinical treatment. The MCTSI score takes into account the comprehensive evaluation of inflammatory response, pancreatic necrosis, and extrapancreatic complications. Both scores may reflect to some extent the severity of the disease. The results of this study showed that on the 6th day of treatment, the APACHE II scores of the three groups of patients, as well as the MCTSI scores of the insulin group and the combination therapy group, were significantly lower than those before treatment (P<0.05). Besides, the MCTSI scores and APACHEII scores of patients in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and the insulin group (P<0.05). The hospital stay and treatment cost in the combined treatment group were significantly lower than those in the low-molecular-weight heparin group and the insulin group (P<0.05), suggesting that the combination treatment could reduce the severity of the disease, shorten the course of the disease, and lower the treatment cost.

Conclusion

In summary, low-molecular-weight heparin combined with insulin treatment can significantly reduce serum TG and serum inflammatory factor levels, reduce the severity of the disease, shorten the course of the disease, and reduce treatment costs. This approach is worthy of clinical promotion and application.

Fund project: Huaibei Science and Technology Project (2022HK002).

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