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To investigate the effect of alprostadil on the efficacy, liver function, inflammatory response, caspase-3 and ICAM-1 in acute liver injury of sepsis.

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Abstract

Objective: To investigate the effects of alprostadil on the efficacy, liver function, inflammatory response, caspase-3 and ICAM-1 in acute liver injury of sepsis.

Methods: Case data of sixty-nine (69) patients with acute liver injury of sepsis in our hospital from January, 2014 to December, 2016 were analysed retrospectively, of whom, 30 cases were given routine anti-sepsis and recruited into the control group. 39 cases were given alprostadil treatment on the basis of the control group and recruited into the observation group. Then liver function, inflammation reaction and caspase-3 and ICAM-1 changes before and after treatment in the two groups were observed.

Results: There were no statistical differences in APACHEII score between the two groups before treatment in two groups (P>0.05). There were significant statistical differences in APACHEII score between the two groups before and after treatment (P<0.05). After three and seven days' treatment in the observation group, APACHEII score lower than the control group obviously. Differences between groups were obvious (P<0.05). There were no significant statistical differences between groups before treatment with respect to ALT and AST levels (P>0.05). There were significant statistical differences between groups before and after treatment with respect to ALT and AST levels (P<0.01). After three and seven days' treatment in the observation group, ALT higher than the control group obviously, after seven days' treatment in the observation group, ALT higher than the control group obviously, differences between groups were obvious (P<0.05). TNF-α in the two groups before treatment had no obvious differences (P>0.05), and there were statistical differences before and after treatment in the two groups (P<0.05). After three and seven days' treatment, TNF-α level in the observation group lower than the control group, differences between groups were obvious (P<0.05). There were no significant differences before treatment between groups with respect to caspase-3 and ICAM-1 levels (P>0.05). There were statistical differences after treatment in two groups with respect to caspase-3 and ICAM-1 levels (P<0.05), After one, three and seven days' treatment in the observation group, caspase-3 and ICAM-1 levels lower than the control group obviously, differences between groups were obvious (P<0.05).

Conclusion: Alprostadil in treating acute liver injury of sepsis can promote recovery of liver function effectively and relieve inflammatory reaction caused by sepsis.

Keywords: Sepsis, Acute liver injury, Alprostadil, Liver function, Inflammatory reaction.

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Introduction

Sepsis is a kind of severe inflammatory reaction syndrome of the whole body caused by infection. It usually causes injury of multiple organs, thus leading to multiple organ dysfunctions syndrome. Liver is one of the most frequently damaged organs [1]. Studies [2] find that abnormal changes of liver structure, function, metabolism produce severe impacts on progress of sepsis. By far, relevant mechanism of liver injury of sepsis is not yet unified. Acute liver injury can occur in different stages of sepsis. Relevant documents [3] show that early liver dysfunction is regarded as one of important factors for sepsis independent prognosis. So improving liver function of acute liver injury of sepsis as soon as possible is the key to improve liver injury of sepsis independent prognosis. Animal studies before [4] have intervened sepsis rats with alprostadil. The results find that alprostadil can effectively relieve inflammatory reaction, thus promoting recovery of liver injury. Relevant clinical studies [3] also show that alprostadil has significant effects applied into acute liver injury of sepsis. This study analyses the influences of effects of alprostadil on acute liver injury of sepsis, liver function, inflammatory reaction, caspase-3 and ICAM-1. Detail reports are shown in the following.

Materials and Methods

General data

Ethical approval was given by the medical ethics committee of affiliated hospital of Nantong university with the following reference number: 2013007, case data of 69 patients with acute liver injury of sepsis in our hospital from January, 2014 to December, 2016 were analysed retrospectively. Inclusive criteria: It was diagnosed as sepsis in clinic; ages were over 18 y old; APACHEII scores were over 80 U/L, STB was over 33 μmol/l, CB was over 33 μmol/l. Exclusive criteria: patients who not met inclusive criteria; patients who had primary liver diseases, obstructive jaundice and so on; patients who had acute myocardial infarction; patients with chronic hepatitis needed to long-time dialysis treatment; patients who had malignant tumor, pregnant and so on; patients who contraindicated to alprostadil relevant drug; patient without complete case data.

Of which, 30 cases were given routine treatment and recruited into the control group. The ratio between males and females was 20/30. The ages were from 38 to 71 y. Mean age was 65.23 ± 15.23 y. The average weight was 62.35 ± 11.26 kg. The body temperature was 38.41 ± 0.32°C. ALT average level was 305.23 ± 62.52 U/L. AST was 308.45 ± 59.36 U/L. WBC average level was (14.23 ± 4.98 × 10^9/L). PACHEII score was 18.12 ± 3.15. 39 cases were given alprostadil on the basis of the control group and recruited into the observation group. The ratio between males and females was 22/17. The ages were from 35 to 75 y. Mean age was 66.23 ± 14.98 y. The average weight was 63.15 ± 12.02 kg. The body temperature was 38.14 ± 0.38°C. ALT average level was 304.15 ± 59.87 U/L. ALT average level was 307.68 ± 58.96 U/L. WBC average level was 14.20 ± 65 × 10^9/L. PACHEII score was 17.99 ± 3.05. There were no statistical differences in general data such as sex, age and conditions of patients in two groups (P>0.05). It had comparability.

Methods

The control group were given routine anti-sepsis treatment to treat primary diseases and control infection, given liquid treatment such as crystoloid solution, protein; when HCT below 30%, they were given appropriate blood products and nutrition *in vivo* promptly; then giving diammonium glycyrrhizinate injection (manufacture factory: Guangdong Shunfeng pharmaceutical Co., LTD, SFDA approval number H20053493) and GSH (manufacture factory: Shandong Lvye pharmaceutical Co., LTD, SFDA approval numberH20030001) to protect liver function.

The observation group were given alprostadil on the basis of the control group. 10 μl alprostadil (manufacture factory: Hainan Kaibi pharmaceutical Co., LTD, SFDA approval number) was added into 10 ml 0.9% NaCl for venous injection treatment. Once medication every 12 h for one week constantly.

Observation indices

Changes of liver function, inflammatory reaction, caspase-3 and ICAM-1 before and after treatment in two groups were observed. Serum detection indexes: 2 ml animal blood in the 1 d, 3 d and 7 d before and after treatment were collected. Closed vacuum blood tube with anti-coagulant was used for extraction and storing. Within 2 h, 3000 r/min used to do centrifugation fully, after serum separation, it was placed EP tube for sealing under minus 80°C to be detected. Serum indices were detected by using ELISA method, then following instructions of kits strictly.

Statistical analysis

Data were analysed by using SPSS 18.0 software. Measurement data was represented as mean ± SD. Comparison between groups was done with independent sample t-test. Enumeration data represented as (n, %) and done with χ^2 test. Statistical significance was assumed at p<0.05.

Results

APACHEII score comparison of patients before and after treatment in the two groups

There were no statistical differences in APACHEII score before treatment between groups (P>0.05); There were significant statistical differences in APACHEII score (P<0.05), and in the 3 d and 7 d after treatment in the observation group, APACHEII score lower than the control group obviously, differences between groups were obvious (P<0.05). Details are shown in Table 1.

Table 1. *APACHEII score comparison of patients before and after treatment in the two groups ($\bar{x}$ ± s).*

Group	Before treatment	1 d after treatment	3 d after treatment	7 d after treatment	F	P
The observation group (n=39)	18.12 ± 3.15	17.65 ± 3.25	15.32 ± 3.06	11.12 ± 2.65	105.32	<0.01
The control group (n=30)	18.46 ± 3.05	18.01 ± 3.65	17.69 ± 3.25	15.89 ± 2.98	7.65	0.042
t	0.451	0.432	3.104	7.126		
P	0.654	0.667	0.003	<0.01		

Analysis of liver function index changes condition before and after treatment in the two groups

There were no statistical differences before treatment with respect to ALT and AST levels (P>0.05); there were significant differences before and after treatment in the two groups with respect to ALT and AST levels (P<0.05), in the 3 d and 7 d after treatment, ALT level in the observation group significantly higher than the control group, in the 7 d after treatment, AST level higher than the control group, differences

between groups were obvious (P<0.05). Details are shown in Table 2.

Table 2. *Analysis of liver function index changes condition before and after treatment in the two groups ($\bar{x} \pm s$).*

Group	Indexes	Before treatment	1 d after treatment	3 d after treatment	7 d after treatment	F	P
The observation group (n=39)	ALT (U/L)	304.15 ± 59.87	305.32 ± 60.12	229.36 ± 46.42	193.25 ± 30.57	206.59	<0.01
	AST (U/L)	307.68 ± 58.96	308.56 ± 59.63	301.32 ± 43.51	211.29 ± 29.86	196.35	<0.01
The control group (n=30)	ALT (U/L)	305.23 ± 62.52	307.45 ± 59.96	285.26 ± 50.26	242.15 ± 38.45	156.47	<0.01
	AST (U/L)	308.45 ± 59.36	308.99 ± 60.42	305.24 ± 49.98	259.32 ± 30.75	132.32	<0.01

Analysis of TNF-α change condition of patients before and after treatment in the two groups

There were no statistical differences in TNF-α level before treatment in two groups (P>0.05); there were statistical differences before and after treatment in two groups (P<0.05), in the 3 d and 7 d after treatment, TNF-α level in the observation group lower than the control group, differences between groups were obvious (P<0.05). Details are shown in Table 3.

Table 3. *Analysis of TNF-α change condition of patients before and after treatment in the two groups ($\bar{x} \pm s$), pg/ml).*

Group	Before treatment	1 d after treatment	3 d after treatment	7 d after treatment	F	P
The observation group (n=39)	295.65 ± 52.36	293.68 ± 53.26	269.65 ± 46.35	129.65 ± 42.14	99.85	<0.01
The control group (n=30)	296.35 ± 53.48	297.42 ± 54.25	300.25 ± 55.44	178.65 ± 39.54	39.65	<0.01
t	0.054	0.287	2.496	4.917		
P	0.956	0.775	0.015	<0.01		

Analysis of caspase-3 and ICAM-1 levels change conditions before and after treatment in the two groups

There were no significant statistical differences before treatment between groups with respect to caspase-3and ICAM-1 levels (P>0.05); there were statistical differences in caspase-3 and ICAM-1 levels of patients after treatment in two groups (P<0.05); in the 1 d, 3 d, 7 d after treatment, caspase-3 and ICAM-1 levels obviously lower than the control group, differences between groups were obvious (P<0.05). Details are shown in Table 4.

Table 4. *Analysis of caspase-3 and ICAM-1 level change conditions before and after treatment in the two groups ($\bar{x} \pm s$).*

Group	Indexes	Before treatment	1 d after treatment	3 d after treatment	7 d after treatment	F	P
The observation group (n=39)	Caspase-3 (μmol/L)	48.35 ± 12.89	30.12 ± 10.21	26.35 ± 9.46	25.45 ± 9.89	169.35	<0.01
	ICAM-1 (μg/L)	406.35 ± 69.68	303.35 ± 56.35	265.32 ± 35.861	135.36 ± 23.16	201.03	<0.01
The control group (n=30)	Caspase-3 (μmol/L)	49.68 ± 13.03	48.32 ± 12.56	35.53 ± 10.45	32.25 ± 10.09	130.21	<0.01
	ICAM-1 (μg/L)	405.62 ± 70.65	402.15 ± 68.19	368.79 ± 42.65	275.32 ± 38.26	186.32	<0.01

Discussion

Inflammatory medium plays an important role when sepsis patients have acute liver injury. Of which, TNF-α has been one of key factors for occurrence, development and prognosis of acute liver injury of sepsis. At the same time, this factor also can promote production of other relevant inflammatory factors, thus inducing infiltration of neutrophil in liver tissue, promoting production of protease and oxygen radical, as well as promoting liver injury and liver function failure [5]. Alprostadil is a kind of lipid mediators, composed of arachidonic acid synthesized by relevant enzyme family such as cyclooxygenase and PG. Alprostadil distributes in human body widely, it not only has biological spectrum vasodilating activities, also can inhibit infiltration of inflammatory cell factors and synthesis of immune compound etc. Studies showed [4] that alprostadil can lower the inflammatory factors such as TNF-α, IL-1 and IL-6 expression levels *in vivo* of sepsis patients, thus inhibiting infiltration of inflammatory factors, lowering expression degree of inflammatory factors and reducing inflammatory reaction of body. Animal studies [6] found that alprostadil can increase c AMP expression in cell by combining with special PGs in cell membrane, thus promoting Epacl activation. Alprostadil has function of protecting vascular endothelial cells. It can dilate vessels, lower peripheral resistance and inhibit synthesis of

thromboxane A2, thus reducing snipe of platelet, improving synthesis of free radical and maintaining stability of cellular structure and metabolic function and so on. By far, alprostadil has been applied into important sectors such as cardiovascular diseases, kidney diseases and liver diseases etc. widely. And it plays an important role. When acute liver injury of sepsis occurs, it not only exist circulation dysfunction of liver microvessel, also severe inflammatory reaction. So Liu et al. [7,8] have applied alprostadil into acute liver injury of sepsis patients. The results show that its treatment effects on liver injury.

The results of this study show that APACHEII score, ALT, AST, TNF-α, caspase-3, ICAM-1 levels of patients who has adopted routine anti-sepsis treatment and combination of alprostadil in two groups have no obvious differences, so conditions of patients before treatment in two groups are similar; the results after treatment find that indexes above of patients in two groups have a certain improvement. Indexes of patients who combine with alprostadil treatment above are better than patients in routine anti-sepsis group. So alprostadil combination application can enhance protection effects on hepatic cells. Studies before [9,10] have showed that ICAM participates in vascular cell adhesion of neutrophil, lymphatic cells and monocyte etc. during inflammatory reaction process, it also plays an important role in the process of leukocyte migrating to inflammatory area. Abnormal ICAM expression can cause endothelial cell injury, also can promote release of leukocytes and other inflammatory factors. Caspase-3 is an important effector caspases participating in apoptotic cell death has been demonstrated. Some scholars [11] find caspase-3 can lower muscle tension through its function on cell apoptosis and inflammatory reaction pathway. This results show that caspase-3 and ICAM-1 levels of patients in two groups decrease with different levels after treatment. The decreased degree of patients in alprostadil group higher than routine anti-sepsis group. These results are in accordance with study results of Jia et al. [12].

Overall, alprostadil in treating acute liver injury of sepsis can promote liver function recovery effectively and relieve inflammatory reaction caused by sepsis.

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