Application of reduced glutathione in the elderly with hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale

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ABSTRACT: OBJECTIVE To investigate the effect of reduced glutathione (GSH) on the hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale in the elderly. **METHOD** A total of 66 patients aged 60 years or older with hepatic dysfunction following acute exacerbation of chronic cor pulmonale were randomly divided into 2 groups. All patients received conventional basic therapy for acute exacerbation of chronic cor pulmonale. The control group (n = 31) received intravenous inosine 1.0g, vitamin C 2.0g, and kali magnesii aspartatis 20mL once daily for 2 weeks. The GSH group (n = 35) received intravenous GSH 1.2g q12h for 2 weeks. The protective effect against hepatic damage was evaluated by measuring alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), total bile acid (TBA), albumin (ALB), prothrombin time (PT) and child-pugh score at admission and after treatment. **RESULTS** The GSH group was superior to the control group in the improvements of hepatic function and symptom. The improvements of ALT, AST, TBIL, TBA and child-pugh score in the GSH group were significantly better than those in the control group (P < 0.01). The 30-day incidence of acute renal failure in the GSH group was lower than that in the control group (P < 0.05). There were no statistical differences in the ALB, PT, mortality at discharge and 30-day incidence of multiple organ dysfunction syndrome (MODS) between the 2 groups (P > 0.05). **CONCLUSION** GSH is an effective and safe treatment for hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale in the elderly. The efficacy of GSH is superior to that of conventional treatment for hepatic dysfunction on the basis of controlling infection, improving hypoxemia and hypercapnia and treating the right heart failure.

KEY WORDS: reduced glutathione (GSH); chronic cor pulmonale; hepatic dysfunction

还原型谷胱甘肽在老年慢性肺心病急性加重期肝损害患者中的应用

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摘要:目的 探讨还原型谷胱甘肽(GSH)对老年慢性肺心病患者急性加重期肝损害的作用。方法 66例60岁以上老年慢性肺心病急性加重期肝损害患者随机分为两组。所有入选患者采用慢性肺心病急性加重期常规方案治疗。对照组($n=31$)护肝采用静脉滴注肌苷1.0g,维生素C 2.0g和门冬氨酸钾镁20mL,1次/d,连用2周。治疗组($n=35$)护肝采用GSH 1.2g经静脉输入,2次/d,连用2周。同时监测治疗前后肝功能指标血丙氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)、总胆红素(TBIL)、总胆汁酸(TBA)、白蛋白(ALB)、凝血酶原时间(PT)及child-pugh评分并进行对照比较。结果 治疗组较对照组在慢性肺心病急性加重期肝损害的肝功能复常方面显示更为良好的治疗效应,ALT, AST, TBIL, TBA和child-pugh评分改善明显好于对照组(P均<0.01);治疗组30d内急性肾功能衰竭的发生率低于对照组($P<0.05$);PT, ALB,出院时的死亡率和30d内多脏器功能障碍综合征(MODS)发生率两组比较无显著性差异(P均>0.05)。结论 GSH治疗老年慢性肺心病急性加重期患者肝损害是有效的和安全的。在慢性肺心病常规方案治疗的基础上应用GSH对老年慢性肺心病急性加重期患者肝损害具有一定的改善作用,其疗效优于常规护肝治疗。

关键词:还原型谷胱甘肽;慢性肺心病;肝损害
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In recent years, with the continuously increased proportion of the elderly in our society the age at which chronic cor pulmonale usually arises has backed from 50 years old in 1950' to 60 or 70 years old. Although dysfunction of heart and lung is the primary characteristic of acute exacerbation of chronic cor pulmonale in the clinical, multiple systems and organs function is usually impaired as a result of hypoxemia and hypercapnia. In the older patients, the more organs were impaired and the worse patients became. The hepatic dysfunction is one of the important and frequent complications in the elderly with acute execration of chronic cor pulmonale. It is reported that incidence of hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale is 42.6% ~60.0% in all acute exacerbation of chronic cor pulmonale patients and the mortality of patients with hepatic dysfunction is 33% higher than that of patients with normal hepatic function[1]. The pathogenic mechanisms of hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale is complicated. But congestion of liver induced by the exacerbation of right heart failure, hypoxemia and hypercapnia resulted from respiration failure and reiterative infection in lung are thought to be the main reasons for hepatic dysfunction[1]. Therefore, controlling infection, improving hypoxemia, hypercapnia and right heart failure are the basis of treatment for hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale. But the hepatic dysfunction usually meliorates slowly when only basic treatment for acute exacerbation of chronic cor pulmonale is selected. So many clinicians treated with conventional drugs for hepatic dysfunction, whereas the efficacy was not satisfying.

Reduced glutathione (GSH) is a tripeptide composed of three amino acids: cysteine, glutamic acid and glycine. And GSH is also one of the most important endogenous water-phase antioxidants and essential cofactor for antioxidant enzymes. It plays the role of a sulfhydryl (SH) group provider for direct scavenging reactions. Many reports of application of GSH in the clinical can be found in recent years, but most of these were applied to the hepatic dysfunction induced by drugs, alcohol and radioactivity. As yet few reports have been found that GSH was applied to hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale in the elderly. In the elderly with acute exacerbation of chronic cor pulmonale the biological synthesis of GSH and the antioxidative ability decrease significantly. As a result of hypohepatia and decreased hepatic compensative ability liver of the elderly is impaired easily. Thus the supplement of GSH in time may prevent, relief and stop the injury of the tissue and cells in the liver and slow the pathologic process. In this study the changes of hepatic function and the prognosis of the elderly treated with GSH for hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale were observed and the significance of GSH treatment in the clinical was explored.

1 MATERIALS AND METHODS

1.1 Selection Criteria

In this randomised clinical trial, 66 patients with hepatic dysfunction induced by acute exacerbation of acute exacerbation of chronic cor pulmonale were included within 24h of diagnosis in the Intensive Care Departments of Zhejiang TCM hospital. Acute exacerbation of chronic cor pulmonale was identified through the criterion which was established by National Academic Meeting of acute exacerbation of chronic cor pulmonale in 1997 in China.

Chronic cor pulmonale was caused by chronic obstructive pulmonary disease (COPD) in all patients enrolled. Hepatic dysfunction was identified through the following criteria: plasma concentration of alanine aminotransferase (ALT) >80U/L or total bilirubin (TBIL) >34.2μmol/L.

1.2 Exclusion Criteria

The following patients were excluded from the trial:

1.2.1 Patients with hepatocirrhosis, viral hepatitis and fatty liver.

1.2.2 Patients with any positive antigen or antibody of any hepatitis virus and sign of hepatocirrhosis, viral hepatitis and fatty liver in Brightness modulated (B-mode) ultrasound examination.

1.2.3 Patients taking any drugs which impair liver or with hepatic dysfunction caused by factors independent of acute exacerbation of chronic cor pulmonale.

1.3 Characteristics of Study Patients at Trail Admission

Eligible patients were randomly divided into 2 groups: the GSH group (n=35) and the control group (n=31). There are no significant differences in clinical characteristics between the 2 groups. Table 1 shows the main clinical data for patients enrolled.

1.4 Treatment Protocol

All patients received conventional therapy for acute exacerbation of chronic cor pulmonale, including sensitive antibiotics, maintaining airway expedite, improving hypoxemia and hypercapnia, treating heart failure and other treatment according to the patient's pathophysiology. The control patients (n=31) received intravenous inosine 1.0g, vitamin C 2.0g, and kali magnesii aspartatis 20mL once daily for 2 weeks. The patients treated with GSH (n=35) received intravenous GSH (Laboratorio Farmaceutico C.T., Sanremo, Italy) 1.2g ql2h for 2 weeks.

Blood samples were collected in 5mL at 6am and determined by biochemical auto-analyzer. The therapeutic effect against hepatic damage was evaluated by measuring ALT, aspartate transaminase (AST), TBIL, total bile acid (TBA), Albumin (ALB), prothrombin time (PT) and child-pugh score at admission and after treatment. Mortality at hospital discharge, 30-day incidence of multiple organ dysfunction syndrome (MODS)[2] and acute renal failure (ARF) were evaluated.

1.5 Statistics

Analysis was based on intent to treat. Results are reported as mean±SD.

The significance of differences between 2 groups and efficacy of each group were evaluated through analysis of Student's test. Mortality and incidence of MODS, ARF data were analyzed using Continuity Correction test.

Statistical significance was accepted as P value <0.05. All analyses were carried out using the SPSS 10.0 statistical package.

Tab 1 Characteristics of study patients at trial admission

表 1 两组病例治疗前相关资料对比

	GSH group (n=35)	Control group (n=31)	P value
Sex (male/female)	21/14	20/11	>0.05
Age (year)	72.9±10.6	73.2±11.3	>0.05
$PaCO_2$ (kPa)	9.47±2.35	9.29±2.61	>0.05
PaO_2 (kPa)	6.71±1.37	6.64±1.89	>0.05
Child-pugh (A/B)	13/22	10/21	>0.05
Child-pugh score	7.5±1.9	7.3±1.7	>0.05
AST (U/L)	175.9±68.9	169.5±70.3	>0.05
ALT (U/L)	142.4±57.4	135.5±49.9	>0.05
TBIL (μmol/L)	39.3±17.5	35.7±19.7	>0.05
TBA (μmol/L)	14.6±4.1	16.9±3.8	>0.05
ALB (g/L)	28.1±7.9	29.5±9.2	>0.05
PT (s)	16.2±3.2	16.7±3.6	>0.05
APACHE II score	27.1±5.3	29.6±6.4	>0.05

2 RESULT

GSH significantly decreased patients' ALT, AST, TBA, TBIL and child-pugh score after treatment as compared with those of the control group (P<0.01). There are no significant differences in PT and ALB between 2 groups (P>0.05).

There were no significant differences in mortality at hospital discharge and 30-day incidence of MODS between the 2 groups (P>0.05), but the 30-day incidence of ARF in the GSH group was lower than that in the control group (P<0.05).

3 DISCUSSION

At present the basic treatment for acute exacerbation of chronic cor pulmonale plus conventional drugs therapy for hepatic dysfunction is the main therapeutic protocol for hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale. But as to the elderly, on account of the difficulty in basic treatment for acute exacerbation of chronic cor pulmonale, recovery is so slow and conventional drugs therapy for hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale are not satisfying. Consequently, to find new drugs for it has been one of the hottest subjects of the current research in the clinical. Furthermore, liver plays a key role in multiple regulatory aspects of host defense during sepsis. And hepatic injury can augments lung inflammation early after sepsis[3]. As sepsis can be found in most patients with acute exacerbation of chronic cor pulmonale, the effective treatment for hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale may be beneficial to the full recovery from acute exacerbation of chronic cor pulmonale.

Tab 2 Hepatic function analysis of patients($\bar{x} \pm s$)

表 2 两组慢性肺心病患者治疗前后肝功能情况

	GSH group (n =35)			Control group (n =31)		
	before treatment	after treatment	decrement	before treatment	after treatment	decrement
ALT (U/L)	175.9 ±68.9	43.3 ±24.5	132.6 ±58.1[2,4)]	169.5 ±70.3	84.6 ±43.1	84.9 ±46.2[2)]
AST (U/L)	142.4 ±57.4	45.2 ±28.9	97.2 ±41.9[2,4)]	135.5 ±49.9	81.3 ±47.6	54.2 ±31.5[2)]
TBIL (μmol/L)	39.3 ±17.5	19.4 ±9.6	19.9 ±9.1[2,4)]	35.7 ±19.7	27.3 ±13.6	8.4 ±5.3[2)]
TBA (μmol/L)	14.6 ±4.1	10.2 ±3.2	4.4 ±1.2[2,4)]	16.9 ±3.8	14.5 ±3.6	2.4 ±0.7[2)]
PT (s)	16.2 ±3.2	15.9 ±2.9	0.3 ±1.1	16.7 ±3.6	16.6 ±3.0	0.1 ±0.7
ALB (g/L)	28.1 ±7.9	29.3 ±8.5	- 1.2 ±3.6	29.5 ±9.2	30.6 ±9.8	- 1.1 ±3.7
Child-pugh score	7.5 ±1.9	6.1 ±1.4	- 1.4 ±0.3[2,4)]	7.3 ±1.7	6.5 ±1.3	- 0.8 ±0.2[2)]

Note: [1)] $P<0.05$, [2)] $P<0.01$: compared with value before treatment; [3)] $P<0.05$, [4)] $P<0.01$: compared with the control group; decrement = value before treatment-value after treatment

注:与本组治疗前比较: [1)] $P<0.05$, [2)] $P<0.01$;与对照组比较: [3)] $P<0.05$, [4)] $P<0.01$;差值 =治疗前 -治疗后)

Tab 3 Prognosis and complication of patients

表 3 两组慢性肺心病患者治疗后转归及并发症情况

	Death	MODS	ARF
GSH group (n =35)	4(11.4%)	5(14.3%)	3(8.6%)[1)]
Control group (n =31)	5(16.1%)	7(22.6%)	9(29.0%)

Note: [1)] $P<0.05$: compared with the control group

注:与对照组比较: [1)] $P<0.05$

GSH is an ubiquitous thiol-containing tripeptide that plays a key role in cell biology and has remarkable protective effect on many kinds of tissue injury. In human, liver is the main place where GSH is synthesized and most concentrated (10mM)[4]. GSH plays an important role in biochemical metabolisms in the liver. And enough GSH concentration is a necessary condition for preventing hepatocyte from necrosis[5]. According to current study, GSH can protect liver in many aspects. Its mechanism may relate to the effect of scavenging free radicals, antioxidation, protecting the cytomembrane and mitochondrion, improving the energy and TBA metabolism of hepatocyte, promoting the restoring and regeneration of hepatocyte and detoxification[6~8]. Especially the formation of GSH peroxidative liposome of membrane can activate the superoxide dismutase (SOD), maintain the concentration of GSH in body, scavenge free radiacals, enhance the detoxifcative ability of liver, protect cell membrane and mitochondrion and finally protect the hepatocytes[6]. In addition, GSH can decrease peroxidative indexes and improve the clinical scores in patients with early septic shock[9], which may be helpful to patients who are attacked by both acute exacerbation of chronic cor pulmonale and sepsis.

Our results confirm the protective effect of GSH on hepatic function parameters in patients with acute exacerbation of chronic cor pulmonale. The improvements of ALT, AST, TBIL, and TBA in the GSH group were superior to those in the control group. The GSH treatment was well-tolerated and no serious side effect was found. In this study, there is no significant difference of ALB between the 2 groups and within each group. The reasons may be complicated, because nutrition, infection and system inflammatory reaction can influence ALB much in critically ill patients. The mechanism of no significant difference of PT between the 2 groups and within each group should be explored and analyzed further. Also, there are no significant differences between the 2 groups in mortality and 30-day incidence of MODS. The reasons may be that the number of patients in the study is too small; on the other hand, the most important problems of acute exacerbation of chronic cor pulmonale are infection, hypoxemia and hypercapnia. Thereby, controlling infection, improving hypoxemia and hypercapnia are still the pivotal treatment which determines the prognosis. We do not expect that antioxidant therapy alone, as a assistant treatment, will greatly improve the survival of patients with acute exacerbation of chronic cor pulmonale, because acute exacerbation of chronic cor pulmonale is not simply induced by free-radicals alone. However, we consider antioxidants to be useful components of multidrug therapies.

Being antioxidant and modifier of cell metabolism, GSH also can modulate immune function, protect kidney, prevent thrombus and protect blood vessel[10~12]. These functions are important for aged patients with acute exacerbation of chronic cor pulmonale. In this study, the 30-day incidence of ARF in the GSH group is lower than that in the control group ($P<0.05$), indicating that GSH can protect kidney to some extent. The protective effect to kidney is very important for patients with acute exacerbation of chronic cor pulmonale and may influence the prognosis. In this study, all patients with ARF received continuous blood purification (CBP) treatment and this may be a reason that there is no difference in mortality between the 2 groups.

In conclusion, intravenous administration of GSH is an effective and safe treatment for hepatic dysfunction induced by acute exacerbation of chronic cor pulmonale in the elderly. The efficacy of GSH is superior to that of conventional treatment for hepatic dysfunction on the basis of controlling infection, improving hypoxemia and hypercapnia and treating the right heart fail-

ure. The GSH treatment is significant for full recovery from critically ill and can increase the efficacy of treatments for acute exacerbation of chronic cor pulmonale in the elderly.

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