



Role of Intravenous Glutathione in Alcoholic Hepatitis

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ABSTRACT

It has been studied and documented that in alcoholic hepatitis and other chronic liver diseases, there is a reduction in hepatocyte glutathione level resulting in reduction of hepatocyte detoxifying action. The administration of high doses of intravenous (iv) glutathione in such patient population has demonstrated a significant improvement in some indices of liver function (SGOT, SGPT, GTT), suggesting the use of glutathione in alcoholic hepatitis.

Keywords: *alcoholic hepatitis, glutathione, hepatic steatosis, hepatocellular Ca.*

INTRODUCTION

Alcoholic liver disease (ALD) is a major cause of chronic liver disease worldwide and leads to fibrosis and cirrhosis. Alcohol related liver deaths account for up to 48 % of cirrhosis associated deaths in the United States and are also major contributors to liver disease related mortality in other countries.¹ The spectrum of ALD includes fatty liver, hepatitis, fibrosis and ultimately cirrhosis which may lead to hepatocellular carcinoma.

Ethanol toxicity on liver is a function of duration of alcohol intake, amount of daily intake of alcohol and patient's nutrition. The threshold of alcohol toxicity on liver is about 40g of ethanol daily in men and 20-30 g in women. Early work on the pathogenesis of ALD focused on ethanol associated oxidative stress, glutathione depletion, abnormal methionine metabolism, malnutrition and production of endotoxins that activate kupffer cells in hepatocytes.^{2,3}

Ethanol is primarily metabolized into acetyldehyde by alcohol dehydrogenase in the cytosol, cytochrome P450 in microsomes, and catalase in peroxisomes. Ethanol metabolism generates reactive oxygen species and causes lipid peroxidation, mitochondrial glutathione depletion and S-adenosylmethionine depletion; all leading to hepatocytes injury.⁴

Acetyldehyde is reactive compound, it is highly toxic to hepatocytes because it forms a variety of protein and DNA adducts that promote glutathione depletion, lipid peroxidation, and mitochondrial damage. Mitochondrial glutathione (GSH) plays a critical role in the maintenance of cell functions and viability. There seems to be no doubt regarding the importance of GSH in the detoxification of exogenous substances but its role in detoxifying endogenous metabolites have received less attention. We took up this study to assess the efficacy of intravenous GSH in alcoholic hepatitis.

AIMS AND OBJECTIVES

The present study is undertaken: To assess the efficacy of intravenous GSH in alcoholic hepatitis.

MATERIALS AND METHODS

Source of Data: The study is a randomized case control study conducted out at R.I.M.S, Imphal, Manipur from september 2016 to february 2017 in patients attending the Hospital. Patients' consents were taken prior to the study.

Inclusion Criteria: Patients diagnosed as alcoholic hepatitis as per AASLD guidelines as evident by elevated AST and ALT to a level of 2 to 6 times the normal with AST/ALT ratio > 2 were included in the study.⁵

Exclusion Criteria: Patients with other pre existing liver conditions such as viral hepatitis, NASH, auto-immune hepatitis, biliary cirrhosis, and patients with conditions and on drugs, that may alter hepatic functions were excluded in this study.

Methods

The study population consists of 100 patients (irrespective of sex and age, 96 males and 4 females; mean age: 45 yrs) with alcoholic hepatitis. Consent was taken from the study population prior to study. Detailed history was taken and patients were screened for other conditions that may affect liver function. The study population was divided into 2 groups of 50 patients each. One group was treated with iv glutathione and the other group was treated conventionally without glutathione therapy. The liver function the tests were assessed in both the groups at admission and after 15 days of admission and compared. Statistical analysis done using SPSS v21, paired t-test was used for comparison.

RESULTS AND ANALYSIS

Out of the total 100 patients enrolled, 50 were treated with intravenous glutathione 1200mg/day and 50 were treated conventionally without glutathione. The mean age of the study population was 46.43 yrs. The administration of glutathione

did not cause any major side effects. An improvement of pre existing symptoms was recorded in 45% of the patients. The improvement was generally reported after 10-15 days of treatment. In the patients treated with 1200mg /day of iv glutathione, significant improvement ($p < 0.010$) were observed in liver function indices (as reflected in table 2).

Table 1: Age and sex distribution

Characteristics	N
Gender	
Male	96
Female	4
Mean age in years (SD)	46.43(11.347)

Table 2: comparison of liver function before and after treatment

Parameter	Cases		P value	Control		P value
	Before Rx	After Rx		Before Rx	After Rx	
S. bilirubin	21.97	15.71	0.004	18.81	28.76	<0.00
SGOT	224.26	139.86	<0.00	243.80	337.10	0.003
SGPT	103.06	58.84	0.020	110.54	171.08	0.045
S. Albumin	2.82	3.00	0.003	2.75	2.35	0.010
GGT	208.42	136.60	0.003	207.44	282.30	<0.00
Alkaline P	263.36	183.00	<0.00	248.42	316.02	<0.00

DISCUSSION

Dentico et al⁶ studied the efficiency of intravenous glutathione in chronic steatohepatitis and found out that treatment with iv glutathione leads to improvement in some of the liver function indices which is consistent with our findings.

Glutathione is a tripeptide consisting of gamma glutamyl cysteinyl glycine and occurs in all living cells. It possesses a thiol group and participates in oxidation reduction reactions, acting as a principal cellular scavenger of free radicles. It was first synthesized in 1935 by Harington and Mead, and its chemistry and biochemical properties have been reviewed by Wieland (1954), Jocelyn (1958), and Isherwood (1959). Although widely

distributed in animal tissues, GSH is present in large concentrations in the liver. GSH in mitochondria originates from the cytosol by a transport system which translocate GSH into the matrix. This transport system is impaired in alcoholics and hence mitochondrial glutathione is reduced.

In man low levels of blood glutathione have been found in chronic liver disease

(De Groote and Vandenbroucke⁷, 1956), the level corresponding approximately to the extent of hepatic dysfunction; the glutathione level rose during recovery. In a study of 103 children with various types of liver disease the level of blood glutathione was usually low during the illness but rose during recovery (Helbeig, 1954).⁸ It therefore seemed reasonable to investigate the effect of glutathione on patients with liver disease.

Alcohol consumption leads to the formation of the toxic ethanol metabolite, acetaldehyde and increased oxidative stress, especially in the liver and the brain. Alcohol metabolism increases the pro-oxidative pressure by:

- generating free radicals and ROS which increase the pro-oxidative pressure on the antioxidant defense
- activating the metabolism of some drugs and chemicals increasing their hepatotoxicity
- suppresses the intrahepatic GSH concentration by:
 - reducing the hepatic GSH concentration via an increased biliary excretion.
 - inhibiting the glutamylcysteine synthetase activity
 - increasing demand for GSH in the hepatic detoxification pathways

Antioxidants and GSH precursors were shown to protect the liver against alcohol-related damage, and the aggravation of the hepatotoxicity when alcohol and certain drugs, medications or chemicals are co-administered.

Restoring the glutathione homeostasis is essential because of the crucial role of GSH in the body as a regulatory factor, a co-factor for enzyme

reactions and in the hepatic detoxification mechanism. Other antioxidants may restore the portion of GSH lost due to oxidation, but they cannot compensate for the lowered de-novo synthesis, or GSH excreted by the liver to other cells. Alterations in the liver GSH content may affect the systemic GSH homeostasis and affect the systemic antioxidant defense. The administration of GSH precursors supports the hepatic GSH synthesis, prevents liver cell damage, supports the body to compensate for oxidative stress.

CONCLUSION

The study results confirmed the good tolerability of glutathione. The administration of iv glutathione in alcoholic hepatitis showed the ability to significantly improve some indices of liver function and subjective complaints of patients. Further experimental tests may be needed to confirm the use of Glutathione in non alcoholic liver diseases and viral hepatitis.

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