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"To determine the effect of treatment with glutathione in acute hepatitis"

Dr. Salam Kenny Singh[1] ,Dr Manna Bhattacharjee[2], Dr. Thangjam Gautam Singh[3], Dr. NingthoukhongjamReema[4] , Dr Lourembam Robin Singh [5], Dr. Chatnera B Marak[6]

[1](*Associate professor, Department of Medicine, Regional Institute of Medical Sciences, RIMS, Imphal, India)*
[2,6,](*Junior Resident, Department of Medicine, RIMS, Imphal, India)*
[3] *(Assistant professor,Shijahospitals,Langol,India)*
[4,5](*Senior Resident, Department of Medicine, RIMS, Imphal, India)*
Corresponding author: Dr Ningthoukhongjam Reema

Abstract
Background*:*
Acute hepatitis is defined as active hepatocellular damage and necrosis, usually with a lobular inflammatory response, less than 6 months duration clinically evident by significant elevation (at least 2.5 x upper normal reference range) of serum ALT or AST. Acute hepatitis may be due to infections likeviral, bacterial; metabolic like alcoholic hepatitis, toxin and drug induced hepatitis, non-alcoholic fatty liver disease; autoimmune like post liver transplant, measles, primary sclerosing cholangitis etc.; genetic causes like alpha 1 antitrypsin deficiency, hemochromatosis, Wilson's disease etc. Viral hepatitis is the most common cause of acute hepatitis. Majority is due to hepatitis A and hepatitis B viruses. HBV and HCV infections are common in Manipur. There is high prevalence of HCV among IVDUs who are in sexually active age group. The administration of GSH precursors supports the hepatic GSH synthesis, prevents liver cell damage and supports the body to compensate for oxidative stress. The present study investigated the treatment effect of Glutathione injection in acute hepatitis.
Methods:*This non-randomized, interventional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from September 2018 to August 2020.84 cases of acute hepatitis patients who attended Medicine /Gastroenterology OPD or admitted in the General Medicine wards were enrolled. Liver function tests, viral markers, prothrombintime, completehemogram, USG whole abdomen and other investigations as per clinical suspicion were done.*
Results:*A total of 84 diagnosed cases of acute hepatitis were included in the study. Baseline characteristics of the study subjects were given in table 1. The mean age of the study population was 42.8 years ± 13.6 with the majority in age group 30-40 years (29.7%) and majority of them were males 67(79.8). Alcoholism was the most important cause of hepatitis in 29 (34.5%) participants followed by viral infection (27.4%). Hepatitis A was detected in 1(6%) participants, HBS Ag in 10(11.9%), HCV antibody in 11(13.1%) and R-antibody in 7(8.3%) patients. Majority of them (46.4%) had hepatomegaly in USG abdomen. There was reduction in mean bilirubin, AST, ALT, GGT and INR level after administration of glutathione for 7 days and the reduction was statistically significant.*
Conclusion: *In the present study glutathione is detected to be more efficacious in treating hepatic injury in acute hepatitis cases compared to placebo. Administration of glutathione in the intervention group was associated with significant reduction in all three principle liver enzymes (AST, ALT, GGT). Whereas placebo group showed reduction only in mean AST and ALT level but not in mean GGT level. From these findings, we can conclude that the treatment with glutathione causes more significant reduction in hepatic enzymes compared to placebo.*
Keyword: *alcohol, alcoholic liver disease, glutathione, hepatitis.*

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I. Introduction

Hepatitis has a broad spectrum of presentations that range from a complete lack of symptoms to severe liver failure. The acute form of hepatitis, generally caused by viral infection, is characterized by constitutional symptoms that are typically self-limiting.[1]Chronic hepatitis presents similarly, but can manifest signs and symptoms specific to liver dysfunction with long- standing inflammation and damage to the organ. [2]

Acute hepatitis is defined as active hepatocellular damage and necrosis, usually with a lobular inflammatory response, less than 6 months duration clinically evident by significant elevation (at least 2.5 x upper normal reference range) of serum ALT or AST.[3,4] Acute hepatitis may be due to infections likeviral, bacterial; metabolic like alcoholic hepatitis, toxin and drug induced hepatitis, nonalcoholic fatty liver disease; autoimmune like post liver transplant, measles, primary sclerosing cholangitis etc.; genetic causes like alpha 1 antitrypsin deficiency, hemochromatosis, Wilson's disease etc. [5]

Around 400 million people all over the world suffer from acute hepatitis. In India, viral hepatitis is a cause for major health care burden. HEV is responsible for majority of the sporadic and epidemic cases of acute viral hepatitis in India. The estimated prevalence of HCV infection in India is about 1–1.9% and the average estimated carrier rate of hepatitis B virus (HBV) in India is 40%, with a total pool of approximately 36 million.[6]

In 2015, entire Worldwide, hepatitis A occurred in about 114 million people, chronic hepatitis B affected about 343 million people and chronic hepatitis C about 142 million people. In the United States, NASH affects about 11 million people and alcoholic hepatitis affects about 5 million people. [7] Hepatitis results in more than a million deaths a year, most of which occur indirectly from liver scarring or liver cancer. In 2015 alone, 325 million people were living with viral hepatitis.[8]In Manipur HBV and HCV infections are very common with high prevalence of HCV among IVDUs who are in sexually active age group. A February 2013 report states that there are 454 persons undergoing treatment in ART center, JNIMS, who are co-infected with HIV and Hepatitis-C. During the same period ART center, RIMS, reported 769 such cases.[9,10]

Amongst the treatment of hepatitis which encompasses numerous varied and wide range of drugs and therapy, intense researches throughout are showing encouraging and proven efficacy of Glutathione. 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. GSH is present in large concentrations in the liver.[11,12] 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 acute hepatitis.[8] 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. [13,14,15]

Glutathione plays an important role in the repair of liver injury caused by virus, alcohol, drugs, and trauma. [16,17,18] However, data regarding the treatment effect of glutathione on all types of acute hepatitis are limited.[19,20] Hence, this present study was conducted to investigate the treatment effect of Glutathione injection in acute hepatitis patients in this part of the country.

II. Materials and Methods

This non-randomized, interventional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from September 2018 to August 2020.84cases of acute hepatitis patients who attended Medicine /Gastroenterology OPD or admitted in the General Medicine wards wereenrolled following the criteria.

Inclusion Criteria

1. Diagnosed cases of acute hepatitis as evident by elevated AST and/or ALT to a level of > 2.5 times the upper limit of normal with duration less than 6 months.
2.Those above 18 years of age giving consent for participation.

Exclusion Criteria include patients who have received glutathione injection within 3 weeks prior to admission, those already diagnosed as a case of chronic liver disease, pregnant ladies and those not giving consent for participation.

Study procedure Independent variables: Personal details including a detailed history of presenting symptoms, past history and personal history were recorded in proper proforma along with age, sex, BMI, dietary habits, alcoholism, smoking, IV drug abuse, clinicovirological profile like signs and symptoms and associated co-morbid conditions. A complete physical examination with emphasis on the disease activity and duration of every subject was also done. Liver function tests, viral markers, prothrombintime, completehemogram, USG whole abdomen and other investigations as per clinical suspicion were done.

WORKING DEFINITIONS:
Acute hepatitis - elevated AST and/or ALT to a level of >2.5 times the upper limit of normal (as per ASSLD guidelines) and duration of illness related to hepatitis < 6 month.
A patient was considered to have Hepatitis A (IgM HAV antibody positive), **Hepatitis B** {positive HBsAg and positive immunoglobulin M antibody to the hepatitis B core antigen (anti-HBcIgM)} ,and **Hepatitis C** if IgM anti HCV positive.

Significant alcoholism was considered if alcohol intake was equivalent to 33-45gm/day in male and 22-30gm/day in female while occasional alcoholism was considered ifalcohol intake was not regular and less than significant amount as mentioned above.

Study tools:
- Glutathione Injection 600 mg.
- 5 Part Autoanalyzer, brand: - Sysmex, model: XS 250, available at Department of Pathology, RIMS, Imphal.
- Clinical Biochemistry Analyzer EM 200, available at Department of Biochemistry, RIMS, Imphal.
- Automated clinical chemistry analyser vitros 250, available at Department of Biochemistry, RIMS, Imphal.
- ELISA Reader, Model: - EMAX Plus (Reader & Washer), available at Department of Microbiology, RIMS, Imphal.

Sample size: Estimated sample size was 84, divided in intervention and control group equally (42 each in intervention group and control group).

Statistical analysis: Study variables were expressed as frequency and percentages, mean (±SD) or median (IQR), depending on the type of distribution. Chi-square test, Fisher's Exact Test, Mann-Whitney U test & Wilcoxon signed rank test (data following non-normal distribution) and Independent sample t test (data following normal distribution) were applied to test the significance. P value less than 0.05 was considered as statistically significant. Analysis of the data was done by IBM SPSS version 20.
Approval of Research Ethics Board and Informed consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal. (Ref No. A/206/REB-Comm (SP)/RIMS/2015/429/47/2018.)

III. Results

A total of 84 diagnosed cases of acute hepatitis were included in the study. Baseline characteristics of the study subjects were given in table 1. The mean age of the study population was 42.8 years ± 13.6 with the majority in age group 30-40 years (29.7%) and majority of them were males 67(79.8). Distribution of etiological factors of acute hepatitis were given in figure 1. Hepatitis A was detected in 1(6%) participants, HBS Ag in 10(11.9%), HCV antibody in 11(13.1%) and R-antibody in 7(8.3%) patients. Most of the participants (75%) were alcoholic, among them 42 participants (50%) were detected to have significant alcoholism. Significant alcoholism was defined as 22-30g alcohol/day for woman and 33-45g/day in man. Alcoholism is detected to be the most important cause of hepatitis in the participants followed by viral infection and drugs.29 (34.5%) subjects detected to have hepatitis due to significant alcohol consumption.8(9.5%) participants have history of IV drug abuse. Most of the subjects were non-vegetarian (89.3%). Most common presenting symptom was nausea and vomiting, which was documented among 85.7%of participants followed by abdominal pain (52.4%). Hepatomegaly was detected in 86.9% of study population and 41(48.8%) participants had icterus on presentation. Majority of the study subjects 83.3% (70) had GCS score of 15. Among the participants 7(8.3%) people were diabetic, 10(11.9%) were hypertensive and 9(10.7%) were on anti-tubercular drugs. 14(16.7) participants were having some existing liver disease other than chronic liver disease and 6% and 7.1% study population was having heart disease and kidney disease respectively. Majority of the subjects (52.4%) had normal BMI.

Baseline biochemical profiles and BMI among intervention and control group were compared and given in table 2. Comparison in intervention group before and after administration of glutathione was given in table3. Similarly, comparison in control group before and after administration of placebo therapy was given in table 4. There was no significant difference among the cases and controls on comparing the demographic data like age, sex diet etc. There was significant difference among cases and controls on comparing day 7 mean ALT, AST and GGT level. Significant reduction of mean ALT, AST and GGT level were also detected before and after administration of glutathione. Therefore, the use of glutathione in acute hepatitis was found to beneficial in improving symptomatology as well as reducing liver enzymes (ALT, AST, GGT).

Table No.1:Baseline characteristics of study population.

Parameter	**Results n(%) 84(100%)**
Age in years, mean (range)	42.8±13.6years
Gender: Male Female	67(79.8%) 17(20.2%)
Alcohol consumption Nil Occasional Significant	 21(25%) 21(25%) 42(50%)
Smoker Intravenous drug user	45(53.6%) 8(9.5%)
Signs Hepatomegaly Jaundice Splenomegaly Altered sensorium Ascites	 86.9% 48.8% 23.8% 13.1% 4.8%
Symptoms Nausea/vomiting Pain abdomen Hematemesis Fever Loss of appetite Fatigue	 85.7% 52.4% 52.4% 51.2% 48.8% 47.6%
Viral markers HbsAg+ve Anti HCV +ve R antibody +ve Hepatitis A +ve Hepatitis E +ve	 11.90% 13.1% 8.3% 6% 10.7%
UGIE Normal Varices	 17.9% 3.6%

Figure No. 1: Distribution of etiological factors of acute hepatitis

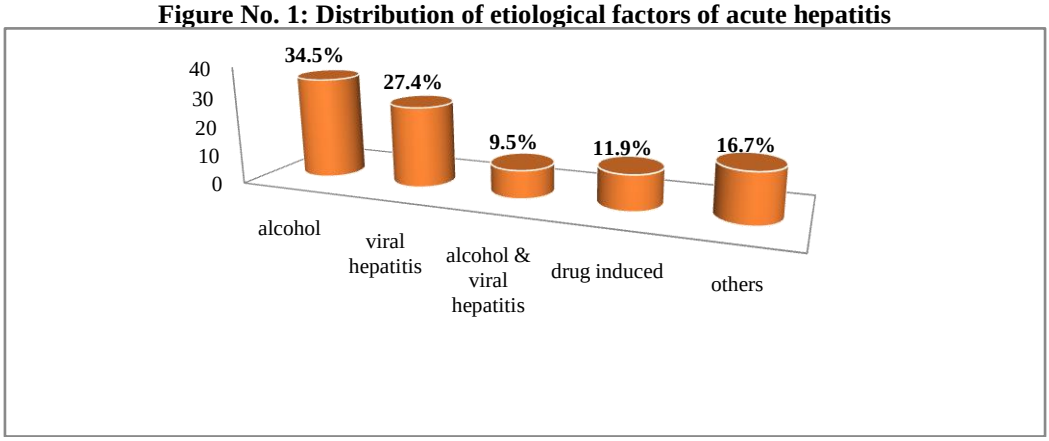

Table No.2: Comparison of baseline biochemical profiles and BMI among intervention and control group

Parameter	Intervention group n=42 (mean ± SD)	Control group n=42 (mean ± SD)	Mean Difference	p value
BMI	20.4±3.1	20.2±3.1	-0.20	.77
Haemoglobin	11.0±2.1	11.4±1.9	0.40	.36
TLC	8702.1±5392.0	8644.3±3992.8	-57.80	.45
RBS	131.6±48.4	122.4±34.1	-9.20	.31
Bilirubin	6.3±6.3	6.7±4.9	0.40	.40
Albumin	3.3±0.46	3.2±0.59	-0.10	.40
AST	612.5±250.6	689.6±322.7	77.10	.23
ALT	553.0±232.1	706.2±265.2	153.20	.006
GGT	463.3±187.8	475.0±255.5	11.70	.97
Creatinine	1.5±0.66	1.6±0.84	0.10	.66
INR	2.4±0.6	2.2±0.56	-0.20	.47

Table No.3: Comparison in intervention group before and after administration of glutathione.

Parameter	Day 0 (mean ± SD)	Day 7 (mean ±SD)	Mean Difference	P value
Haemoglobin	11.20±2.00	11.40±1.70	0.20	0.48
TLC	8673.20±4715.70	7159.70±2905.80	-1513.50	0.01
RBS	127.00±41.90	121.00±33.60	-6.00	0.30
Bilirubin	6.55±5.63	3.15±2.16	-3.40	0.00
Albumin	3.28±0.53	3.41±0.41	0.13	0.07
AST	651.00±289.80	331.70±292.90	-319.30	0.00
ALT	629.60±321.40	259.40±109.60	-370.20	0.00
GGT	469.10±298.74	222.96±152.10	-246.14	0.00
Creatinine	1.59±1.42	0.77±0.41	-0.82	0.00
INR	2.33±1.22	1.92±0.15	-0.41	0.00

Table No.4: Comparison in control group before and after administration of placebo therapy.

Control group		Mean ± SD	Mean Difference	p value
GGT	Day 0	475.0±255.5	-37.90	.171
	Day 7	437.1±258.6		
Bilirubin	Day 0	6.7±4.9	-4.00	.000
	Day 7	2.7±2.1		
AST	Day 0	689.6±322.7	-199.90	.000
	Day 7	489.7±294.1		
ALT	Day 0	706.2±265.2	-226.00	.000
	Day 7	480.2±309.7		
Haemoglobin	Day 0	11.4±1.9	-0.20	.593
	Day 7	11.2±1.7		
TLC	Day 0	8644.3±3992.8	-1478.80	.04
	Day 7	7165.5±2883.0		
Creatinine	Day 0	1.6±0.86	-0.20	.317
	Day 7	1.4±0.29		
INR	Day 0	2.2±0.56	-1.10	.000
	Day 7	1.1±0.14		

IV. Discussion

Alcoholism is the most common etiological factor for acute hepatitis in this part of the country followed by viral hepatitis, mostly affecting young adults in the age group of 30-40 years.The specific mechanism varies and depends on the underlying cause of the hepatitis. Generally, there is an initial insult that causes liver injury and activation of an inflammatory response, which can become chronic, leading to progressive fibrosis and cirrhosis. [21,22,23] The pathway by which hepatic viruses in hepatitis B and C cause viral hepatitis is not by apoptosis (cell death)[24,25] but rather by infection of liver cells which activates the innate and

adaptive arms of the immune system leading to an inflammatory response which causes cellular damage and death.[26,27] Depending on the strength of the immune response, the types of immune cells involved and the ability of the virus to evade the body's defense, infection can either lead to clearance (acute disease) or persistence (chronic disease) of the virus.[28]The chronic presence of the virus within liver cells results in multiple waves of inflammation, injury and wound healing that overtime lead to scarring or fibrosis and culminate in hepatocellular carcinoma.[29,30] Individuals with an impaired immune response are at greater risk of developing chronic infection.[31]Natural killer cells are the primary drivers of the initial innate response and create a cytokine environment that results in the recruitment of CD4 helper T-cells and CD8 Cytotoxic T-Cells.[22] Type 1 interferons are the cytokines that drive the antiviral response.[6] In chronic Hepatitis B and C, natural killer cell function is impaired.[32,16,17,18]

In all steatohepatitis the progression of events is similar in both alcoholic and non-alcoholic liver disease and begins with accumulation of free fatty acid (FFA) and their breakdown products in the liver cells in a process called steatosis.[33,34]. This initially reversible process overwhelms the hepatocyte's ability to maintain lipid homeostasis leading to a toxic effect as fat molecules accumulate and are broken down in the setting of an oxidative stress response. Overtime, this abnormal lipid deposition triggers the immune system via toll-like receptor 4 (TLR4) resulting in the production of inflammatory cytokines such as TNF that cause liver cell injury and death.[35] and eventually leading to fibrosis ,cirrhosis and hepatocellular carcinoma.[27]

Glutathione is a commonly prescribed drug in India, especially in acute and chronic liver diseases. The administration of GSH precursors supports the hepatic GSH synthesis, prevents liver cell damage, supports the body to compensate for oxidative stress. [28,29] and reduces the activation of nuclear factor κB (NF-κB) and inhibits the synthesis of interleukin 6 (IL-6), IL-8, and tumor necrosis factor α (TNF-α) .[32]

In our study of 84 subjects, Alcoholism is detected to be the most important cause of hepatitis 29 (34.5%) in the participants followed by viral infection and drugs. we have found the correlation between administration of glutathione and improvement of acute hepatitis in both clinical and biochemical parameters. Statistically significant differences were observed on comparing the change in mean values of ALT, AST, GGT level among intervention and control group.There was reduction in mean bilirubin, AST, ALT, GGT and INR level after administration of glutathione for 7 days and the reduction was statistically significant. On the other hand, in the placebo group also there was statistically significant reduction in mean bilirubin, AST, ALT, TLC, INR level but not in mean GGT level. So, treatment with glutathione causes more significant reduction in hepatic enzymes compared to placebo. Mean AST among the cases was 173.7±189.9 and in the control group was 489.7±294.1 on day 7 of therapy and the difference was found to be statistically significant ($p<0.05$). Similarly, on comparing ALT level on day 7, cases were having mean of 162.6±215.5, whereas control was having mean of 480.2±309.7. The difference here also was statistically significant($p<0.05$) which is consistent with study by Honda Y et al[36] ·Dentico P et al[37] studied the efficiency of intravenous glutathione in acute and chronic steatohepatitis and found out that treatment with iv glutathione leads to improvement in some of the liver function indices.

Clinical improvement or subjective improvement was compared on study and control group on day 7 of therapy. Among the cases 95.2% were symptomatically partially or completely improved. In control group it was 83.3%. Although the number of clinical improvements was more in cases but the difference was not statistically significant ($p=0.156$).

Therefore, in our study we have found the correlation between administration of glutathione and improvement of acute hepatitis in both clinical and biochemical parameters. There were statistically significant difference in the cases and controls on comparing improvement in liver enzymes as well as symptomatology. Hence the study clearly depicts the beneficial effect of glutathione in cases of acute hepatitis irrespective of etiology.

V. **Conclusion**

Alcoholism is the most common etiological factor for acute hepatitis in this part of the country followed by viral hepatitis, mostly affecting young adults in the age group of 30-40 years. In the present study glutathione is detected to be more efficacious in treating hepatic injury in acute hepatitis cases compared to placebo. Administration of glutathione in the intervention group was associated with statistically significant reduction in all three principle liver enzymes (AST, ALT, and GGT) and the improvement in liver enzymes support the superior effect of glutathione in cases of acute hepatitis. Glutathione is found to be effective in all cases of acute hepatitis irrespective of etiology and age group.

Hence this study supports the use of glutathione in recommended dosage in cases of acute hepatitis and adds to the literature regarding the beneficial effects of glutathione in acute hepatitis.Thus, randomized study involving a large population is required to obtain more conclusive results.

Declarations:
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Conflict of Interest: None declared
Approval of research ethics board**:** Taken

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