*Original research article*

A Study on the Safety and Efficacy of combination therapy of Pentoxifylline with Glutathione and Pentoxifylline with Prednisolone in Alcoholic Hepatitis

# Abstract Background:

Chronic alcohol use leads to Alcoholic Liver Disease (ALD) which mainly include Liver Cirrhosis, a condition that causes scarring in the liver tissues ultimately results in decompensated conditions. Pentoxifylline (PTX), a nonspecific phosphodiesterase inhibitor, also decreases the production of TNF-α, IL-5, IL-6, IL-10 and IL-12. Most commonly given dose is 400mg for adults. Steroid mainly Prednisolone represent most widely accepted therapy for severe ALD. It act by reducing cytokine production, IL-1, IL-6, IL-8. Administration of oral dose of Prednisolone with dose 40-60mg/day for a total duration of 4 weeks. Glutathione plays a critical role in the maintenance of cell function and viability.

# Method:

A Prospective longitudinal study contains total of 43 patients, 23 patients in group A (Pentoxifylline + Glutathione) and 20 patients in group B (Pentoxifylline + Prednisolone) was evaluated for a period of 6 months consist of data collection and follow-up using structured performa.

# Result:

A total of 42 patients were analyzed during the study. Alcoholic Hepatitis was found to be mostly affect the age group of 41 to 50 years and the mean age group was found to be 47.7 + 10.5 for group A and 48.1 + 8.3 for group B. Efficacy of given drugs was assessed by laboratory parameters and study tools. The p value for most of the parameters such as Liver Function Test, Hemoglobin, INR showed high significance in group A than group B. Study tools such as Maddrey Discriminant Function score, Model for End Stage Liver Disease score, Child Pugh score, Chronic Liver Disease Questionnaire showed equal high significance in both groups. Safety was determined by development of adverse events, group A had less incidence of adverse events when compared to group B.

# Conclusion:

Pentoxifylline plus Glutathione combination has a better treatment outcome when compared to Pentoxifylline plus Prednisolone combination. Both the study drugs are equally effective in improving the Liver parameters but, more efficacy and safety were shown by group A drugs (Pentoxifylline + Glutathione). It also improved the quality of life who suffered from severe complication of Alcoholic Hepatitis such as Ascites, Jaundice, Hepatic Encephalopathy etc.

# Key words:

Alcoholic Hepatitis, Pentoxifylline, Prednisolone, Glutathione, MDF score, MELD, Child Pugh score, CLDQ, Naranjo ADR Probability Assessment scale.

# Introduction

Alcoholic liver Disease (ALD) is one of the main causes of habitual liver complaint worldwide and accounts for over to 48 of cirrhosis associated deaths in the United States. Alcohol is also a frequent co-factor in cases with other type of liver complaint similar as hepatitis C Virus (HCV) infection where it accelerates hepatic fibrosis [1-4] Ethanol metabolism can induce reactive oxygen species and neo-antigens, promoting inflammation. This ‘Alcoholic Hepatitis’ (AH) occurs in 10 – 35 of heavy drinkers [5-7] .

Pentoxifylline (PTX), a nonspecific phosphodiesterase inhibitor, also decreases the production of TNF-α, IL- 5, IL-6, IL-10 and IL-12. As there is increased production of TNF- α and Interleukins by kupffer cells and monocytes in Alcoholic Hepatitis, Pentoxifylline appear to be most effective treatment with MDF score >32. Also it has a significant role in prevention of developing HepatoRenal Syndrome (HRS). Most commonly given dose is 400mg for adults. An oral phosphodiesterase inhibitor, pentoxifylline, also inhibits production of several cytokines, including tumor necrosis factor alpha [8]

Glutathione (GSH), or l-γ-glutamyl-l-cysteinyl-glycine, is a tripeptide present in mammalian cells at surprisingly high levels (1–10 mM) and particularly concentrated in the liver. Glutathione (GSH) is the most important low-molecular-weight antioxidant synthesized in cells, as it is a reducing molecule which can react to oxygen species by neutralizing the unpaired electrons that make them highly reactive and dangerous. [9]

In the absence of contraindications, the American Association for Study of Liver Disease (AASLD) recommends starting corticosteroids in cases with severe alcoholic hepatitis, defined as an MDF score of 32 or advanced. The preferred agent is oral prednisolone 40 mg diurnal or parenteral methylprednisolone 32 mg daily for 4 weeks and also tapered over the coming 2 to 4 weeks or suddenly discontinued. [10]

# Materials and methods

It was a Prospective longitudinal study conducted in Gastroenterology department at NIIMS hospital Neyyattinkara, Thiruvananthapuram, Kerala, India. The study was conducted for a period of 6 months which include data collection and follow up of the study subjects. The study subjects was enrolled by purposive sampling technique and required sample size was 48.

The participants who had been fulfilled inclusion criteria include Male patients having age between 18-70 years, Cases of severe Alcoholic Hepatitis, Patients with MDF score between > 32 and < 52, Patients who are prescribed with Pentoxifylline Glutathione combination and Pentoxifylline Prednisolone combination and those who are willing to participate in the study. Patient with Hepatitis B, Hepatitis C, HIV, Psychiatric patients and Tuberculosis patients on ATT drugs were excluded from the study.

Informed consent was obtained and confidentiality was ensured to study subjects while collecting data. All the data were entered in Microsoft excel spreadsheet and statistical analysis was done using SPSS version 29.0. Chi square test was used for calculating P value and <0.05 was considered as significant.

The study was conducted after protocol approval by institutional Research Committee of Ezhuthachan College of Pharmaceutical Sciences and Institutional Ethics Committee of NIIMS, Neyyatinkara, Thiruvananthapuram.

# Results

A prospective longitudinal study was conducted to compare the safety and efficacy of combination therapy of Pentoxifylline with Glutathione and Pentoxifylline with Prednisolone. In this study a total number of 43 patients were participated.

**Fig 1: Allocation of study participants**

Study conducted in the Gastroenterology department (Total number of Alcoholic Hepatitis patients visited per month n = 15)

Total four months of data collection, n = 60

According to inclusion and exclusion criteria, calculated sample size, n = 48

24 patients were included in group A (Pentoxifylline + Glutathione)

24 patients were included in group B (Pentoxifylline + Prednisolone)

-1 not willing to give consent

-1 drop out due to death, - 4 not willing to give consent

23 patients were included and no drop outs.

Baseline data collected for 20 patients, 1 patient drop out, hence follow up data collected for 19 patients.

Hence total number of samples collected n = 43

**Table 1: Patient demographic details**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age in years** | **GROUP A** | | **GROUP B** | | **χ2** | **df** | **p** |
| **n** | **%** | **n** | **%** | 2.997 | 3 | 0.392 |
| 31-40 | 6 | 26.1 | 3 | 15 |
| 41 - 50 | 8 | 34.8 | 9 | 45 |
| 51 - 60 | 5 | 21.7 | 7 | 35 |
| 61-70 | 4 | 17.4 | 1 | 5 |
| Total | 23 | 100 | 20 | 100 | - | | |
| **BMI** | **Group A** | | **Group B** | | **χ2** | **df** | **p** |
| **n** | **%** | **n** | **%** | 0.393 | 2 | 0.822 |
| Normal (18.5-24.9) | 9 | 39.1 | 6 | 30 |
| Over weight (25-  29.9) | 11 | 47.8 | 11 | 55 |
| Obese (>30.0) | 3 | 13 | 3 | 15 |
| Total | 23 | 100 | 20 | 100 |  | | |

The mean age was found to be 47.7 + 10.5 for group A and 48.1 + 8.3 for group B. This study result was similar to the study conducted by *Evangelos Akriviadis et al* [110]*,* in which the mean age was 42.4 + 8.2 years for the Pentoxifylline group and 40.8 + 8.7 years for control group. Most of patients with Alcoholic Hepatitis were overweight. Similar study by *Alice R et al* [113] in which mean BMI was 26.2 + 4.3, which conclude interventions to reduce both BMI and alcohol consumption might reduce liver injury.

**Table 2: laboratory parameters**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter** | **Group A (n=23)** | | | | | **Group B (n=20)** | | | | | **Group A vs Group B**  **(Base line)** | **Group A vs Group B (Follow up)** |
| **Baseline** | | **Follow up** | | **p** | **Baseline** | | **Follow up** | | **p** |
| **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| Hemoglobin | 11.8 | 3.1 | 12.0 | 2.3 | 0.0  12 | 10.1 | 2.8 | 11.4 | 1.4 | 0.3  14 | 0.064 | 0.342 |
| WBC | 10994.  8 | 498  7.5 | 8728.6 | 186  5.6 | 0.2  24 | 11626.  5 | 801  8.4 | 8976.6 | 268  5.4 | 0.0  32 | 0.755 | 0.73 |
| Total Bilirubin | 11.7 | 3.5 | 9.2 | 3.4 | 0.0  01 | 11.2 | 4.5 | 8.7 | 3.3 | 0.0  00 | 0.684 | 0.659 |
| Direct Bilirubin | 7.0 | 3.7 | 5.5 | 3.1 | 0.0  00 | 7.5 | 4.1 | 5.1 | 3.0 | 0.0  10 | 0.677 | 0.634 |
| Indirect Bilirubin | 5.1 | 3.1 | 3.3 | 1.8 | 0.0  73 | 4.4 | 3.1 | 3.4 | 2.4 | 0.0  06 | 0.504 | 0.835 |
| ALT | 84.6 | 39.  5 | 71.0 | 31.  3 | 0.0  14 | 97.6 | 62.  2 | 65.8 | 30.  8 | 0.0  23 | 0.412 | 0.592 |
| AST | 135.7 | 99.  6 | 89.5 | 50.  2 | 0.0  07 | 141.7 | 109  .1 | 75.5 | 36.  3 | 0.0  07 | 0.854 | 0.318 |
| ALP | 140.4 | 53.  8 | 107.1 | 41.  8 | 0.0  00 | 153.5 | 54.  2 | 104.4 | 21.  3 | 0.0  05 | 0.437 | 0.802 |
| Total protein | 7.4 | 1.3 | 7.6 | 0.9 | 0.3  52 | 6.7 | 1.1 | 6.9 | 0.9 | 0.2  38 | 0.108 | 0.022 |
| Albumin | 3.5 | 0.7 | 4.0 | 0.7 | 0.0  00 | 2.9 | 0.7 | 3.7 | 0.5 | 0.0  10 | 0.011 | 0.208 |
| Globulin | 4.2 | 0.8 | 4.2 | 1.3 | 0.1  52 | 3.9 | 1.0 | 3.7 | 0.8 | 0.8  68 | 0.398 | 0.181 |
| INR | 1.5 | 0.1 | 1.4 | 0.2 | 0.5  28 | 1.7 | 0.5 | 2.3 | 3.9 | 0.0  00 | 0.171 | 0.286 |

By comparing the efficacy of group A and group B the p value less than 0.05 was observed in 9 parameters (hemoglobin, monocyte, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, Albumin) in group A, 8 parameters (WBC, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, Albumin) in group B, but more significant value observed in 7 parameter (Hemoglobin, monocyte, Direct bilirubin, ALT, AST, ALP. Albumin) in group A and 4 parameters (WBC, total bilirubin, indirect bilirubin, AST) in group B. Since, a significant reduction of parameter were found in group A, it concludes that group A drugs had more efficacy than group B. It indicates group A drug combination were more effective than group B drug combination.

**Table 3: study tools**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Tools** | **Group A (n=23)** | | | | | **Group B (n=20)** | | | | | **Group A vs Group B**  **(Base line)** | **Group A vs Group B**  **(Follow up)** |
| **Baseline** | | **Follow up** | | **p** | **Baseline** | | **Follow up** | | **p** |
| **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| MDF  score | 45.5 | 5.5 | 33.3 | 5.6 | 0.00  0 | 49.2 | 4.0 | 34.7 | 8.3 | 0.000 | 0.017 | 0.515 |
| MELD | 23.1 | 3.9 | 19.0 | 5.6 | 0.01  8 | 23.3 | 5.6 | 21.1 | 4.1 | 0.002 | 0.907 | 0.199 |
| Child Pugh Score | 10.0 | 1.4 | 8.4 | 1.2 | 0.00  0 | 11.0 | 1.1 | 9.0 | 1.0 | 0.000 | 0.018 | 0.141 |
| CLDQ | 81.3 | 22.  1 | 155.5 | 27.0 | 0.00  0 | 76.8 | 22.  4 | 137.9 | 17.  4 | 0.000 | 0.506 | 0.019 |

In the study subjects, the MDF score was found to be significant in both groups. Child Pugh score found to be significant for both groups. Both groups have effectiveness in reducing mortality rate. CLDQ was found to be significant for both group. It indicates that both groups showed improvement in their quality of life.

**Table 4: Adverse effects**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adverse Events** | **Group A** | | **Group B** | | **χ2** | **df** | **p** |
| **n** | **%** | **n** | **%** |
| Yes | 1 | 4.3 | 2 | 10.5 | 0.599 | 1 | 0.439 |
| No | 22 | 95.7 | 17 | 89.5 |
| Total | 23 | 100.0 | 19 | 100.0 | - | | |

In the study population, safety was determined by development of adverse events. The reported adverse events are bleeding with a mean Naranjo causality score of 6.66. It indicates that Group A drugs are safer than group B drugs.

# Discussion:

Alcoholic Hepatitis is a liver inflammation and damage caused by drinking too much alcohol overtime. The study was conducted among 43 Alcoholic Hepatitis patients, in a tertiary care hospital. The study demonstrated that incidence of Alcoholic Hepatitis was highest in age group of 41-50 years and also severe among overweighed patients [11,12]. Study population was divided into two groups, group A received Pentoxifylline+ Glutathione and group B received Pentoxifylline + Prednisolone. After four months of study efficacy, safety and quality of life were assessed. In case of efficacy there exist a significant change from baseline laboratory parameters to follow up. But more significance was shown by group A as compared to group B in terms of improving Hemoglobin, WBC, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, ALP and albumin levels. After analysing study tools it was evident that both groups improved quality of life, survival rate, and mortality rate in an equal way. After comparing the safety, it was obvious that group B patients are more prone to adverse event that is bleeding than group A patients.[13,14]

Conclusion

By concluding all the study objectives both the study drugs are effective in treating Alcoholic Hepatitis patients but, more efficacy and safety were shown by group A drugs that is Pentoxifylline

+ Glutathione. It also improving the quality of life of patients who were suffer from severe complications of Alcoholic Hepatitis

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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