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Traverse the Impact of Pentoxifylline in alcoholic hepatitis –A Review

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ABSTRACT
Chronicalcohol use leads to Alcoholic Liver Disease(ALD) which mainly include liver cirrhosis, a condition that causes carring in the liver tissues ultimately results in decompensated conditions.
Steatohepatitis is the major histological finding seen in 90% of heavy drinkers but is easily reversible with alcohol withdrawal. Alcoholic Steatohepatitis is a clinical pathological syndrome indicates hepatocellularnecrosis and inflammation. Factors such as genetic, impaired immune response, mitochondrial dysfunction and free radical injury induced by alcohol have important roles in acute Alcoholic Hepatitis.
Pentoxifylline (PTX), is a nonspecific phosphodieste rase 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 Kupffercells and monocytes in Alcoholic Hepatitis, Pentoxifylline appear to be most effective treatment with Maddrey Discriminant Function Score (MDF) ≥32. Also, it has a significant role in prevention of developing Hepato-Renal Syndrome (HRS). Most commonly given dose for Alcoholic Liver Disease is 400mg in adults for four weeks.
Effectiveness of Pentoxifylline in Alcoholic Hepatitis is reviewed. This review mainly focuses on the action of Pentoxifylline in Alcoholic Hepatitis.

KEYWORDS: Alcoholic Hepatitis, Pentoxifylline, Steatohepatitis, Maddrey Discriminant Function Score

I. INTRODUCTION

Alcoholic Hepatitis is a type of acute hepatic inflammatory response syndrome that result from alcohol induced liver injury [1,2]. Hepatitis has a wide range of clinical presentations that include a stage of lack of symptoms to severe liver failure [3]. Alcoholic Hepatitis is a condition that occur in patients with history of current or previous heavy alcohol use that cause jaundice with increased liver parameters [4,5]. It is a serious condition with a death rate of 60% among the first 4 week of diagnosis in critical cases [6,7]. This disease is most commonly seen in chronic alcoholic abusers which may lead to life threatening condition such as Jaundice, Ascites, GIbleeding and Encephalopathy[8].

The pathological characteristics of acute Alcoholic Hepatitis includes development of Mallory Alcoholic Hyaline, prominent intra sinusoidal collagen deposition, and infiltration with polymorph nuclear leukocytes of the hepatic parenchyma. The pathogenesis of liver injury in Alcoholic Liver Disease remains difficult [9]. One of the well accepted mechanism is the impact of Tumor Necrosis Factor on hepatocytes[10,11].

The severity of Alcoholic Hepatitis is measured using Maddrey Discriminant Function Score (MDF).MDF ≥32 indicate severe prognosis [12,13]. Model for End Stage Liver Disease (MELD) also used to predictseverity, which also gives information regarding the need for liver transplantation [14,15]. But bedside calculation of MELD is difficult[16]. Other measuresare Glasgow Alcoholic Hepatitis Score (GAHS), Lille Score[17,18].

On the basis of these findings, different treatment options have been studied for Alcoholic Hepatitis. Some of the mis the Corticosteroids, Nacetylcysteine, Pentoxifylline, Infliximabetc. among these corticosteroids are most studied one[19,20].

Steatohepatitis shows path physiological features like hepatic fat storage, increased hepatic uptake ofgut derived endotoxin triggering Kupffer

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cell activation and release of proinflammatory mediators, induction of cytochrome P4502E1 producing to xicacetaldehyde and reactive oxygenspecies[21,22,23,24].

Pentoxifyllineisanon-selective phosphodiesterase in hibit or which inhibits TNF production. The drug is safe, cheap and found to be effective in the development of Hepatorenal syndrome and reduced mortality among severe Alcoholic Hepatitis[25-28].

PREVALENCE OF ALCOHOLICHEPATITIS

Acute Alcoholic Hepatitis in India occur due to Alcohol abuse. According to global status report on alcohol and health4.8% of general population has Alcohol Related Liver Disease(ARLD). Europe has the highest prevalence [29,30].

In India alcohol abuse is rapidly increasing and is showing trends to replace Hepatitis B virus as the predominant cause of Chronic Liver Disease (CLD). Based on recent studies alcohol induced Chronic Liver Disease including cirrhosis has a prevalence rate of 10.9 - 31.9 with 20-25% contribution to mortality. Alcohol induced liver cancer has a prevalence of 9.6% with 15-20% contribution to mortality. Alcoholism which is increasing across the country with younger age and have a high per capita consumption of alcohol, potentially harmful drinking patterns and co-existence of comorbidities. In many alcoholics, the rear evidences of increased impact of alcohol on liver disease [31]. According to the 2018 National Survey on Drug Use and Health, 14.4 million adults ≥ 18years old suffered from alcohol disease in the United States, including 9.2 million men and 5.3 million women[32]. Since 2000, men has been drinking about 3 times as much as women, according to the latestWHO data [33]. The current data also showed that prevalence of ARLD in male was 2.9% which was nearly 6 timesthat in female. The global alcohol consumption is increasing, with the average level of alcohol consumption in2005 was 5.5Lof use alcohol percapita, and in2016was6.1L[34].

Some studies revealed that moderate drinking is beneficial to health, but increased alcohol intake and types of alcohol are health hazards. American Association for the Study of Liver Disease has set a safe threshold of alcohol consumption for men (no more than 2 standard drinks per 24 hour) and women (1 standard drink per24 hour)[35].

Overall, the global prevalence of ARLD is 4.8% and the prevalence varies greatly among different regions which can be influenced by different factors such as comorbidities, gender, period of alcohol consumption etc.

DIAGNOSIS OF ALCOHOLIC HEPATITIS

Since, there are no diagnostic tests for Alcoholic Hepatitis taking an accurate history of alcohol usefromapatientisbeneficialtoitsdiagnosis.PatientswithAlcoholicHepatitiscommonlystop alcoholic use for a period prior to their hospital visiting. Therefore it is important to find alcohol use histories over discrete time periods[36].

Liver biopsy is found to be the most accurate diagnosis of Alcoholic Hepatitis. However, there are certain conditions in which liver biopsy cannot be utilized in clinical practice. Most patients with severe Alcoholic Hepatitis already have portal hypertension, As cites oral ready Cirrhotic as a consequence of Alcoholic Hepatitis. Studies show that 84.5% biopsies showed histological evidence of Alcoholic Hepatitis and a total bilirubin level >4.7mg/dL increased the accuracy of Alcoholic Hepatitis diagnosis upto 96%. Although liver biopsy is not essential to diagnose Alcoholic Hepatitis. But it is useful in case of differentiating severe Alcoholic Hepatitis from non-alcoholic diseases. Several prediction models are used in the diagnosis of AlcoholicHepatitis[37,38].

Maddrey Discriminant Function Score (MDF):

The MDF was first described by William Maddrey in 1978. Patients with a MDF score of ≥32 has aonemonth mortality of 30-50%.The MDF uses prothrombin time (PT), control PT and serumbilirubin[39].

The formula forcal culating MDF is,

MDF=(4.6×[PT–control PT])+Serum Bilirubin

Model for End Stage Liver Disease (MELD):

MELD accurately predicts outcome in Alcoholic Hepatitis and also identifying the renal function. Patients withmild Alcoholic Hepatitis and severe Acute Kidney Injury have a low MDF score but a high MELD score. This can be mis leading. In clinical practice, a MELD score above21,with a minimum total bilirubin of 5mg/d Llikely to have a poor prognosis[40].

$MELD=9.57\times\log_e^{(creatinine)}+3.78\times\log_e^{(totalbilirubin)}+11.2\times\log_e^{(INR)}+6.43$

GlasgowAlcoholic Hepatitis Score(GAHS):

The GAHS has a higher specificity and accuracy when compared to DF and MELD score, but it is less sensitive in predicting mortality

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rates[41]. It can be measure by using WBC, Urea, INR and Bilirubin level a score of 9 or more identify patients most at risk of death.

Child Pugh Score

In the Child Pugh Score, a composite score of the degree of hepatic syntheticdys function (based on prothrombin time and serum levels of albumin and bilirubin), degree of as cites, and presence of hepatic encephalopathy yields a total score that ranges from well-compensated cirrhosis (class A, 5 to 6 points) to mild (classB, 7 to9 points) and severe (class C, 10 to 15 points) decompensation[42]. The Child Pugh classification is shown below in Table 1.

Table 1: Child Pugh Classification

Clinical and Lab Criteria	**Points**		
	1	**2**	**3**
Encephalopathy	None	Mild to Moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
Child-Pugh Classification is obtained by adding score for each parameter. ➢ Class A – 5 to 6 points (least severe liver disease) ➢ Class B – 7 to 9 points (moderately severe liver disease) ➢ Class C – 10 to 15 points (most severe liver disease)			

*Source: Pugh RN, Murray- Lyon IM, Dawson JL, *et al*. Transection of the Oesophagus for bleeding Oesophageal Varices. Br J Surg 1973; 60:646

ROLEOFPENTOXIFYLLINEINALCOHOLIC HEPATITIS:

Recent guidelines of American College of Gastroenterology recommended the use of glucocorticoids inthe treatment of patient with MDF score ≥ 32 [43,44]. Primary use of Pentoxifylline in the treatment of Alcoholic Hepatitis patients notre commended due to lack of evidence in improving clinical outcomes. Also, early replacement of steroid to Pentoxifylline if no improvement after 7 days of treatment has proved to be effective[45,46]. Studies showed that Pentoxifylline could reduce Hepatorenal syndrome and mortality in comparison to place botreated patients[47]. The positive effect of Pentoxifyl line on treating Alcoholic Hepatitis is due to its ability to inhibit the synthesis of Tumour Necrosis Factor (TNF) which plays a major role in alcohol induced liver disease [48,49]. Also Pentoxifyl line has a beneficial effect on renal function by increasing renal micro circulation and hemodynamics.

Pentoxifylline (PTX), a nonselective phosphodiesterase (PDE) inhibitor that has been shown to have survival benefit in Alcoholic Hepatitis. PTX treatment increases cAMP and cGMP concentration intracellularly. Increased cAMP has been shown to positively modulate cytokine mediated inflammatory response. PTX is referred when MDF score is above 32 and below 52. Also, it shown to have efficacy in prevention of Hepato Renal Syndrome.

CLINICALTRIAL CONDUCTE DONPEN TOXIFYLLINE VS PLACEBO

A study conducted by Rasmirekha Behera et al in the department of Gastroenterology, Apollo Hospital Bhubaneswar consist of 20 patients with severe Alcoholic Hepatitis. In this 10 patients received Pentoxifylline 400mg TDS for 4weeks and other 10 patients received place bo(no treatment).The result showed that, compared to place bo, Pentoxifylline reduced mortality,

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improved risk of benefit profile. Hence it is suggested that Pentoxifylline is found to be more effective in the treatment of severe Alcoholic Hepatitis [50].

A study conducted by Arun. S et al in Kasturba Medical college Hospital, Mangalore and Government Wenlock Hospital evaluated patients with Alcoholic Hepatitis. In this 20 of the 49 patients treated with Pentoxifylline 400mg TDS and supportive care (symptomatic management) and remaining patients treated onlywith supportive care. Study result showed that Pentoxifylline is safe, economical, and appears to be useful in improving short term mortality especially in Indian population[51].

A study conducted by Evangelos Akriviadis et al in University of Southern California at Rancho Los Amigos Medical Centre, in Downey, California was a double blind placebo controlled trial performed on 101 patient's hospitalized between August1992 and May1997 with severe Alcoholic Hepatitis. Pentoxifylline 400mg orally TDS given to the treatment group for 4 weeks and the other group received identical capsule containingplacebo (tablets of vitamin B12 500 or 1000mcg). The result showed that Pentoxifylline improve short term survival in patients with severe Alcoholic Hepatitis. The benefit appears to be related to a significant decline in the risk of developing Hepatorenal syndrome. Increasing TNF levels during the hospital course are associated with an increase in mortality rate[52].The place bodoes not show any significant improvement.

SL.NO	FIRST AUTHOR	YEAR	COUNTRY	NO.OF PARTICIPANTS	INCLUSION CRITERIA	EXCLUSION CRITERIA	DOSE OF PTX	CONTROL	OUTCOME MEASURES	FOLLOW UP AND RESULTS
1.	Rasmirekha Behera *et al*	2016	India	20 (10 PTX, 10 control)	1. MDF ≥32	1. Heart failure 2. Infection, 3. Sepsis 4. Spontaneous bacterial peritonitis 5. Hepatorenal syndrome 6. Acute pancreatitis 7. Uncontrolled Diabetes 8. Pulmonary disease	400mg TDS	placebo	1. Mortality 2. Risk benefit profile 3. MDF score	4 weeks Pentoxiffylline reduce mortality and improve risk benefit profile in patients with severe ALD
2.	Arun S *et al*	2014	India	49 (20 PTX, 29 control)	1. History of chronic alcohol intake or a recent alcohol binge 2. Hepatic encephalopathy	1. Acute or chronic viral Hepatiits. 2. History of abstinence from alcohol in last month. 3. HIV positive 4. Autoimmuneliver disease 5. Heartfailure, Infection, Sepsis, Spontaneous bacterial peritonitis, Hepatorenal syndrome, Acute, pancreatitis,uncontrolled Diabetes, Pulmonary disease	400mg TDS	Supportive care	1. Mortality 2. MDF score 3. GAHS 4. Short term survival 5. Biochemical parameters.	4 weeks Pentoxifylline significantly reduced mortality
3.	Evangelos Akriviadise *t al*	2001	California	101 (49 PTX, 52 control)	1. Jaundice 2. MDF >32 3. Palpable tender hepatomegaly 4. Fever 5. Leucocytosis 6. Hepatic encephalopathy	1. Bacterial infection 2. Severe cardiovascular or pulmonary disease 3. Advanced alcoholic cirrhosis	400mg TDS	Placebo(tablets of vitamin B12 500OR1000mcg)	1. Short term survival 2. Progression to Hepato renal syndrome 3. Serum TNF level	4 weeks Pentoxifylline improved short term survival and decreased the risk of developing Hepato Renal Syndrome

Table 2 : Various clinical trials conducted on Pentoxifylline Vs Placebo

SIGNIFICANCE:

Pentoxifylline is not selected as standard treatment regimen for Alcoholic Hepatitis in majority of hospitals. Thisreview point out the effectiveness and benefits of including Pentoxifylline as a treatment option for Alcoholic Hepatitis with the supportive evidence of various studies.

II. CONCLUSION:

Pentoxifylline has a significant role in treatment of Alcoholic Hepatitis, which occurs due to the overproduction of TNF alpha in the liver. Pentoxifylline which is a phosphodiesterase inhibit or that inhibits the production of TNF alpha. It has a promising role in the prevention of further development of disease condition and also the progression of Hepatorenalsyndrome. The various trials suggest that Pentoxifylline reduces the short term morbidity and mortality rate in Alcoholic Hepatitis patients. The effective dose for treating severe Alcoholic Hepatitis is found to be 400mg three times daily for 4 weeks. It is a safe, economic and clinically proven drug. Corticosteroids, the

most studied drug group and proved its efficacy for Alcoholic Hepatitis. But above mentioned trials suggest that Pentoxifylline is an effective replacement for corticosteroid in Alcoholic Hepatitis.

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