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Original Article

Internal Medicine Section

Pentoxifylline in the Treatment of Acute Alcoholic Hepatitis

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ABSTRACT

Background/Aim: It has recently been reported that treatment with pentoxifylline, an inhibitor of tumour necrosis factor, improves survival in severe alcoholic hepatitis. The present study was initiated to test the hypothesis that pentoxifylline improves short term survival in patients with acute alcoholic hepatitis in Indian scenario.

Materials and Methods: Single center prospective observational study. We evaluated patients diagnosed with alcoholic hepatitis who were admitted to our hospitals from September 2008 to September 2010. Patients with history of chronic alcohol intake or a recent alcoholic binge, Jaundice and one or more of the following clinical and laboratory findings: palpable tender hepatomegaly, Leucocytosis, hepatic encephalopathy and AST:ALT ratio>2 with absolute values of AST < 500 IU/L and ALT < 200 IU/L were included in the study. Patients with gastrointestinal hemorrhage and other possible causes of hepatitis were excluded.

Results: Twenty of the 49 patients were treated with pentoxifylline. Pentoxyfylline treatment did not affect mortality significantly (p=0.081). However, treatment with pentoxyfylline in those with severe alcoholic hepatitis with DF≥32, MELD score≥21 and GAHS ≥9 significantly reduced mortality (p=0.037, 0.025, 0.001 respectively). Baseline bilirubin, creatinine, urea, MELD score and GAHS were significantly high among the patients who succumbed to the disease as compared to those who survived.

Conclusion: Patients with severe alcoholic hepatitis (Maddrey's discriminant function ≥32; or MELD score ≥21: or GAHS ≥9), can be treated with pentoxifylline, as it is safe, economical, and appears to be useful in improving short term mortality, especially in the Indian scenario.

Keywords: Acute alcoholic hepatitis, Pentoxifylline, India

INTRODUCTION

Alcoholic liver disease is a major cause of liver related morbidity and mortality in the world. Despite of extensive research for more than five decades, it remains a challenging enigma for both scientists and clinicians.

Alcoholic hepatitis is an acute form of alcohol induced liver injury, and carries significant morbidity and mortality. Severe alcoholic hepatitis causes a high short-term mortality, and also places an enormous burden on healthcare resources .The clinical hallmarks of alcoholic hepatitis are jaundice and acute inflammation manifested as elevated WBC count, fever and tender hepatomegaly. Many patients have ascites and hepatic encephalopathy.

The severity of alcoholic hepatitis may be measured using Maddrey's discriminant function (DF). DF≥32 indicates severe hepatitis and poor outcome [1,2]. Recently model for end stage liver disease (MELD) score was found superior to DF in predicting severity [3]. MELD score also gives prognosis and need for liver transplantation. But as bedside calculation of MELD score is difficult and creatinine values are underestimated in the context of hyperbilirubinemia the Glasgow alcoholic hepatitis score (GAHS) was proposed. GAHS seems a substantial improvement in alcoholic hepatitis clinical phenotyping, but further research is needed [4,5].

There are several mechanisms by which alcohol damages liver and causes inflammation in acute hepatitis. One of the well accepted and extensively studied mechanisms is the action of Tumour Necrosis Factor (TNF) on liver cells. Several studies proved that TNF is responsible for liver injury in alcoholic hepatitis [6-13]. On the basis of these findings several treatment options have been studied in the treatment of acute alcoholic hepatitis. Some of them are corticosteroids, pentoxifylline, infliximab, etanercept etc [14,15]. Among these, corticosteroids are the most extensively studied and have proven to be useful in some studies [16-18]. However, physicians are reluctant to use them because of potential risk of side effects. Pentoxifylline is a nonselective phosphodiesterase inhibitor which inhibits TNF production. The drug is safe, cheap and found effective in improving short term survival in severe acute alcoholic hepatitis [19-22].

As there are only few studies published till date, the drug is not commonly used by general practitioners but is being used regularly by most of the gastroenterologists for treatment of acute severe alcoholic hepatitis. The complications and safety profile of the drug is well documented and also time tested as

S no	Parameter	Group I (n=20)	Group II (n=29)	p value
1	Age	43.40±6.83	46.66±8.92	0.176
2	Fever	15	27	0.075
3	Distension of abdomen	18	19	0.05
4	Pain abdomen	7	10	0.97
5	Hepatomegaly	19	26	0.50
6	Total bilirubin(mg/dl)	15.65 ±8.6	11.56 ±6.7	0.70
7	AST	145.45 ±36.24	137.97 ±53.17	0.587
8	ALT	47.25±15.29	47.66±23.32	0.946
9	Albumin(mg/dl)	2.76±0.80	2.91±0.86	0.543
10	Creatinine(mg/dl)	1.58±1.03	1.55±1.02	0.912
11	Urea(mg/dl)	54.45±38.14	48.14±42.12	0.595
12	INR	1.92±0.56	1.95±0.92	0.908
13	Mean TLC	14882.80 ±5628.06	13135.52 ±3690.35	0.195
14	Discriminant function	67.65 ±33.06	64.31 ±51.13	0.798
15	MELD score	25.60±7.33	24.72±8.30	0.705
16	GAHS	9.05±1.27	8.38±1.47	0.105

[Table/Fig-1]: Comparison of baseline parameters of patients receiving pentoxifylline (group I) with those not receiving pentoxifylline (group II) in the treatment of alcoholic hepatitis. (mean±SD)
P<0.05 considered statistically significant. TLC: Total leukocyte count.

the drug is already in use for the treatment of peripheral vascular disease since decades. So with the present study, we want to compare the outcome of patients treated with pentoxifylline with other patients who were given only supportive care in the Indian scenario. A positive outcome of this study will help us to find a safe, economical and effective treatment for patients with acute alcoholic hepatitis and contribute to the ongoing research process.

MATERIALS AND METHODS

Fifty patients with acute alcoholic hepatitis admitted in Kasturba Medical College Hospitals, Mangalore and Government Wenlock Hospital, Mangalore were evaluated at the time of admission and relevant history along with examination findings was noted. The study was carried out from September 2008 to September 2010. The study protocol was approved by the institutional ethics committee. Informed written consent was taken from all the patients. Patients with history of chronic alcohol intake or a recent alcoholic binge, Jaundice and one or more of the following clinical and laboratory findings: palpable tender hepatomegaly, Leucocytosis -WBC count>12000/mm^3, hepatic encephalopathy and AST:ALT ratio>2 with

	Group	Mortality	p value
Unstratified(n=49)	Group I(n=20)	15%	p=0.081
	Group II(n=29)	37.9%	
DF≥32(n=41)	Group I(n=18)	16.7%	p=0.037
	Group II(n=23)	47.8%	
MELD score≥21(n=32)	Group I(n=14)	21.4%	p=0.025
	Group II(n=18)	61.1%	
GAHS≥9(n=25)	Group I(n=13)	23.1%	p=0.001
	Group II(n=12)	91.6%	

[Table/Fig-2]: Mortality in patients with respect to treatment with pentoxifylline
DF-Maddrey's discriminant function, MELD- Model for end stage liver disease. GAHS-Glasgow alcoholic hepatitis score, Group I- patients treated with pentoxifylline, Group II-Patients not treated with pentoxifylline

S no	Parameter	Improved (n=35)	Expired (n=14)	p value
1	Age	45.14±8.13	45.79±8.71	0.808
2	Total bilirubin	11.50±7.30	17.55±7.45	0.012
3	AST	145.43±46.36	130.00±47.50	0.301
4	ALT	50.43±22.00	40.14±12.85	0.109
5	Albumin(mg/dl	2.98±0.90	2.50±0.54	0.065
6	Creatinine(mg/dl)	1.23±0.83	2.39±0.98	<0.001
7	Urea	39.69±32.20	78.29±46.12	0.002
8	INR	1.87±0.76	2.11±0.84	0.345
9	Mean TLC	13233.03 ±4848.83	15387.86 ±3652.97	0.141
10	Discriminant function	59.89 ±43.32	80.14 ±44.87	0.150
11	MELD score	22.09±7.06	32.57±3.54	<0.001
12	GAHS	8.20±1.38	9.79±0.69	<0.001

[Table/Fig-3]: Comparison of baseline parameter of patients, those who improved and those who expired at the end of the study
All values are expressed as mean±SD. p<0.05 considered statistically significant

absolute values of AST < 500 IU/L and ALT < 200 IU/L were included in the study. Patients with any other potential aetiology of liver injury (acute or chronic viral hepatitis, autoimmune liver disease) even in the background of chronic alcohol intake were excluded from the study. Also, patients with a history of abstinence from alcohol in the last month, or who were positive for human immunodeficiency virus antibodies were excluded. Patients with infection, sepsis or spontaneous bacterial peritonitis, gastrointestinal bleeding, hepatorenal syndrome, acute pancreatitis or any other severe associated disease (uncontrolled diabetes, hypertension, heart failure, pulmonary disease or malignancy) at the time of inclusion or in the previous 3 months were also excluded.

Investigations like Total count, Differential count, Platelet count ,Total bilirubin, PT/INR, HBsAg, anti HCV, blood urea, serum creatinine, blood culture, ECG, X ray Chest PA view were done and documented in the proforma. Relevant investigations were done where ever required to rule out other causes of liver disease. Discriminant function, MELD score and GAHS were calculated from the above investigations.

Patients were enrolled into the present study within first two days of admission. The included patients were divided into two groups based on the treatment started within two days of admission. Group I was designated to patients who were started on tablet pentoxifylline (Trental tablets, Sanofi Aventis, Mumbai, India) 400mg thrice daily orally along with supportive care and group II was designated to rest of the patients who were treated with only supportive care. None of the patients were treated with any other potential therapeutic agents like corticosteroids other than pentoxifylline. The decision of starting pentoxifylline was solely based on the treating physician of the corresponding unit to which the patient belongs. Patients were examined on weekly basis with regard to the development of possible complications like gastrointestinal bleeding, pain abdomen, dyspepsia, diarrhea, leucopenia, thrombocytopenia, renal impairment, skin rash and hepatic encephalopathy. Patients were hospitalized as long as medically indicated and treatment was continued on outpatient basis if discharged within 4 weeks. The discharged patients were asked to review after completion of treatment or if they notice any fresh symptoms.

STATISTICAL ANALYSIS

The collected data was analysed using SPSS version 11.5. Student's t-test was used for analysis of continuous variables and the chi- square test was used for categorical variables. All results of continuous variables are expressed as mean ± SD. A p-value of <0.05 was considered statistically significant.

End point: Completion of 28 days of treatment or death of the patient.

RESULTS

Fifty patients with acute alcoholic hepatitis were initially evaluated. One patient presented with upper gastrointestinal bleed in the form of hematemesis and was excluded from the analysis. The patients were divided into two groups based on the treatment received. 41% received pentoxifylline whereas 59% did not receive pentoxifylline or any other potential therapeutic agents and treated only with supportive care. The mean age of presentation in group I (pentoxifylline group) was 43.40±6.83 yr and in group II was 46.66±8.92 yr, all of them being males. The baseline clinical and biochemical parameters of the 2 groups are summarized in [Table/Fig-1] and were found to be comparable.

Four patients from group I and 6 patients from group II had 1 or more previous episodes of decompensated liver disease requiring hospitalization. Eight patients had creatinine ≥2.5 and 13 patients had hepatic encephalopathy at the time of admission. Other prominent clinical features for both groups were fever without evidence of infection, pain abdomen, distension of abdomen and hepatomegaly. There were no significant differences in the frequency of these clinical features between the groups [Table/Fig-1].

In group I pentoxifylline therapy had to be stopped prematurely in three patients because of the development of life-threatening complications, all of whom unfortunately succumbed to the disease. One patient expired following massive gastrointestinal bleeding in the second week of starting treatment and two patients expired due to progressive hepatic encephalopathy, in the third week.

In group II 11 patients succumbed to the illness before 28d of treatment. Six patients died of hepatorenal syndrome not responding to conservative management (two in the second week and four in the third week), two patients had upper gastrointestinal bleed and succumbed to hemodynamic failure in the second week, one patient expired due to progressive hepatic encephalopathy in the second week and two patients died of septic shock in the third week. The mortality in pentoxifylline treated group was 15% compared to 37.9% in patients who did not receive pentoxifylline ($\chi 2=3.050$ p=.081), indicating there is no statistically significant difference in mortality among the two groups.

Patients were stratified as severe alcoholic hepatitis based on the three widely used scoring systems, the Maddrey's discriminant function (DF), the Model for End-Stage Liver Disease (MELD) score and the Glasgow alcoholic hepatitis score (GAHS). In the present study 84% of patients had severe alcoholic hepatitis with DF≥32, 66% had MELD score≥21 and 52% had GAHS≥9. Though all the three groups had a considerable overlap, few patients with DF<32 had a MELD score≥21. However, all the patients with GAHS≥ 9 had DF and MELD score ≥32 and ≥21 respectively. The baseline clinical and biochemical parameters of the two groups of patients stratified as acute alcoholic hepatitis based on DF, MELD score and GAHS were also found to be comparable.

In patients with severe alcoholic hepatitis stratified based on DF≥32, the mortality in pentoxifylline treated group was 16.7% compared to 47.8% in patients who did not receive pentoxifylline ($\chi 2=4.360$, p=0.037, [Table/Fig-2]). In patients with severe alcoholic hepatitis stratified based on MELD score 21, the mortality in pentoxifylline treated group was 21.4% compared to 61.1% in the untreated group ($\chi 2=5.039$, p=0.025, [Table/Fig-2]), and in patients with severe alcoholic hepatitis stratified based on GAHS 9, the mortality in pentoxifylline treated group was 23.1% compared to 91.6% in the other group ($\chi 2=11.914$, p=0.001, [Table/Fig-2]). In spite of the increased occurrence of nausea, and to a lesser extent vomiting, among patients in the pentoxifylline group, they were not severe enough to warrant stoppage of therapy. Also, with time, the occurrence of these complications was reduced.

[Table/Fig-3] shows the baseline profile of patients who succumbed to various complications as compared to those surviving at the end of the study. It shows that baseline total bilirubin, creatinine, urea, MELD score and GAHS were

significantly different among the patients who succumbed to the disease as compared to those who survived.

DISCUSSION

Alcoholic hepatitis is an acute or acute-on chronic hepatic inflammatory response syndrome, which is a part of the spectrum of diseases that result from alcohol-induced liver injury, ranging from the most common asymptomatic fatty liver to fulminant hepatitis and cirrhosis in the long term.

The treatment of alcoholic hepatitis is one of the most debated topics in medicine. Current guidelines of the American College of Gastroenterology recommend the use of corticosteroids in treatment of patients with severe alcoholic hepatitis as defined by the Maddrey score (DF ≥ 32) [15,23]. Primary use of pentoxifylline in treatment of severe alcoholic hepatitis patients is not recommended due to the lack of evidence for improvement in patient-oriented outcomes [15]. However, these guidelines may not hold well in developing countries like India where patients are at a higher risk of infections. We find that pentoxifylline is a reasonable alternative to corticosteroids for severe acute alcoholic hepatitis based on the favorable results of previous studies [19-21]. The present study was initiated to test the hypothesis that pentoxifylline improves short term survival in patients with acute alcoholic hepatitis in Indian scenario.

Forty nine patients with acute alcoholic hepatitis were analysed. The diagnosis of alcoholic hepatitis is based on the history of heavy alcohol use, jaundice and the absence of other possible causes of hepatitis. The most important observation in our study was the significantly reduced mortality among patients in the pentoxifylline group (16.7%) as compared to those not receiving pentoxifylline (47.8%, p=0.037) in patients with severe alcoholic hepatitis stratified based on DF≥32. These findings were in consistent with studies by McHutchison et al.,[8]and Akriviadis et al.,[19].However, there was no significant reduction in mortality when the two groups were compared with out stratification into severe alcoholic hepatitis indicating that pentoxifylline may not be helpful in patients with DF< 32.

One of the unique features of our study is that, we calculated DF, MELD score and GAHS in all the patients, stratified the patients having severe acute alcoholic hepatitis based on these scoring systems and compared the results separately. To the best of our knowledge none of the studies conducted so far compared all the three scoring systems as prothrombin time both as seconds and INR was not available in many studies. Forrest et al compared DF and GAHS and established that GAHS is superior to DF in identifying patients with severe alcoholic hepatitis who benefit from steroids. However, MELD score was not calculated in their study [24]. In the present study we found that there is statistically significant reduction in mortality in all the three groups of patients with severe acute alcoholic hepatitis, stratified as DF≥32, MELD score ≥21 and GAHS≥9 treated with pentoxifylline. In patients with severe alcoholic hepatitis stratified based on MELD score 21, the mortality in pentoxifylline treated group was 21.4% compared to 61.1% in the untreated group (p=0.025), and in patients with severe alcoholic hepatitis stratified based on GAHS 9, the mortality in pentoxifylline treated group was 23.1% compared to 91.6% in the other group (p=0.001). These findings were in converse with a small sample size, retrospective, observational study by McAvoy et al., published as an abstract, finding a treatment benefit with pentoxifylline only in patients stratified to GAHS ≥ 9, but not in patients with DF ≥ 32 [20]. This reduced mortality among patients in the pentoxifylline group can at least in part be explained by the renoprotective effects of pentoxifylline and the lower occurrence of gastrointestinal bleeding.

Retrospectively, on analysing the biochemical profile at the time of inclusion, baseline total bilirubin, creatinine, urea, MELD score and GAHS were significantly different among the patients who succumbed to the disease as compared to those who survived. The baseline DF was not significantly different among the patients who expired as compared to those who survived. This finding was in contrary to the findings by De et al in which the authors compared the efficacy of pentoxifylline and prednisolone in the treatment of severe alcoholic hepatitis in a randomized controlled trial where only a higher Maddrey's DF score was found to be associated with the occurrence of increased mortality among patients with severe alcoholic hepatitis [21].

Our study had several limitations. As the study was a descriptive study, the patients were not randomized. The decision of treating the patients with pentoxifylline was totally based on the choice of the concerned unit treating physician. A randomized double blind control trial would have been more appropriate in this setting and would have had more significance but could not be done as some of the physicians were reluctant in using pentoxifylline. The second limitation of this study is the absence of evidence of histological improvement and survival among patients receiving pentoxifylline, because of the lack of availability of transjugular liver biopsy. However, a liver biopsy is not recommended to confirm histological improvement, since it is difficult to assess the timeline of the resolution of the histologic features. Also, the assessment of immunological and inflammatory status (e.g. TNF-α) of the patients was not possible. Nevertheless, a reduced mortality and more advantageous risk-benefit profile of pentoxifylline in patients with severe alcoholic hepatitis suggest that pentoxifylline is an agent worth considering for some patients in the treatment of severe alcoholic hepatitis especially in Indian scenario. However, further studies with a larger cohort of patients are warranted to decide if pentoxifylline is actually useful in the treatment of severe alcoholic hepatitis.

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