DOI: 10.14260/jemds/2015/156

ORIGINAL ARTICLE

STUDY OF PENTOXIFYLLINE ROLE ON PROGNOSIS IN PATIENTS WITH ACUTE ALCOHOLIC HEPATITIS ADMITTED IN GGH, GUNTUR

G. Chakradhar Rao[1], D. Sudheer Babu[2], G. K. Rajeswari[3], K. Sriram[4], J Siva Kalyani[5], L. K. V. Kumar[6], Sekhar Reddy M. V[7]

HOW TO CITE THIS ARTICLE:
G. Chakradhar Rao, D. Sudheer Babu, G. K. Rajeswari, K. Sriram, J Siva Kalyani, L. K. V. Kumar, Sekhar Reddy M. V. "Study of Pentoxifylline Role on Prognosis In Patients with Acute Alcoholic Hepatitis Admitted in GGH, Guntur". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 07, January 22;
Page: 1098-1111, DOI: 10.14260/jemds/2015/156

ABSTRACT: **BACKGROUND**: Alcoholic hepatitis is an acute form of alcohol induced liver injury. Its severity is measured using Maddrey's discriminant function (DF). DF>32 indicates severe hepatitis and poor outcome. TNF is responsible for liver injury in alcoholic hepatitis. Pentoxifylline (PTX) 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. The present study compares the outcome of patients treated with pentoxifylline with other patients who were given only supportive care in the Indian scenario. **MATERIALS AND METHODS**: 50 patients with signs and symptoms of acute alcoholic hepatitis admitted at GGH, Guntur were studied. Diagnosis was done based on clinical and biochemical profile. **RESULTS**: Majority of the patients (54%) were in the age group of 40-50 years. All the patients presented with jaundice; others include fever (84%), abdomen distension (74%), generalized weakness (68%). Altered sleep pattern and altered sensorium were present in 34% and 10% of patients respectively. All the patients had hyperbilirubinimia, elevated AST with AST/ALT ratio>2:1 and prolonged prothrombin time. Most of the patients 68% had INR < 2 and 32% > 2.The mortality in pentoxifylline treated group was 16.7% compared to 47.8% in patients who did not receive pentoxifylline, indicating that there is significant difference in the mortality in the above two groups. (p=0.037). **CONCLUSIONS:** Patients with severe alcoholic hepatitis (Maddrey's discriminant function, ≥32; or MELD score, ≥21: or GAHS, ≥9) who do not have sepsis should be given a trial of prednisolone at a dose of 40 mg per day for 28 days. In situations where corticosteroids are contraindicated, pentoxifylline is safe, economical, and useful in improving short term mortality in severe acute alcoholic hepatitis in Indian scenario.

KEYWORDS: Pentoxifylline, alcoholic hepatitis, meld.

INTRODUCTION: Alcoholic liver disease is a major cause of liver related morbidity and mortality in India. Despite of extensive research for more than 5 decades, it remains a challenging enigma for both scientists and clinicians.[1]

The severity of alcoholic hepatitis may be measured using Maddrey's discriminant function (DF). DF>32 indicates severe hepatitis and poor outcome.[2-3] Recently MELD score was found superior to DF in predicting severity.[4] 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 hyper bilirubinemia the Glasgow alcoholic hepatitis score (GAHS) was proposed. GAHS seems a substantial improvement in alcoholic hepatitis clinical phenotyping, but further research is needed.[5-6]

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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 Tumor Necrosis Factor (TNF) on liver cells. Several studies proved that TNF is responsible for liver injury in alcoholic hepatitis.[7-14] 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.[1,15]

Pentoxifylline (PTX) 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.[16]

As there are few studies from India, with the present study, we want to study the clinical profile of patients with acute alcoholic hepatitis and 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.

AIMS & OBJECTIVES:

1. To study the clinical profile of patients with acute alcoholic hepatitis.
2. To study the effect of pentoxifylline on short term mortality in patients with acute alcoholic hepatitis.

MATERIALS AND METHODS:

STUDY DESIGN: Descriptive Prospective Study.

STUDY POPULATION: Patients admitted in Guntur Medical College and Hospital with acute alcoholic hepatitis.

STUDY PERIOD: December 2013 to December 2014.

Inclusion Criteria:

1. Age > 18 years.
2. History of chronic alcohol intake or a recent alcoholic binge.
3. Jaundice.
4. One or more of the following clinical and laboratory findings:
    a. Palpable tender hepatomegaly.
    b. Leucocytosis -WBC count>12000.
    c. Hepatic encephalopathy.
    d. AST: ALT ratio > 2.

Exclusion Criteria:

1. Patients with active GI bleeding.
2. Severe cardiovascular or pulmonary disease.
3. Concomitant bacterial infection. (When neutrophilia is taken as a inclusion criteria).
4. HBsAg and anti HCV positive.

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Fifty patients with acute alcoholic hepatitis were evaluated at the time of admission and relevant history along with examination findings was noted.

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. Discriminant function, MELD score and GAHS were calculated from the above investigations.

Patients were enrolled into the present study within first 2 days of admission. The included patients were divided into two groups based on the treatment started within 2 days of admission. Group I was designated to patients who were started on tablet pentoxifylline 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 GI 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: Student's t test was used for analysis of continuous variables and the $\chi 2$ test was used for categorical variables. All results of continuous variables are expressed as mean ± SD. A 'p value' of <0.05 with one degree freedom was considered significant.

End Point: Completion of 28 days of treatment or Death of the patient.

RESULTS: Fifty patients admitted in Guntur Medical College & Hospital, Guntur and with acute alcoholic hepatitis between 1st December 2013 and 1st December 2014 were studied.

Age in years	Number	Percentage
20-30	1	2%
30-40	10	20%
40-50	27	54%
50-60	10	20%
60-70	2	4%

Table 1: Age distribution of patients (n=50)

Impression: Majority of the patients (54%) were in the age group of 40-50 years. The mean age of presentation was 45.62 ± 8.39 years.

Sex Distribution: All the cases studied were males.

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Type of alcohol Consumption: Most the patients were consuming locally made liquor which varies in alcohol content from time to time and place to place between 30-80%.

Alcohol History: The mean duration of alcohol consumption was 17.6 years. Most of the patients started consuming alcohol between 18 to 22 years of age.

Duration of alcohol consumption in years	Number of patients	Percentage
10-15	21	42%
15-20	22	44%
20-25	4	8%
25-30	2	4%
30-35	1	2%

Table 2: Distribution of alcoholics according to duration of alcohol consumption (n=50)

The above table shows that majority of patients (86%) had 10-20 years of alcohol history. 44% falling in 15-20 years group and 42% falling in 10-15 years. None of the patients had an alcohol history less than 10 years.

21 patients (42%) had a history of recent alcohol binge, just one or two days before the onset of symptoms.

SYMPTOMS:

Symptoms	No. of patients	Percentage
Jaundice	50	100
Fever	42	84
Distension of Abdomen	37	74
Pain Abdomen	17	34
Vomiting	8	16
Altered Sensorium	5	10
UGI Bleed	1	2
Generalised Weakness	34	68
Altered sleep	17	34

Table 3: Symptoms (n=50)

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All the patients presented with jaundice; the other common clinical presentations were fever (84%), distension of abdomen (74%), generalized weakness (68%) and pain abdomen (34%). Altered sleep pattern and altered sensorium were present in 34% and 10% of patients respectively.

SIGNS:

Signs	No of patients	Percentage
Pallor	9	18%
Icterus	50	100%
Edema	17	38%
Alopecia	9	18%
Parotid enlargement	23	46%
Spider Angiomata	10	20%
Palmar Erythema	2	4%
Gynecomastia	5	10%
Testicular Atrophy	5	10%
Flaps	13	26%
Muscle wasting	17	34%
Hepatomegaly	46	92%
Splenomegaly	4	8%
Tenderness	47	94%
Free Fluid	25	50%
Engorged Veins	12	24%

Table 4: Signs (n=50)

In addition to icterus, majority of patients had abdominal tenderness (94%), hepatomegaly (92%) and shifting dullness (50%). 46% of patients has parotid enlargement. Signs of liver cell failure like alopecia, spider angiomata, palmar erythema gynecomastia, testicular atrophy and muscle wasting were present in 18%, 20%, 4%, 10%, 10% and 34% respectively. Flapping tremors were present in 26% of patients. Engorged veins and splenomegaly were present in 24% and 8% of patients respectively. Pedal edema was present in 38% of patients.

Biochemical Profile: All the patients had hyper bilirubinimia and elevated AST with AST/ALT ratio>2.

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Total Bilirubin in mg/dl	Number of Patients	Percentage
5-10	23	46%
10-15	11	22%
15-20	7	14%
20-25	6	12%
25-30	2	4%
>30	1	2%

Table 5: Serum Bilirubin

Impression: Majority of patients (46%) had a serum bilirubin levels between 5-10mg/dl.

Albumin in mg/dl	Number of Patients	Percentage
>4	6	12%
3.5-4	3	6%
3-3.5	5	10%
2.5-3	14	28%
2-2.5	17	34%
<2	5	10%

Table 6: Serum Albumin

Impression: Hypoalbuminemia (Serum albumin < 3.5mg/dl) was present in 82% of patients. Majority of patients (34%) had serum albumin level between 2-2.5 mg/dl, 28% had serum albumin level between 2.5-3mg/dl. Only 6% of patients had a serum albumin level >4mg/dl.

Serum creatinine in mg/dl	Number of Patients	Percentage
<1.5	29	58%
1.5-2.5	13	26%
2.5-3.5	2	4%
3.5-4.5	6	12%

Table 7: Serum Creatinine

Impression: Most of the patients (58%) had a normal serum creatinine level (<1.5mg/dl). Only 16% of patients had a creatinine level >2.5.

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INR	Number of Patients	Percentage
1-2	34	68%
2-3	13	26%
3-4	1	2%
>4	2	4%

Table 8: INR

Impression: All the patients had a prolonged prothrombin time. Most of the patients 68% had INR < 2 and 32% > 2.

SL. No	Parameter	Mean±SD
1	Total bilirubin(mg/dl)	13.14±7.72
2	Direct bilirubin(mg/dl)	10.30±6.08
3	AST	140.80±46.27
4	ALT	47.46±20.03
5	ALP	171.92±70.74
6	Total protein(mg/dl)	6.94±1.17
7	Albumin(mg/dl)	2.84±0.83
8	Creatinine(mg/dl)	1.55±1.01
9	Urea(mg/dl)	50.64±39.85
10	INR	1.94±0.78
11	Total count	13803.72±4571.97
12	Platelet count	170400.00±69414.75

Table 9: Mean biochemical and hematological parameters of patients (n=50)

Stratification of patients with alcoholic Hepatitis: Patients were stratified for prognostic evaluation based on discriminant function (DF), Model for End-Stage Liver Disease (MELD) score and the Glasgow alcoholic hepatitis score (GAHS).

Prognostic indicator		Number of patients	Percentage
Discriminant function(DF)	≥ 32	42	84%
	< 32	8	16%
Model for End-Stage Liver Disease (MELD)score	≥ 21	33	66%
	< 21	22	44%
Glasgow alcoholic hepatitis score (GAHS)	≥ 9	26	52%
	< 9	24	48%

Table 10: Stratification of patients with alcoholic hepatitis based on various prognostic indicators. (n=50)

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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.

After detailed clinical evaluation and stratification of patients based on various scoring systems, the patients were divided into two groups based on the treatment started within 2 days of admission, as discussed above.

All the patients satisfied the inclusion and exclusion criteria except one patient who presented with hematemesis and was excluded from the study.

20 patients (41%) received pentoxifylline compared to 29 patients (59%) who did not.

Table 11: 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)

SL. 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 11

P<0.05 considered statistically significant. TLC: Total leukocyte count.

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Impression: The above table shows that there is no significant difference between the patients receiving pentoxifylline (group I) with those not receiving pentoxifylline (group II).

Mortality in patients with severe alcoholic hepatitis with respect to treatment with pentoxifylline

	Treated		Total
	Yes	No	
Expired Count	3	11	14
percentage	15%	37.9%	28.6%
Improved Count	17	18	35
percentage	85%	62.1%	71.4%
Total count	20	29	49
percentage	100%	100%	100%

Table 12: Mortality in patients with respect to treatment with pentoxifylline (n=49)

$\chi 2=3.050$ p=.081

Impression: The mortality in pentoxifylline treated group was 15% compared to 37.9% in patients who did not receive pentoxifylline, indicating that there is no significant difference in the mortality in the above two groups. (p=0.81).

Table 13: Comparison of baseline parameters of patients receiving pentoxifylline (group I) with those not receiving pentoxifylline(group II) in the treatment of severe alcoholic hepatitis with DF≥32.(mean±SD)

Sl. No.	Parameter	**Group I** (n=18)	**Group II** (n=23)	p value
1	Age	43.67±7.17	45.65±8.52	0.433
2	Fever	13	21	0.107
3	Distension of abdomen	16	16	0.138
4	Pain abdomen	7	8	0.786
5	Hepatomegaly	17	21	0.702
6	Total bilirubin(mg/dl)	16.32±8.79	12.95±6.94	0.178
7	AST	143.33±35.17	134.00±52.41	0.520
8	ALT	44.83±14.02	48.43±24.76	0.585
9	Albumin(mg/dl)	2.66±0.73	2.83±0.91	0.505
10	Creatinine(mg/dl)	1.51±0.95	1.71±1.09	0.541
11	Urea(mg/dl)	54.39±38.70	52.13±45.92	0.868
12	INR	2.01±0.52	2.15±0.93	0.568
13	Mean TLC	15392.56±5343.02	13325.65±3762.57	0.154
14	Discriminant function	73.06±30.15	76.70±50.47	0.615
15	MELD score	26.06±7.02	27.22±7.45	0.25
16	GAHS	9.28±1.27	8.83±1.30	0.105

Table 13

P<0.05 considered statistically significant. TLC: Total leukocyte count.

DOI: 10.14260/jemds/2015/156

Impression: The above table shows that there is no significant difference between the patients receiving pentoxifylline (group I) with those not receiving pentoxifylline (group II) with DF≥32.

DF ≥32	Treated		Total
	Yes	No	
Expired Count	3	11	14
percentage	16.7%	47.8%	34.1%
Improved Count	15	12	27
percentage	83.3%	52.2%	65.9%
Total count	18	23	41
percentage	100%	100%	100%

Table 14: Mortality in patients with severe alcoholic hepatitis- DF ≥32 (n=41)

$\chi 2=4.360$ p=.037

Impression: The above table shows the mortality in patients with severe alcoholic hepatitis with DF≥32. The mortality in pentoxifylline treated group was 16.7% compared to 47.8% in patients who did not receive pentoxifylline, indicating that there is significant difference in the mortality in the above two groups. (p=0.037).

Table 15: Comparison of baseline parameters of patients receiving pentoxifylline (group I) with those not receiving pentoxifylline(group II) in the treatment of severe alcoholic hepatitis with MELD score≥21.(mean±SD).

Sl. No.	Parameter	Group I (n=14)	Group II (n=18)	p value
1	Age	41.57±6.16	44.61±8.59	0.273
2	Fever	12	16	0.788
3	Distension of abdomen	12	14	0.568
4	Pain abdomen	6	4	0.212
5	Hepatomegaly	13	16	0.702
6	Total bilirubin(mg/dl)	17.80±9.21	14.47±7.00	0.254
7	AST	147.21±36.54	130.67±51.50	0.317
8	ALT	47.07±16.57	45.72±21.92	0.850
9	Albumin(mg/dl)	2.67±0.76	2.46±0.48	0.364
10	Creatinine(mg/dl)	1.97±1.01	1.97±1.10	0.998
11	Urea(mg/dl)	69.86±35.44	62.94±46.40	0.648
12	INR	2.02±0.60	2.30±1.01	0.368
13	Mean TLC	14483.29±6476.49	13918.33±3938.60	0.762
14	Discriminant function	75.50±33.97	86.28±53.20	0.515
15	MELD score	29.29±5.21	30.00±5.63	0.716
16	GAHS	9.21±1.31	9.22±1.16	0.986

Table 15

P<0.05 considered statistically significant. TLC: Total leukocyte count.

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Impression: The above table shows that there is no significant difference between the patients receiving pentoxifylline (group I) with those not receiving pentoxifylline (group II) with MELD score≥21.

MELD ≥21	Treated		Total
	Yes	No	
Expired Count	3	11	14
percentage	21.4%	61.1%	43.8%
Improved Count	11	7	18
percentage	78.6%	38.9%	56.2%
Total count	14	18	32
percentage	100%	100%	100%

Table 16: Mortality in patients with severe alcoholic hepatitis- MELD ≥21(n=32)

$\chi 2=5.039$ p=.025

Impression: The above table shows the mortality in patients with severe alcoholic hepatitis with MELD score≥21. The mortality in pentoxifylline treated group was 21.4% compared to 61.1% in patients who did not receive pentoxifylline, indicating that there is significant difference in the mortality in the above two groups. (p=0.025).

Table 17: Comparison of baseline parameters of patients receiving pentoxifylline (group I) with those not receiving pentoxifylline (group II) in the treatment of severe alcoholic hepatitis with GAHS≥9. (mean±SD)

Sl. No.	Parameter	Group I (n=13)	Group II (n=12)	p value
1	Age	42.62±7.54	47.50±7.99	0.13
2	Fever	11	11	0.588
3	Distension of abdomen	11	10	0.930
4	Pain abdomen	5	2	0.225
5	Hepatomegaly	12	11	0.953
6	Total bilirubin(mg/dl)	17.46±9.48	16.72±7.32	0.829
7	AST	139.23±34.95	128.17±50.96	0.530
8	ALT	43.69±12.42	43.17±18.69	0.934
9	Albumin(mg/dl)	2.73±0.84	2.48±0.34	0.356
10	Creatinine(mg/dl)	1.64±0.97	2.4±1.1	0.083
11	Urea(mg/dl)	62.31±39.38	75.17±51.79	0.490
12	INR	2.12±0.51	2.18±0.88	0.829
13	Mean TLC	16922.15±4357.32	15327.50±3425.72	0.322
14	Discriminant function	81.15±29.44	82.92±47.42	0.911
15	MELD score	27.92±6.76	32.58±3.94	0.05
16	GAHS	9.85±0.68	9.92±0.66	0.798

Table 17

P<0.05 considered statistically significant. TLC: Total leukocyte count.

DOI: 10.14260/jemds/2015/156

Impression: The above table shows that there is no significant difference between the patients receiving pentoxifylline (group I) with those not receiving pentoxifylline (group II) with GAHS≥9.

GAHS ≥9	Treated		Total
	Yes	No	
Expired Count	3	11	14
percentage	23.1%	91.6%	56%
Improved Count	10	1	11
percentage	76.9%	8.4%	44%
Total count	13	12	25
percentage	100%	100%	100%

Table 18: Mortality in patients with severe alcoholic hepatitis- GAHS ≥9 (n=25)

$\chi 2=11.914$ p=0.001

Impression: The above table shows the mortality in patients with severe alcoholic hepatitis with GAHS≥9. The mortality in pentoxifylline treated group was 23.1% compared to 91.6% in patients who did not receive pentoxifylline, indicating that there is significant difference in the mortality in the above two groups. (p=0.001)

The above chart shows that mortality in patients with DF≥32 treated with pentoxifylline are 16.7% whereas it is 47.8% in control group. In patients with MELD score ≥21 the mortality in treatment group is 21.4% and in control group is 61.1%. In patients with GAHS≥9 the mortality is 23.1 whereas mortality in control group is 91.6%.

SL. 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 19: Comparison of baseline parameters of patients 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

Impression: The above table shows the baseline profile of patients who succumbed to the illness 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. The baseline DF was not significantly different among the patients who expired as compared to those who survived.

CONCLUSION: The diagnosis of alcoholic hepatitis is based on a history of heavy alcohol use, jaundice, and the absence of other causes. Abstinence from alcohol is the cornerstone of recovery. Patients with severe alcoholic hepatitis (Maddrey's discriminant function, ≥32; or MELD score, ≥21: or GAHS, ≥9) who do not have sepsis should be given a trial of prednisolone at a dose of 40 mg per day for 28 days. After 7 days of corticosteroid treatment, patients with a Lille score of more than 0.45 may have disease that will not respond to continued treatment with corticosteroids or to an early switch to pentoxifylline.

When the clinical situation is such that clinicians are reluctant to prescribe corticosteroids, pentoxifylline is safe, economical, and appears to be useful in improving short term mortality in patients with severe acute alcoholic hepatitis in Indian scenario. The efficacy of combined treatment with pentoxifylline and corticosteroids has not been studied and warrants a randomized, controlled trial. Patients with less severe alcoholic hepatitis (DF<32) should not be treated with pentoxifylline as there appears be no significant benefit. Higher bilirubin, creatinine, urea, MELD score and GAHS were found to be associated with the occurrence of increased mortality among patients with severe alcoholic hepatitis.

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AUTHORS:

1. G. Chakradhar Rao
2. D. Sudheer Babu
3. G. K. Rajeswari
4. K. Sriram
5. J Siva Kalyani
6. L. K. V. Kumar
7. Sekhar Reddy M. V.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor and Professor I/C, Department of General Medicine, Guntur Medical College, Guntur.
2. Associate Professor, Department of General Medicine, Guntur Medical College, Guntur.
3. Assistant Professor, Department of General Medicine, Guntur Medical College, Guntur.
4. Senior Resident, Department of General Medicine, Guntur Medical College, Guntur.
5. Junior Resident, Department of General Medicine, Guntur Medical College, Guntur.
6. Junior Resident, Department of General Medicine, Guntur Medical College, Guntur.
7. Junior Resident, Department of General Medicine, Guntur Medical College, Guntur.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. G. Chakradhar Rao,
Professor of Medicine,
Department of General Medicine,
GGH, Guntur.
E-mail: profguduri@gmail.com

Date of Submission: 12/01/2015.
Date of Peer Review: 13/01/2015.
Date of Acceptance: 14/01/2015.
Date of Publishing: 20/01/2015.