A Randomised Double-Blind Trial of Pentoxifylline Alone versus Pentoxifylline Plus N Acetyl Cysteine in the Treatment of Severe Alcoholic Hepatitis in a Tertiary Care Hospital in Mysore, Karnataka

Anurag Lavekar[1], Deepak Suvarna[2], Aradya V.[3], Nandeesh P.[4], Vijayakumar R.[5], Rithesh Reddy[6]

[1, 2, 3, 4, 5, 6] Department of Gastroenterology, JSS Academy of Higher Education and Research, Mysore, Karnataka, India.

ABSTRACT

BACKGROUND

Proven therapeutic options for treating severe alcoholic hepatitis are limited. The study was conducted to compare pentoxifylline alone versus combination of Pentoxifylline plus N acetylcysteine in severe alcoholic hepatitis patients.

METHODS

A randomised, parallel, double blind, active controlled trial was conducted in which, 240 cases were considered for analysis and were divided into two study groups i.e. tablet pentoxifylline alone versus tablet pentoxifylline plus tablet N acetylcysteine. The pentoxifylline group received 400 mg thrice daily for one month and the other group received tablet pentoxifylline 400 mg thrice daily with tablet N–acetyl cysteine 600 mg twice daily for one month. Enrolled patients were called for follow up at one and three months. The parameters were compared between the two study groups statistically and the results were obtained.

RESULTS

Forty-nine (20.4 %) patients expired in 3 months, out of which 35 (14.5 %) expired at the end of 1st month. There was no significant difference in survival between two groups at the end of one and three months (P = 0.58 and 0.10 respectively). Although liver function test (LFT), PT-INR (prothrombin time-international normalised ratio) improved significantly from baseline in both the groups (P < 0.0001), no significant difference was observed between the two groups. Prevalence of hepatic encephalopathy was significantly low in pentoxifylline plus N-acetylcysteine group at one and three months (P = 0.04 and 0.02 respectively).

CONCLUSIONS

Addition of N acetyl cysteine to pentoxifylline helps in reducing hepatic encephalopathy in patients with severe alcoholic hepatitis; however, it does not improve the short-term survival.

KEYWORDS

Pentoxifylline, N-acetylcysteine, Alcoholic Hepatitis, Liver Disorder

Corresponding Author:
Dr. Deepak Suvarna,
JSS Hospital, Mysore,
Karnataka, India.
E-mail: drdeepaksuvarna@gmail.com

DOI: 10.18410/jebmh/2021/78

How to Cite This Article:
Lavekar A, Suvarna D, Aradya V, et al. A randomised double-blind trial of pentoxiphylline alone versus pentoxiphylline plus N acetyl cysteine in the treatment of severe alcoholic hepatitis in a tertiary care hospital in Mysore, Karnataka. J Evid Based Med Healthc 2021;8(08):399-404. DOI: 10.18410/jebmh/2021/78

Submission 07-09-2020,
Peer Review 14-09-2020,
Acceptance 29-12-2020,
Published 22-02-2021.

BACKGROUND

Severe alcoholic hepatitis (SAH), in the spectrum of alcoholic liver disease carries dismal prognosis. The short-term mortality due to severe alcoholic hepatitis as defined by discriminant function of greater than 32, ranges from 30 – 40 %.[1-3] Unfortunately, there is a dearth of good treatment options for SAH.

Although a number of newer drugs are being explored for treating SAH, their use is still investigational. Corticosteroids are the most extensively studied intervention in SAH, including a dozen placebo-controlled trials. These trials have yielded inconsistent results, due to heterogeneity and lack of power to detect differences in survival.[4] In a meta-analysis done by Mathurin et al., corticosteroids improved short term survival in patients with severe alcoholic hepatitis. However, Christensen et al. performed a meta-analysis and found corticosteroids to be ineffective in alcoholic hepatitis.[5]

In a randomised controlled trial (RCT) in SAH where steroids or pentoxifylline were used for alcoholic hepatitis (STOPAH) trial, the study did not demonstrate a statistically significant survival benefit at 28 days in patients receiving corticosteroids compared with placebo (odds ratio [OR] 0.72; 95 % CI 0.52 - 1.01, P = 0.06), whereas, on a post hoc multivariable analysis, corticosteroids were associated with improved 28-day survival (OR 0.609; P = 0.015), but not at 90 days (OR 1.02) or 1-year (OR 1.01). However, in a study done in patients with SAH with discriminant function (DF) greater than 54, it was found that patients receiving corticosteroids had lower survival compared with placebo, suggesting a ceiling of DF beyond which corticosteroids are harmful.[6]

In spite of limited availability of therapeutic options with proven beneficial effects in SAH, corticosteroids are not routinely used in clinical practice for concerns about sepsis, GI bleed, etc. and a wide range of adverse-effect profile. Infection is a serious concern and 25 % patients of alcoholic hepatitis do have active infections.[7] Further if responders to corticosteroids get an infection, their survival is similar to that of non-responders.[7] The STOPAH trial has also demonstrated higher incidence of infection with steroids when compared with pentoxiphylline (PTX) (13 % vs. 7 %).

A survey has revealed that only 25 - 45 % of practicing gastroenterologists and hepatologists reported routine use of corticosteroids for treating SAH.[8,9] Moreover, a retrospective analysis of medical electronic records has shown that only 8 - 9 % patients of SAH were treated with corticosteroids.[10] This highlights apprehensions on part of physicians for routine use of corticosteroids in SAH. However, this situation further adds to the crisis by depriving clinicians of treatment options, emphasising the need for other safe and effective pharmacotherapies.

PTX is a phosphodiesterase inhibitor; also, an inhibitor of tumour necrosis factor (TNF) α. TNF α is a principal cytokine involved in the pathogenesis of alcoholic hepatitis. In a double-blind randomised placebo-controlled trial on 101 patients, PTX was beneficial in providing mortality benefit (P = 0.037).[11] In another study, PTX was better than prednisolone for 28 day mortality (P = 0.04).[12] A network meta-analysis by Singh et al. did find low-level evidence of benefit of PTX.[13]

However, subsequent trials have failed to confirm this survival benefit, but have shown a reduction in the development of hepatorenal syndrome (HRS) in patients with SAH who received pentoxifylline.[14]

The levels of markers of oxidative stress and free radicals are increased in alcoholic hepatitis. N-acetylcysteine (NAC) has a thiol group which is able to reduce levels of free radicals. Supplementing NAC in SAH can replenish the glutathione stores of the hepatocytes. Importantly, NAC is being used routinely for acute liver failure due to paracetamol poisoning.

Given the lack of proven effective therapies for SAH, it is logical to see whether the efficacy of already existing therapies (e.g. corticosteroids or PTX) can be enhanced. In an RCT done by Nguyen-Khac et al. co-administration of intravenous N-acetylcysteine (NAC) with corticosteroids reduced infection and HRS compared with corticosteroids alone. Furthermore, the prednisolone plus NAC arm improved 1-month mortality compared with prednisolone plus placebo (8 % versus 24 %; P = 0.006).[15] A network meta-analysis of 22 RCTs (2,621 patients) also supported the addition of NAC providing survival benefit beyond corticosteroids alone.[13]

As long as there is no effective pharmacotherapy with proven benefits for treatment of alcoholic hepatitis, it would be interesting to see whether adding NAC to PTX would result in improvement in patients' clinical condition.

Thus, the study was conducted to compare the efficacy of pentoxifylline alone versus N-acetylcysteine plus pentoxifylline in patients of severe alcoholic hepatitis.

METHODS

After setting the study protocol, approval was obtained from institutional ethical committee. The study was randomised, controlled, double blinded trial registered with national clinical trial registry of India (CTRI Reg. No. – 2018 / 03 / 012577). The study was conducted in the Department of Gastroenterology and Hepatology of a tertiary care hospital in Mysore, India between March 2018 and February 2019.

Patients with severe alcoholic hepatitis [Maddrey's Discriminant Function > 32 calculated by Serum bilirubin plus 4.6 (prolongation of prothrombin time)], without or with cirrhosis (presence of oesophageal and gastric varices, ascites), in the age group of 18 - 70 years, of either sex were included in study. Patients with suspected or proven hepatocellular carcinoma, active infection, GI Bleed, and hepatitis due to any aetiology other than alcohol, jaundice for > 3 months and alcohol abstinence for > 2 months before enrolment for study and refusal of patients for participation were excluded from the study. Informed consent was taken from the recruited patients.

The estimated sample size for the two-arm study was 240 (120 each); however, in view of the loss to follow up, nearly 10 % additional subjects were recruited in the study. Thus, 262 patients were recruited for study

Referring to the study by Nguyen-Khac et al.,[15] the proportion of deaths due to hepatorenal syndrome was 9 % in the prednisolone-N acetylcysteine group as against 22 % in the prednisolone only group at the end of six months. Thus, to obtain at least this difference between the two treatment arms in the proposed study, with 95 % confidence and 80 % power of test, the expected sample size required was 120 cases per group (total 240), as per z-test of proportions in two independent groups.

Two hundred and forty cases were divided into two study arms (120 subjects in each arm). Randomisation was carried out by using computer generated random number and patients were allocated to either arms.

Thus, 240 patients were randomised to receive either PTX (group PTX) or PTX plus NAC (PTX + NAC group). One study arm in the (even numbers) received tab. pentoxifylline (PTX-group) 400 mg thrice daily for one month and the other arm (odd numbers) received pentoxifylline 400 mg thrice daily and tab. N–acetyl cysteine 600 mg twice daily for one month (PTX + NAC group). The Patient and the analyst were not aware of which group received which drug to ensure double blindness.

All the patients who were enrolled for the purpose of the study were first admitted in the hospital for initial evaluation and the treatment was started as per the protocol. Once the patients were fine after the first dose of the drugs were discharged and further followed up regularly on OPD basis. The Enrolled patients were called for follow up at one and three months. Primary end point was the survival of the patients between the two groups at one and three months and secondary outcome was improvement across two groups in liver function test and prothrombin time-international normalised ratio (PT-INR) at 1 month and 3 months.

Patients were treated on outpatient basis and were instructed regarding probable side effect and danger signs of liver injury and any such symptoms seen, they were asked immediately to report to the hospital and they were hospitalised only for indications like hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, gastro-intestinal bleed etc.

Statistical Analysis

The data on demographic and metabolic parameters was summarized according to treatment groups, referring to scale of measurement. The continuous parameters were expressed in terms of mean and standard deviation and compared between the groups using t-test for independent samples, while categorical parameters were expressed in terms of frequencies and compared using Pearson chi-square test. Such comparisons were made at 1 month and 3 months between two treatment groups. Further, the comparison of parameters was also carried out in each treatment group, across times, using repeated measure analysis of variance for continuous parameters and McNemar's test for categorical parameters. All the analyses were performed using Statistical Package for the Social Sciences (SPSS) ver. 20.0 and the statistical significance was tested at 5 % level.

RESULTS

Twenty-two (9.16 %) patients complained of adverse events such as nausea, belching, bloating, diarrhoea, headache and dizziness. The adverse events were comparable between both the groups (P > 0.05). Forty-nine (20.4 %) patients expired in 3 months, out of which 35 (14.5 %) died in 1st month. In the first month, 16 patients expired from PTX group and 19 from PTX plus NAC group. At the end of 3rd month, 14 more expired, among which 10 were from PTX and 4 were from PTX plus NAC group.

Among all 240 cases, 67 patients continued consuming alcohol and 173 patients adhered to alcohol abstinence. Of 67 patients who continued alcohol consumption after discharge from hospital, 23 (34.3 %) expired and from 173 abstinent patients the number of deaths were 26 (15 %). The P-value was 0.00086, which means there was significant difference in mortality of patients in both groups; mortality being higher in patients with ongoing alcohol abuse. Out of 67 patients, 29 from PTX group and 38 from PTX + NAC group had alcohol abuse. Out of 29, 8 patients expired in PTX group during follow up, while out of 38, 15 expired from PTX + NAC group. The difference in the proportion of expired cases with alcohol abuse in the two groups was statistically insignificant with P-value of 0.4498.

	Pentoxifylline (N = 120)	Pentoxifylline + N Acetyl Cysteine (N = 120)	P Value (Independent T test)
Age (years)	47.6 ± 9.42	49.13 ± 10.43	0.234
Gender [M:F], n #	113:7	112:8	0.790
Ascites, n #	81	79	0.891
HB	9.56 ± 2.77	9.23 ± 2.56	0.334
TC	9270.12 ± 3916.14	9588.71 ± 5886.12	0.622
Platelet count	1.27 ± 1.50	1.59 ± 6.2	0.577
Urea	38.20 ± 20.35	38.34 ± 21.92	0.959
Creatinine	1.21 ± 0.64	1.24 ± 0.70	0.712
Bilirubin	8.79 ± 7.38	7.08 ± 6.54	0.058
Direct bilirubin	5.66 ± 5.39	4.69 ± 5.43	0.171
AST	135.22 ± 102.36	135.6 ± 133.65	0.981
ALT	64.21 ± 57.71	64.54 ± 58.11	0.964
ALP	322.33 ± 151.81	311.57 ± 135.13	0.562
PT	25.85 ± 7.62	24.84 ± 4.92	0.221
INR	2.11 ± 1.35	1.89 ± 0.44	0.091
DF	65.91 ± 54.91	57.53 ± 24.67	0.129
MELD	22.57 ± 5.72	21.83 ± 5.45	0.311
CTP	9.73 ± 1.30	9.59 ± 1.59	0.451

Table 1. Baseline Characteristics of Patients in the Two Treatment Groups

Data was expressed as mean ± SD otherwise mentioned.
HB-Haemoglobin; TC-Total leukocyte count; AST-Aspartate aminotransferase; ALT-Alanine aminotransferase; ALP-Alkaline phosphatase; PT-Prothrombin time; INR-International normalised ratio; DF-Discriminant function; MELD-Model for end-stage liver disease; CTP-Child Turcotte Pugh
Chi-square Test applied

The descriptive statistics for various study parameters of patients in two treatment groups at baseline are given in Table 1. It is evident from the table that all the parameters were not significantly different between two groups. Thus, the samples in two groups were balanced and the randomisation was effective. Such comparison was also performed at one month and three months between two groups as shown in Table 2.

	One Month			3-Months		
	Pentoxifylline (N = 120)	Pentoxifylline + N Acetyl Cysteine (N = 120)	P value (Independent T test)	Pentoxifylline (N = 120)	Pentoxifylline + N Acetyl Cysteine (N = 120)	P value (Independent T test)
HB	8.84 ± 2.62	8.70 ± 2.83	0.691	9.79 ± 2.35	10.97 ± 10.61	0.271
TC	7836.71 ± 2590.08	7455.83 ± 2736.04	0.269	8327.99 ± 2209.65	8472.54 ± 2046.58	0.628
Platelets	1.25 ± 1.01	1.44 ± 2.24	0.688	1.22 ± 1.13	1.39 ± 2.09	0.434
Urea	39.47 ± 19.25	38.20 ± 18.91	0.605	39.82 ± 17.65	38.01 ± 18.86	0.479
Creatinine	1.59 ± 0.57	1.70 ± 0.68	0.188	1.52 ± 0.63	1.42 ± 0.48	0.226
Bilirubin	3.09 ± 0.96	3.22 ± 0.96	0.317	3.28 ± 0.91	2.74 ± 0.96	< 0.0001***
Direct bilirubin	2.16 ± 0.67	2.25 ± 0.67	0.317	2.59 ± 0.96	2.17 ± 0.93	0.002**
AST	109.02 ± 53.63	121.48 ± 57.67	0.084	99.46 ± 35.67	95.33 ± 33.52	0.395
ALT	50.38 ± 31.98	56.36 ± 33.27	0.157	44.70 ± 20.78	43.03 ± 18.34	0.542
ALP	119.33 ± 80.72	135.66 ± 88.02	0.136	96.45 ± 47.19	95.86 ± 37.64	0.921
PT	19.74 ± 5.20	20.27 ± 5.17	0.421	18.36 ± 2.86	17.82 ± 2.02	0.119
INR	1.770 ± 0.55	1.79 ± 0.62	0.211	1.57 ± 0.40	1.54 ± 0.27	0.415
DF	58.84 ± 22.94	59.51 ± 25.70	0.832	55.72 ± 20.41	56.65 ± 19.07	0.736
MELD	19.93 ± 6.17	21.01 ± 7.06	0.211	18.97 ± 5.35	17.70 ± 4.25	0.062
CTP	8.27 ± 2.01	8.03 ± 2.12	0.366	6.87 ± 1.63	6.40 ± 1.46	0.031*
HE, n #	62	46	0.038*	43	25	0.016*
HRS, n #	34	25	0.177	27	19	0.219
SBP, n #	36	28	0.243	29	20	0.175
GI Bleed, n #	43	38	0.495	33	26	0.344
Survival, n #	104	101	0.583	94	97	0.109

Table 2. Comparison of Patient Characteristics between the Two Treatment Groups at 1 Month and 3 Months

Data was expressed as mean ± SD otherwise mentioned.
HB-Haemoglobin; TC-Total leukocyte count; AST-Aspartate aminotransferase; ALT-Alanine aminotransferase; ALP-Alkaline phosphatase; PT-Prothrombin time; INR-International normalised ratio; DF-Discriminant function; MELD-Model for end-stage liver disease; CTP-Child Turcotte Pugh; HE-Hepatic encephalopathy; HRS-Hepatorenal syndrome, SBP-Spontaneous bacterial peritonitis; GI bleed-Gastrointestinal bleed
*Significant; **highly significant, ***very highly significant
Chi square test used

At one month, there was no statistically significant difference in the parameters evaluated between two treatment groups, except hepatic encephalopathy (P-value: 0.038). Further, at 3 months, the mean total bilirubin was significantly lower in PTX + NAC treated group as compared to PTX treated group, with a P-value of 0.016. Mean CTP was significantly lower in PTX + NAC treated group (6.40 ± 1.46) as compared to those treated with PTX (6.87 ± 1.63) with a P-value of 0.031. The incidence of hepatic encephalopathy was significantly higher in PTX group as compared to PTX + NAC group (P-value: 0.038). The survival of patients between two groups at 1 month and 3 months was not significantly different. Remaining parameters were not significantly different between the groups.

Further, the comparison of parameters was performed between baseline, one and three months in each treatment group and the results are shown in Table 3 A and Table 3 B. In the PTX treated group, all the parameters showed statistically significant change in the means using repeated measure analysis of variance, except platelets, blood urea and discriminant function. Similar was the observation in PTX + NAC treated group. In short, the two treatments were equally effective when observed over time.

	Baseline (N = 120)	1 Month (N = 120)	3 Months (N = 120)	P Value (Independent T Test)
HB	9.56 ± 2.77	8.84 ± 2.62	9.79 ± 2.35	0.016*
TC	9270.12 ± 3916.14	7836.71 ± 2590.08	8327.99 ± 2209.65	0.001**
Platelets	1.27 ± 1.50	1.25 ± 1.01	1.22 ± 1.13	0.512
Urea	38.20 ± 20.35	39.47 ± 19.25	39.82 ± 17.65	0.797
Creatinine	1.21 ± 0.64	1.59 ± 0.57	1.52 ± 0.63	< 0.0001***
Bilirubin	8.79 ± 7.38	3.09 ± 0.96	3.28 ± 0.91	< 0.0001***
Direct bilirubin	5.66 ± 5.39	2.16 ± 0.67	2.59 ± 0.96	< 0.0001***
AST	135.22 ± 102.36	109.02 ± 53.63	99.46 ± 35.67	< 0.0001***
ALT	64.21 ± 57.71	50.38 ± 31.98	44.70 ± 20.78	0.001**
ALP	322.33 ± 151.81	119.33 ± 80.72	96.45 ± 47.19	< 0.0001***
PT	25.85 ± 7.62	19.74 ± 5.20	18.36 ± 2.86	< 0.0001***
INR	2.11 ± 1.35	1.77 ± 0.55	1.57 ± 0.40	< 0.0001***
DF	65.91 ± 54.91	58.84 ± 22.94	55.72 ± 20.41	0.103
MELD	22.57 ± 5.72	19.93 ± 6.17	18.97 ± 5.35	< 0.0001***
CTP	9.73 ± 1.30	8.27 ± 2.01	6.87 ± 1.63	< 0.0001***

Table 3A. Comparison of Parameters with Time in Patients Treated with Pentoxifylline

Data were expressed as mean ± SD otherwise mentioned.
HB-Haemoglobin; TC-Total leukocyte count; AST-Aspartate aminotransferase; ALT-Alanine aminotransferase; ALP-Alkaline phosphatase; PT-Prothrombin time; INR-International normalized ratio; DF-Discriminant function; MELD-Model for end-stage liver disease; CTP-Child Turcotte Pugh
*Significant; **highly significant, ***very highly significant

	Baseline (N = 120)	1 Month (N = 120)	3 Months (N = 120)	P Value (Independent T Test)
HB	9.23 ± 2.56	8.70 ± 2.83	10.97 ± 10.61	0.021*
TC	9588.71 ± 5886.12	7455.83 ± 2736.04	8472.54 ± 2046.58	< 0.0001***
Platelets	1.59 ± 6.2	1.44 ± 2.24	1.39 ± 2.09	0.318
Urea	38.34 ± 21.92	38.20 ± 18.91	38.01 ± 18.86	0.992
Creatinine	1.24 ± 0.70	1.70 ± 0.68	1.42 ± 0.48	< 0.0001***
Bilirubin	7.08 ± 6.54	3.22 ± 0.96	2.74 ± 0.96	< 0.0001***
Direct bilirubin	4.69 ± 5.43	2.25 ± 0.67	2.17 ± 0.93	< 0.0001***
AST	135.6 ± 133.65	121.48 ± 57.67	95.33 ± 33.52	0.003**
ALT	64.54 ± 58.11	56.36 ± 33.27	43.03 ± 18.34	0.001**
ALP	311.57 ± 135.13	135.66 ± 88.02	95.86 ± 37.64	< 0.0001***
PT	24.84 ± 4.92	20.27 ± 5.17	17.82 ± 2.02	< 0.0001***
INR	1.89 ± 0.44	1.79 ± 0.62	1.54 ± 0.27	< 0.0001***
DF	57.53 ± 24.67	59.51 ± 25.70	56.65 ± 19.07	0.647
MELD	21.83 ± 5.45	21.01 ± 7.06	17.70 ± 4.25	< 0.0001***
CTP	9.59 ± 1.59	8.03 ± 2.12	6.40 ± 1.46	< 0.0001***

Table 3B. Comparison of Parameters with Time in Patients Treated with Pentoxifylline Plus N Acetyl Cysteine

Data were expressed as mean ± SD otherwise mentioned.
HB-Haemoglobin; TC-Total leukocyte count; AST-Aspartate aminotransferase; ALT-Alanine aminotransferase; ALP-Alkaline phosphatase; PT-Prothrombin time; INR-International normalized ratio; DF-Discriminant function; MELD-Model for end-stage liver disease; CTP-Child Turcotte Pugh
*Significant; **highly significant, ***very highly significant

DISCUSSION

Our study reinforces use of pentoxifylline in treatment of severe alcoholic hepatitis as evidenced by a significant improvement in Bilirubin, INR, CTP score and MELD at the end of one and three months from the baseline. These

findings were also supported by Akriviadis et al.[13] In a meta-analysis done by K Whitfield using five trials showed that pentoxifylline reduced mortality compared with controls (RR 0.64; 95 % CI 0.46 to 0.89). However, this result was not supported by further trial sequential analysis.[16]

Our attempt was to see whether addition of NAC to PTX is useful in treatment of severe alcoholic hepatitis. Pentoxifylline was found to be useful particularly in patients with hepatorenal syndrome in a study.[17] In the present study, there was worsening of creatinine at the end of first and third month across both groups as compared to baseline. The studied parameters did not improve on adding NAC to pentoxifylline. However, no difference between the mortality was observed across groups.

One of the most striking features of our study was significantly low prevalence of hepatic encephalopathy in PTX + NAC group at the end of one month which was consistent till the third month. NAC is used commonly in treatment of acute liver failure.[18] It is also found to improve transplant free survival in non-acetaminophen acute liver failure.[18] It is thought to have a role in preventing hepatic encephalopathy.[19] It helps in reducing hepatic encephalopathy by reducing the oxidative stress.[20]

There are a few studies on the use of antioxidants in SAH.[21,22,23] We used NAC owing to its antioxidant properties, given the crucial role of oxidative stress in development of alcoholic hepatitis. Moreover, liver protective ability of NAC in alcoholic hepatitis has been demonstrated in animal models.[24,25,26]

The difference between overall mortality across two groups was insignificant in our study. Nguyen-Khac E et al. also had derived similar results.[15] However, they had administered NAC intravenously for shorter duration (5 days). We have overcome this limitation by giving NAC for one month in our study.

Even though the current and other studies support the use of pentoxifylline for treating alcoholic hepatitis,[11,10] two systematic reviews showed no benefit of pentoxifylline for the same.[16,17] Currently, steroids continue to be standard of care for severe alcoholic hepatitis. Hence, comparison of treatment groups with steroids would have strengthened the present study. Other treatment options such as granulocyte colony stimulating factor (G-CSF) and early liver transplantation for alcoholic hepatitis were promising but need further studies for validation. Nonetheless, cost of treatment is also a major deciding factor in developing countries like India.[27,28]

CONCLUSIONS

Addition of NAC to PTX helped in reducing the hepatic encephalopathy as compared to PTX alone but did not help to reduce the overall mortality.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Maddrey WC, Boitnott JK, Bedine MS, et al. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75(2):193-199.
[2] Mathurin P, O'Grady J, Carithers RL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut 2011;60(2):255-260.
[3] Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372(17):1619-1628.
[4] Lieber SR, Rice JP, Lucey MR, et al. Controversies in clinical trials for alcoholic hepatitis. J Hepatol 2018;68(8):586-592.
[5] Christensen E, Gluud C. Glucocorticoids are ineffective in alcoholic hepatitis: a meta-analysis adjusting for confounding variables. Gut 1995;37(1):113-118.
[6] Mendenhall C, Roselle GA, Gartside P, et al. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two veterans administration cooperative studies. Alcohol Clin Exp Res 1995;19(3):635-641.
[7] Louvet A, Wartel F, Castel H, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137(2):541-548.
[8] Singal AK, Salameh H, Singal A, et al. Management practices of hepatitis C virus infected alcoholic hepatitis patients: a survey of physicians. World J Gastrointest Pharmacol Ther 2013;4(2):16-22.
[9] Cohen SM, Ahn JMT. Review article: the diagnosis and management of alcoholic hepatitis. Aliment Pharmacol Ther 2009;30(1):3-13.
[10] Nguyen TA, DeShazo JP, Thacker LR, et al. The worsening profile of alcoholic hepatitis in the United States. Alcohol Clin Exp Res 2016;40(6):1295-1303.
[11] Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119(6):1637-1648.
[12] Krishna De B, Gangopadhyay S, Dutta D, et al. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World J Gastroenterol 2009;15(13):1613-1619.
[13] Singh S, Murad MH, Chandar AK, et al. Comparative effectiveness of pharmacological interventions for severe alcoholic hepatitis: a systematic review and network meta-analysis. Gastroenterology 2015;149(4):958-970.
[14] Mathurin P, Louvet A, Duhamel A, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. JAMA 2013;310(10):1033-1041.
[15] Nguyen-Khac E, Thevenot T, Piquet MA, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365(19):1781-1789.
[16] Whitfield K, Rambaldi A, Wetterslev J, et al. Pentoxifylline for alcoholic hepatitis. Cochrane Database Syst Rev 2009;2009(4):CD007339.

[17] Parker R, Armstrong MJ, Corbett C, et al. Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther 2013;37(9):845-854.
[18] Polson J, Lee WM, American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. Hepatology 2005;41(5):1179-1197.
[19] Dhanda S, Kaur S, Sandhir R. Preventive effect of N-acetyl-L-cysteine on oxidative stress and cognitive impairment in hepatic encephalopathy following bile duct ligation. Free Radic Biol Med 2013;56:204-15.
[20] Atluri DK, Prakash R, Mullen KD. Pathogenesis, diagnosis and treatment of hepatic encephalopathy. J Clin Exp Hepatol 2011;1(2):77-86.
[21] Phillips M, Curtis H, Portmann B, et al. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis--a randomised clinical trial. J Hepatol 2006;44(4):784-790.
[22] Stewart S, Prince M, Bassendine M, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 2007;47(2):277-283.
[23] Moreno C, Langlet P, Hittelet A, et al. Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: a randomized multicenter controlled trial. J Hepatol 2010;53(6):1117-1122.
[24] Wang AL, Wang JP, Wang H, et al. A dual effect of N-acetylcysteine on acute ethanol-induced liver damage in mice. Hepatol Res 2006;34(3):199-206.
[25] Ronis MJ, Butura A, Sampey BP, et al. Effects of N-acetylcysteine on ethanol induced hepatotoxicity in rats fed via total enteral nutrition. Free Radic Biol Med 2005;39(5):619-630.
[26] Ozaras R, Tahan V, Aydin S, et al. N-acetylcysteine attenuates alcohol-induced oxidative stress in rat. World J Gastroenterol 2003;9(1):125-128.
[27] Singh V, Sharma AK, Narasimhan RL, et al. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. Am J Gastroenterol 2014;109(9):1417-1423.
[28] Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365(19):1790-1800.