

Short term outcome in severe alcoholic hepatitis patients treated with Methylprednisolone plus N acetylcysteine or Pentoxifylline plus N acetylcysteine.

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ABSTRACT

Introduction: Severe Alcoholic hepatitis (AH) is an acute form of alcohol induced liver injury. Often it present as fetal diseases with very high (30-50%) short term (28 days) mortality. This study was conducted from period May 2016 to July 2017 in Liver unit, Bir hospital. The main objective was to find out 28 days mortality in patients with severe alcoholic hepatitis who had Discriminant function (DF) ≥ 32 . This was a prospective, comparative, randomized interventional hospital based study.

Methodology: Hundred and ten diagnosed patients of severe alcoholic hepatitis who fulfilled the criteria were enrolled and randomized into two groups (odd number and even number). Group 1 received methylprednisolone and group 2 received pentoxifylline for 28 days. In both groups N acetylcysteine were added. Lille score was calculated in methylprednisolone group at day 7 and patients with score of ≤ 0.45 were continued methylprednisolone for total 28 days otherwise stopped. Data were recollected at day 28. They were compared in relation to survival, complications of drugs and causes of mortality.

Results: Mean age of presentation were 40.21 ± 10.5 yrs in methylprednisolone and 42.1 ± 12.1 yrs in pentoxifylline group. In both groups complications were nausea, vomiting, bloating, anorexia and swelling of limb. However, hyperglycemia (16.4%) and renal impairment (9.1%) were more common in methylprednisolone group. Mortality rates were 34.5% in methylprednisolone and 37.8% in pentoxifylline group within 28 days. Common causes of death in both groups were hepatic encephalopathy, hepatorenal syndrome, sepsis or the cause was undetermined.

Conclusion: Alcoholic hepatitis is common manifestation of alcoholic liver disease with high short term mortality in both the groups however adverse effects of drugs are more common in methylprednisolone groups.

Keywords: Alcoholic hepatitis, methylprednisolone, pentoxifylline, discriminant function, model for end stage liver diseases.

INTRODUCTION

AH is a clinical entity with rapid onset of jaundice with elevated serum aspartate transaminase (AST), arising on the background of heavy alcohol use. The thresholds for amount and duration of alcohol use causing AH are not known, although an average consumption of more than 3 drinks (~40 g) per day for women and 4 drinks (~50–60 g) per day for men

are reasonable minimal thresholds for the diagnosis of AH. Patients typically have history of heavy drinking for >5 years, but may be intermittently abstinent. For the diagnosis of AH, heavy alcohol use should have occurred for >6 months, with <60 days of abstinence before the onset of jaundice.¹

Heavy drinkers are at risk for a spectrum of histologic alcohol-related liver injury: steatosis, alcoholic

steatohepatitis (ASH), alcohol-related fibrosis, and cirrhosis. Alcoholic hepatitis (AH), the clinical entity associated with severe ASH, has high short-term mortality.¹ In a study short term mortality (30 days) in severe alcoholic hepatitis was 12-15%² or high as 21%.³ Jaundice is often accompanied by malaise, tender hepatomegaly, and decompensation (ascites, encephalopathy, bacterial infection, and variceal bleeding). Serum bilirubin is usually elevated (>3 mg/dL), as is AST (>50 IU/L), and AST to alanine aminotransferase (ALT) ratio of >1.5. The AST and ALT do not typically exceed 400 IU/mL, distinguishing AH from other liver diseases such as drug-induced liver injury (DILI) and ischemic hepatitis.¹

As alcohol related disorders are common in Nepalese population and there are no study regarding severe AH. This study aimed to find out the short term (28 days) mortality in severe AH.

MATERIALS AND METHODS

This is a prospective, randomized and interventional study conducted in the Liver unit of Bir hospital, Nepal. Consecutive patients of alcoholic hepatitis who were attended Out Patients Department (OPD) or In Patients Department (IPD) of Liver unit or Emergency department between periods of May 2106 to July 2017 was enrolled. Study was approved by Institutional Review Board (IRB) of NAMS, Bir hospital. The required sample size was calculated on the assumption that the survival rate would be 67% at 6 months in the methyl prednisolone-only group. With an alpha error of 0.05, a beta error of 0.20, and a hypothetical improvement in survival of 20% at month 6 for the methyl prednisolone plus N-acetylcysteine group⁴ the required sample size was 108 patients. Inclusion criteria were any patients who had ongoing alcohol drinking or consumed during last 2 months period with discriminant function (DF) \geq 32 and AST /ALT ratio more than 2. Exclusion criteria include age less than 18 years, pregnancy, viral hepatitis, hepatocellular carcinoma, patients who did not gave consent and patients who were also enrolled in other clinical trials at the same period.

Detailed history, examinations (general and systemic) with recording of vital signs, abdominal girth were taken. Relevant baseline investigations like complete blood counts, Liver function tests, Prothombin Time/ International normalization ratio, renal function tests and random blood glucose were sent. Other tests like Hepatitis B surface antigen, Anti Hepatitis C virus

antibody and Human immunodeficiency virus (rapid kit test) were also sent. B mode ultrasound of abdomen and Doppler Ultrasound abdomen were done in all cases to look for absence/presence of liver cirrhosis and hepatocellular carcinoma. Upper Gastrointestinal endoscopy was carried out in all patients before starting methylprednisolone or pentoxifylline. Special tests like antinuclear antibody, anti smooth muscle antibody, liver kindey microsomal antibody, anti mitochondrial antibody, pANCA along with iron profile, ceruloplasmin, were sent in selected patient when required to rule out other causes of hepatitis. CAGE questionnaire was complied in all patients with score of \geq 2 taken as significant alcohol abusers or dependent requiring intervention.

CAGE questionnaire comprise of four questions:

1. Have you ever felt you needed to Cut down on your drinking?
2. Have people Annoyed you by criticizing your drinking?
3. Have you ever felt Guilty about drinking?
4. Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?

After detail examinations and admission these patients DF and ratio of AST to ALT were calculated. Patients were considered for therapy if DF \geq 32 and AST/ALT \geq 2 and if there were no contraindications. Daily, detailed examinations and routine blood tests along with necessary other tests were carried out. Clinical measures observed were daily weight, abdominal girth, urine output, features of hepatic encephalopathy sign of sepsis, bleeding or rashes.

Those patients were divided into two groups for randomization, odd number got methylprednisolone plus N acetylcysteine (Group 1) and even number got pentoxifylline plus N acetylcysteine (Group 2). In group 1, patients were given oral methylprednisolone 32 mg daily for 4 weeks plus N acetylcysteine 140 mg/kg loading dosages, followed by 70 mg/kg every 4 hourly for next 17 dosages. Lille score was carried out at day 7 following treatment in the first group and if it was \leq 0.45 treatment was continued for 28 days then tapered and stopped (16 mg methylprednisolone for 3 days followed by 8 mg daily for 3 days then 4 mg daily for 3 days and then 2mg daily for 3 days before stopping). Group 2 were given oral pentoxifylline 400 mg three times daily plus oral N acetylcysteine (140 mg/kg loading dosage, then 70 mg/kg every 4 hourly

for next 17 dosages). These patients (in both groups) stayed in hospital for minimum 5 days. Following discharge they were reviewed at end of first week and at 28 days. However they were followed up whenever felt necessary by patients or by attendant. Data were taken at the end of the first week and at first month. Different scoring like discriminant function (DF), Albumin Billirubin INR Creatinine (ABIC), Glasgow alcoholic hepatitis score (GAHS) Model for end stage liver disease (MELD), Child Turchotte Pugh (CTP) score) were calculated by different formulas as they are mathematical model.⁵ During follow up detailed clinical examination were done together with routine blood tests and recording of any complications. They were also asked for compliance to drugs, nutrition, and abstinence of alcohol.

Data were entered by using Microsoft excel 2007. Statistical analysis was done using SPSS (version 23) software. Quantitative variable expressed as means ±SD and compared with the use of the Wilcoxon test, Kruskal-Wallis tests or Student t tests as appropriate. Qualitative variables were expressed as percentage, and compared with chi squared test. Kaplan–Meier survival curves was plotted at the end of 28 days and compared with use of log rank test. A 95% confidence interval was taken and P value less than 0.05 were termed as statistically significant.

RESULTS

During study period 116 patients fulfilled the inclusion criteria. 6 patients were excluded (two patients with chronic hepatitis B viral infection, two patients with anti nuclear antibody positive, two patients had active peptic ulcer diseases). Finally, 110 patients were available for the study. 55 patients each were randomized into 2 groups. Male patients were predominant in both groups. Minimum age was 25 years and maximum age was 78 years.

Most common age group at presentation was between 31 to 40 years n = 35(31.5%) followed by 41 to 50 years n=30(27.27%). Similarly, 20 to 30 years n=23(20.90%), age between 51 to 60 years n=16(14.54%), age between 61 to 70 years n=5(4.5%) and age between 71 to 80 years n= 1(0.9%).

At presentation, various clinical features included jaundice, abdominal distension, altered sensorium, fever, abdominal pain as shown in figure 1. Similarly on abdominal examination abdominal distension was most common (72.7%) in both groups and other

findings were as shown in table 1.

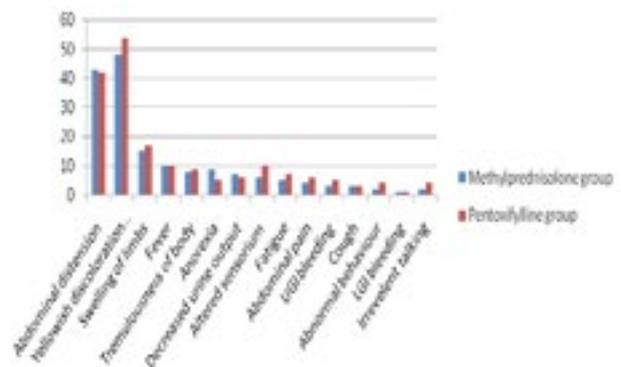


Fig 1: Clinical features

Table 1: Findings of Abdominal examination

Abdominal examination	Methylprednisolone group	Pentoxifylline group	Chi square	P value
Abdominal distension	40(72.7)	40(72.7)	0	1
Liver tenderness	14(25.5)	9(16.4)	1.374	0.241
Mean liver size(cm)	15.5±2.0(11-20)	15.5±1.9 (12-20)	-0.647	0.519
Hepatomegaly	29(52.72)	31(56.36)	0.147	0.702
Palpable spleen	15(27.3)	22(40)	1.96	1.58
Ascites	33(60)	40(72.2)	1.99	0.158
Hepatic bruit	3(5.5)	4(7.3)	0.806	0.369

At admission these patients were evaluated and different scoring (Discriminant function, Lille score, AIBC score, MELD score, GASH score and CTP score) were calculated and similar calculation were also carried out on day 28. The results of different scores are as depicted on table 2 and 3.

Table 2: Different scoring on admission.

Scoring (Mean)	Methylprednisolone group	Pentoxifylline group	T test	P value
DF	61±24(33-129)	59.8±35(32-214)	0.383	0.702
AIBC	6.9±1.2(4.5-10)	7.17±1.2(4.9-10.27)	-0.736	0.463
MELD	21±4.9(10-29)	21.2±5.7(11.2-40)	0.013	0.990
GAHS	8.54±0.6(7-10)	8.5±0.6(7-10)	0.144	0.886
CTP	10.5±0.9(8-13)	10.5±1.0(7-12)	-0.193	0.847

Table 3: Different scoring in Day 28.

Scoring (Mean)	Methylprednisolone group	Pentoxifylline group	T test	P value
DF	34.8±19.7(5.8-124)	40.6±21(13-107)	-1.294	0.200
ABIC	6.2±1.1(3.9-8.7)	6.2±1.3(2.15-8.9)	-0.110	0.913
MELD	17.7±4.7(8-33)	18.9±5.5(7.17-40)	-0.965	0.338
GAHS	8.0±0.6(7-9)	7.9±0.7(7-9)	0.850	0.398
CTP	9.7±1.1(8-12)	10.2±1.2(7-12)	-1.795	0.077

Several complications were noted in both groups

during study period. Among them most common are shown in fig 2

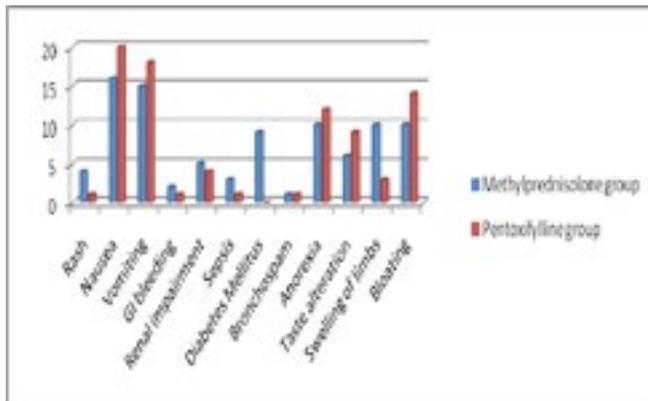


Fig: 2 Complications of drugs

Mortality in methylprednisolone group was 34.5% and pentoxifylline group 37.8% which was not statistically significant (P=0.692). In methylprednisolone group commonest cause of death was hepatic encephalopathy n=6(10.9%) followed by hepatorenal syndrome n=3(5.5%) and sepsis n=3(5.5%). Similarly in pentoxifylline group commonest cause of death was hepatic encephalopathy n=5(9.1%) and undetermined n=5(9.1%) followed by GI bleeding n=4(7.3%). In CTP grading most of the patients in both groups were CTP C (87.27%) and CTP B. Regarding survival there were no statistically significant difference between both groups which is shown in fig. 3

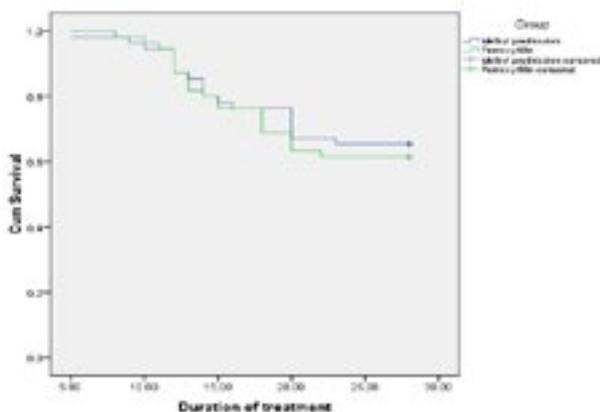


Fig 3: Survival among groups

DISCUSSION

Alcoholic hepatitis is clinical entity which is further divided into mild form and severe form. Severe form had discriminant function ≥ 32 or MELD score >21 or GAHS >9 . Mild AH have 90% survival within 90 days⁶ with supportive care like abstinence of

alcohol, good nutrition (30-40 kcal/day), multivitamins and management of alcohol dependence with benzodiazepines. Nutritional support improves liver function and short-term follow-up studies suggest that improved nutrition might improve survival times and histological findings in patients with AH.⁷ A large multicentre randomized (STOPAH) trial was conducted in the United Kingdom between 2011 and 2014, in patients with clinical diagnosis of severe AH. There was controversy regarding use of corticosteroids or pentoxifylline (PTX).⁸ This study reported a borderline reduction in mortality at 28 days for patients treated with prednisolone 40 mg/day compared with control patients. In a meta analysis, after one month prednisolone therapy provided no benefit in patients of alcoholic hepatitis.⁹ In AAC- NAC4 trial where 174 patients of severe AH were included and divided into two groups and treated with prednisolone only or with NAC plus prednisolone, 6 month mortality was 38% in prednisolone group and 27% in NAC plus prednisolone group, however it was not statistically significant (P=0.07). Hepatorenal syndrome were observed less in NAC plus prednisolone group compared to prednisolone group only (P=0.02). Similarly 1 month mortality was lower in combination group than in prednisolone group (P=0.006).

In other studies Mathurin and colleagues¹⁰ observed higher mortality in patients who were not treated with steroid than treated with steroid (34.3% vs. 20.03%) within 28 days period.

However in our study mortality rate was quite high 34.5% in methylprednisolone group and in 37.8% in pentoxifylline group in 28 days period. Most clinical trials for AH have used this score based on its use in the original corticosteroid trials. A number of other scoring systems have also been validated and generally performed similar to the Maddrey score, including the MELD score, Age Bilirubin INR Creatinine (ABIC) score, and the Glasgow scale¹¹ A MELD score >20 has been proposed as defining severe AH with an ~20% mortality.¹² Lille score (a continuous score with a scale from 0 to 1) at 4–7 days of corticosteroids therapy can be used to assess the response to corticosteroids. Lille score ≤ 0.45 ¹³ combined score has been compared to the CTP score, MELD, and MDF, and shown to have an overall sensitivity of 73% and specificity of 83%, which was at least as good as other scoring systems.¹⁴ In a study by Carinthers¹⁵

and colleagues where 66 patients were enrolled with severe alcoholic hepatitis and randomized to take placebo or methylprednisolone 32 mg for 4 weeks followed by tapering in next 2 week. Major outcome were in placebo group (n=31) where 11(35%) patients died in 28 days while in methylprednisolone group (n= 35) where 2(6%) patients died in same period (P=0.02).

However in our study, mortality rate was quite high 34.5% in methylprednisolone group and in 37.8% in pentoxifylline group in 28 days period. In our study most of the patients in both group were CTP C (87.2%) and had very high DF score. Most of the patients visited hospital in late phase. This finding suggest that the transplantation is probable other modality of treatment that remain for the CTP C patients with high DF score at presentation.

This is small study and required larger scale study to support this finding. Limitation of our study were liver biopsy not performed before starting the treatment and study period being quite short (28 days).

CONCLUSIONS

Alcohol is most common beverages which are abused worldwide. Alcoholic hepatitis is common manifestation of alcoholic liver diseases. Short term (28 days) mortality is quite high in our population and most of these patients presented late with high DF. Most effective way to decrease the incidence of AH is to avoid alcohol drinking and early diagnosis and treatment.

Conflict of Interest:

None

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