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CLINICAL PROFILE OF ALCOHOLIC HEPATITIS AND ROLE OF STEROID THERAPY IN MANAGEMENT OF SEVERE ALCOHOLIC HEPATITIS : A TERTIARY CARE CENTRE EXPERIENCE

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ABSTRACT **BACKGROUND :** Alcoholic hepatitis(AH) is a serious form of acute decompensation of alcoholic liver disease (ALD)and is characterized by rapid onset of jaundice, and features of systemic inflammatory response syndrome(SIRS). Severe alcoholic hepatitis (SAH), defined by a modified Maddrey discriminant function(mDF) >32 is associated with high short term mortality of 30%-50%. There are limited pharmacological agents available that have shown any benefit in patients with severe AH. Various meta-analyses have confirmed the short term survival benefit of steroids. **OBJECTIVE :** We aimed to evaluate the clinical spectrum of AH, proportion of patients who are eligible for corticosteroids based on standard clinical criteria, and response to steroid therapy. **METHODOLOGY :** Consecutive patients admitted with a diagnosis of AH were prospectively enrolled after informed consent. **RESULT :** 101 patients of AH were enrolled. All were male. Mean age of patients was 44.511±.8Years. Mean ethanol consumption was 117±38 grams. Mean duration of alcohol intake was 36±8 months. Ascites was present in 77(76%) patients. Esophageal varices(EV)was seen in 75(74%) patients. Median mDF of the patients on admission was 81(17-150). Median MELD score was 27(15-39). Only 12(11.6%) patients were eligible for corticosteroid therapy. Out of 12 patients in which steroid was prescribed, only 3(33%) patients had response to steroid therapy with decrease of Lille score to less than 0.45 after one week. Overall mortality was seen in 30 (29.7%) patients at 1 month follow up. **CONCLUSION :** AH is a severe disease with high mortality. Very few patients are eligible for steroid therapy and response rate to steroids is also very low. In Indian subcontinent, rate of response to steroids may even be lower. So, use of steroids may not confer any survival advantage in Indian subcontinent in contrast to western world where nutritional status of patient is good and disease is relatively less severe.

KEYWORDS : Alcoholic hepatitis, Corticosteroids, mDF

INTRODUCTION :

Alcoholic liver disease(ALD) represents a spectrum of conditions ranging from reversible fatty liver, alcoholic hepatitis(AH) and cirrhosis. Alcoholic hepatitis(AH) is a serious form of acute decompensation of alcoholic liver disease(ALD)and is characterized by rapid onset of jaundice, malaise, anorexia, tender hepatomegaly, and features of systemic inflammatory response syndrome(SIRS).[1,2] Patients with AH are systemically ill with a high risk of nutritional deficiency, infections, acute kidney injury(AKI), and development of multi-organ failure(MOF)syndrome.[3] Mild AH without encephalopathy, jaundice, or coagulopathy has a mortality of less than 5%.Severe alcoholic hepatitis(SAH), defined by a modified Maddrey Discriminant Function(mDF)>32 is associated with high short term mortality of 30%-50%[4-6].Short-term prognosis of alcoholic hepatitis(AH)is worse than that of decompensated cirrhosis as defined by the Baveno IV consensus conference; 1-year mortality is 20% in decompensated cirrhosis[7]. Hence,it is important to distinguish patients with AH, from those with decompensated cirrhosis so that the former group can be targeted by specific potentially effective treatment. There are limited pharmacological agents available that have shown any benefit in patients with severe AH. Corticosteroids are time tested to treat severe AH. Various meta-analyses have confirmed the short term survival benefit of steroids[8]. However, only a subgroup of carefully selected patients with severe AH are considered eligible for corticosteroids. Recently, Early Liver transplantation was proposed in patients with severe Alcoholic hepatitis who fail to respond to medical therapy.[9] Therefore, it is apparent that despite the rising burden of Alcohol Liver Disease, there is limited therapeutic options available for these patients. There is limited data from India on role of steroids in severe AH. Therefore, we aimed to evaluate the clinical spectrum of AH, proportion of patients who are eligible for corticosteroids based on standard clinical criterion, and response to steroid therapy.

MATERIALS AND METHODS:

Consecutive patients admitted with a diagnosis of AH, at RNT Medical College and Attached Group of Hospitals, Udaipur during the study period from December 2020 to January 2022, were prospectively enrolled after informed consent for participation in the study. Diagnosis of AH was made as per NIAAA Alcoholic hepatitis consortia - chronic alcohol abuse (> 60 g per day for men and > 40 g per day for women) till the last 2 months of onset of jaundice, serum billirubin exceeding > 3 mg/dL, and AST/ALT > 1.5, both values <400 IU/L.12

EXCLUSION CRITERION :

1. Concomitant acute viral hepatitis.
2. Concomitant chronic HBV or HCV infection.
3. HIV infection.
4. Autoimmune disease.
5. Wilson disease
6. Jaundice for more than 3 months
7. AST > 500 U/L or ALT > 300 U/L
8. Concomitant hepatocellular carcinoma
9. Pregnant or lactating wome
10. Refusal to give consent.

The Ethics Committee of the hospital approved the study, and the study conformed to the Helsinki declaration of 1975 as revised in 1983.

STATISTICAL ANALYSIS:

All results were expressed as mean±standard deviation, median or range as appropriate. SPSS version 21 was used for data management and statistical analysis. For discrete variables, a comparison among the different groups was made with a chi square test .Continuous variables in different groups were compared with Student-t test. A two-tailed P value of less than 0.05 was considered statistically significant.

EVALUATION :

The patients were evaluated with a detailed history and thorough clinical examination. Biochemical tests : complete blood count, liver function test, kidney function test , viral markers(HBsAg ,anti-HCV, anti-HEV, anti-HAV) were done. Data from imaging studies like ultrasound with color Doppler spleno-portal axis was analyzed. Upper gastrointestinal (UGI) endoscopy to look for evidence of portal hypertension was done in all patients. The following severity scores were calculated for each patient : mDF, MELD, Child-Turcotte-Pugh(CTP), Lille score.

TREATMENT:

All patients received the following treatment: alcohol abstinence, prevention and treatment of alcohol withdrawal(with chlordiazepoxide), fluid management, nutritional support(either oral or enteral) with adequate calories, proteins, vitamins and minerals, infection surveillance and if present, treatment with appropriate antibiotics, lactulose and/or rifaximin for hepatic encephalopathy, and intravenous albumin infusion. Patients with Maddrey's DF <32 were treated with supportive therapy and nutritional support.

Patients with severe AH with mDF >32 were treated with corticosteroids (Tab. Prednisolone 40 mg)after ruling out all contra-indications. Patients were excluded from steroid therapy if there was evidence of active infection (culture proven or clinically suspected bacterial infections), recent or past evidence of tuberculosis, history of chronic hepatitis B or hepatitis C infections, acute variceal bleed within 5 days(malena or hematemesis), uncontrolled diabetes, or deranged renal functions(creatinine > 1 .4mg/dL). After starting steroids (Tab. Prednisolone 40 mg), Lille score was calculated on day 7.If day 7 Lille score decreased to <0.45, steriods were continued for 28 days followed by tapering in 2 weeks. If day 7 Lille score was >0.45, steroids were discontinued.

In patients with severe alcoholic hepatitis in whom steroid therapy was contraindicated, pentoxyphylline 400 mg tds was used and were counselled about liver transplant.

RESULTS:

Table1- Baseline Characteristics of Patients

Mean Age	44 .5+-11.8Years(18-65)
SEX (Male:female)	All males
Men Hb (g/dl)	8.92±1.5
Mean TLC ,X10^{9}cells/litre	11.2±5.1 x109
Mean Platelet Count ,x10^{9} /litre	0. 90±.5 x109)
Mean Bilirubin (mg/dl)	8.4±4.3
AST U/L	138(50-340)
ALT U/L	87 30-210)
SAP U/L	98(50-210)
Total Protein, gram/dl	5.8± 0.815
Albumin, gram/dl	2.7±0.47
BUN, mg/dl	34±12
S.creatinine , mg/dl	1.2±0.7
S.sodium , meq/litre	129±13
Prothrombin Time , seconds	21(13-40)
INR	2.09(1.1-5.7)
Ascites	77 (76%)
Mild	30 (29.7%)
Moderate to tense	47(46.5%)
Hepatic Encephalopathy	51(50.4%)
Grade 1,2	22
Grade 3,4	29
Esophageal Varices	75
Grade 1	56
Grade 2/3/4	19
UGI BLEED	28
Mean Mid Arm Circumference (cm)	19.4±2.5
Mean Alcohol Consumption (grams)	117±38

DEMOGRAPHIC PROFILE :

Total 101 patients of AH were enrolled. Baseline characteristics of all patients are shown in Table1. All were male. Mean age of patients was 44.511±.8Years. Mean ethanol consumption was 117±38 grams. Mean duration of alcohol intake was 36±8 months. Mean Mid arm circumference (MAC)was 19.46±2.5 cm.

CLINICAL PROFILE :

Ascites was present in 77 (76%) patients. Mild ascites was seen in 30 patients(29.7%)while moderate to tense ascites was seen in 47 patients (46%). HE on admission was seen in 51 patients (50.4%). Grade1 to grade2 HE was seen in 22(21.7%) patients and grade3 to grade 4 HE was seen in 29(29%) patients. Esophageal varices (EV) were seen in 75(74%) patients. Grade I EV was seen in 56 (55%) patients and grade II -III EV were seen in 19(18.1%) patients. Upper gastrointestinal bleed (hematemesis, malena) was present in 28 (27.7%) patients on admission. Acute kidney injury (AKI) was present in 29 patients (28.7%).

Table 2- Baseline Severity Scores of Patient

Median mDF		81(17-150)
mDF<32	N=28	
mDF >32	N=73	
Median MELD	26 (15-39)	
Median CTP	11(8-13)	

Median mDF of the patients on admission was 81(17-150). Number of patients with mDF <32 were 28, patients with mDF >32 were 73. Median MELD score was 27(15-39 . Median CTP score was 11(8-13). 23 patients were Child B class, 78 patients were Child C class on admission.

Table3-Various Contraindications of Steroids-n=89

Infections	N=32
UTI	N=12
SBP	N=11
Pneumonia	N=6
Cellulitis	N=3
Acute Kidney injury	N=29
UGI bleed	N=28

At admission, various infections were present in 32(31%)patients. Urinary tract infection(UTI)was present in 12 patients, pneumonia in 6 patients, spontaneous bacterial peritonitis(SBP)was present in 11 patients, and cellulitis in 3 patients. Upper gastrointestinal bleed(hematemesis, malena)was present in 28 (27.7%). Acute kidney injury(AKI) was present in 29 patients(28.7%).

Table4- Outcome of Steroid Treatment

Steroids eligible patients	N=12
Response to steroids (D7 Lille score <0.45)	N=3
Infections developing post steroid therapy	N=5
SBP	N=3
Pneumonia	N=2

Only 12(11.6%) patients were eligible for corticosteroid therapy. Various contraindications to steroid therapy were: active infections in 32 patients, acute kidney injury in 29 patients, upper GI bleed in 28 patients. 89(88.1%) patients were not eligible for steroid therapy. Steriods ineligible patients were prescribed Tab. Pentoxyphylline 400 mg tds for 3 weeks.

Steroid eligible patients were treated with prednisolone 40 mg for 28 days followed by two weeks tapering. Out of 12 patients in which steroid were prescribed, only 3(33%) patients had response to steroid therapy with decrease of Lille score to less than 0.45 after one week. 5(41%) patients developed infections while on steroid therapy: 3 patients developed SBP and 2 patients developed pneumonia.

Table5- Mortality of Patients at 1 month n=30 (29%)

Mortality at Day 7	6
Mortality at Day 30	24

Overall mortality was seen in 30(29.7%)patients at 1 month follow up. 6(5.9%)patients died during first week of admission and 24(23.7%)patients died in next 3 weeks.

DISCUSSION :

In the present study, all patients were male. The absence of female patients could be due to hesitation on the part of the alcoholic females in seeking medical help. In the present study, mean age of patients was 41 years of age which corroborates with the study done by Amrapurkar et al and Daswani et al[11,12] .Evidence of portal hypertension(ascites, esophageal varices)were seen in 75 % of patients.

In the present study, only 12 % of the patients were eligible for steroid therapy which is similar to a study done by Daswani et al[12]. In another study by Shasthry et al, only 26.8 % were eligible for steroid therapy[13]. Only a small percentage of patients of alcoholic hepatitis are eligible

for steroids because of the presence of contraindications to steroids in majority of the patients. Various contraindications to steroid therapy in present study were active infections in 33(32%) patients, acute kidney injury in 22(21%) patients, upper GI bleed bleed in 21(20%) patients.

5(41%) patients developed infections while on steroid therapy - 3 patients developed SBP and 2 patients developed pneumonia. In a meta-analysis of 10 randomized studies on severe AH patients involving 512 patients, out of which 257 were treated with corticosteroids, without infection at the baseline, 20% of patients developed infection on follow-up.[14] In the STOPAH study, 13.5% of corticosteroid treated patients developed infections as compared to 7.9% of patients not receiving corticosteroids(vs.7.9%, $p = 0.003$)[15]. In our study, 41 % of patients developed infections post steroid therapy. More patients in our study developed infections post steroid therapy, this may be due to poor nutritional status of our patients. Mean MAC in our study was 19.46 cm signifying severe malnutrition. In Stopah trial, median mDF was 60 and median MELD was 20 whereas in our study median DF is 81, median MELD is 26, signifying very severe disease, therby predisposing to more infections.[15]

Overall mortality was 29.7% at 1 month follow up. 6(5.9%)patients died during first week of admission and 24(23.7%)patients died in next 3 weeks. This mortality was similar to study by Daswani et al in which one month mortality was 31%. In another study by Shasthry et al, 1 month mortality was 29% in severe alcoholic hepatitis.[12,13] High mortality rate is due to aggressive disease course and limited treatment options.

Strength of our study is that it is one of the few studies from Indian subcontinent where role of steroids in severe AH is studied.

Limitations of our study is the follow-up period which was only one month and liver biopsy was not done.

CONCLUSION:

We can conclude that alcoholic hepatitis is a severe disease with high mortality and there are limited management options available. Steroid therapy is associated with decrease 28 day mortality but do not have long term survival benefit. Very few patients are eligible for steroid therapy due to various contraindications and moreover response rate to steroids is also very low .Steroid therapy also increases the risk of acquiring life threatening infections thereby further increasing mortality. So, steroids act like double edge sword in AH.

In Indian subcontinent, rate of response to steroids may even be lower with very high predispositions of infections due to poor nutritional status and more severe disease in Indian patients. So, use of steroids may not confer any survival advantage in Indian subcontinent in contrast to Western World where nutritional status of patients are good and disease is relatively less severe. In Indian patients, improving nutritional status may be associated with decreased mortality and improved survival.

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