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PREDNISOLONE IMPROVES SHORT-TERM SURVIVAL IN SELECTED PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS-RELATED ACUTE ON CHRONIC LIVER FAILURE

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ABSTRACT **Background and Aims** Acute on chronic liver failure (ACLF) is an acute hepatic insult on an underlying chronic liver disease or cirrhosis resulting in rapidly progressing liver cell failure with multi-organ failure and is associated with a high mortality rate. The most common cause of acute insult in developed countries is sepsis and in India, it is due to heavy alcohol usage or alcoholic hepatitis. The aim of the study is to assess the efficacy of prednisolone in reducing 28-day and 3-month mortality rates in ethanol-related ACLF. **Methods** This is a prospective cohort single-centre study done at the Department of medical gastroenterology, Tirunelveli medical college from time period July 2022 to July 2023. The Institutional Ethics Committee approved the study and all patients gave informed written consent. 27 patients were enrolled in the study, but only 17 patients could be initiated on prednisolone 60mg once daily for 28 days and only 12 patients completed prednisolone. Primary outcomes were 28-day and 3-month survival rates in the prednisolone vs non-prednisolone group. The secondary outcomes were to assess the effect of sepsis, MELD (Model for end-stage liver disease) score, and AARC(APASL ACLF research consortium) grade on 3-month mortality. **Results** 62.9% patients were initiated on prednisolone and the survival rate was 48.1%(p=0.004). 44.4% completed 28-day prednisolone course and 3-month survival in these patients was 100% (p<0.001). Sepsis was the most common cause of death, 72.7% with sepsis did not survive 3 months(p=0.014). MELD score>25(p=0-001) and AARC grade 3 (p=0.031)were independent risk factors for poor survival. **Conclusion** Corticosteroids are beneficial in improving survival rate in a handful of cases with severe alcohol hepatitis (SAH) related ACLF. Sepsis remains the challenging factor in the initiation of prednisolone as well as maintaining therapy and is associated with high mortality. Higher AARC grade responds poorly to steroids corresponding with poor 3-month survival.

KEYWORDS : Prednisolone, ACLF, Alcoholic hepatitis, Survival

INTRODUCTION

ACLF is a clinical syndrome characterised by an acute liver insult to an already existing chronic liver disease (CLD) or cirrhosis resulting in sudden deterioration of liver function and multi-organ failure with a high mortality rate. The definition of ACLF varies with different competent authorities but the most accepted one in Asia is the definition by the Asia-Pacific Association for Study of the Liver (APASL). According to them, ACLF is an acute hepatic insult manifesting as jaundice (bilirubin>=5mg/dl) and coagulopathy (International normalization ratio(INR)>1.5) complicated within 4 weeks by clinical ascites and/or hepatic encephalopathy in a patient with previously diagnosed or undiagnosed CLD [1]. According to APASL, there should not be a previous decompensated event. The salient features of ACLF are its high mortality rate and its ability to reverse when the acute insult is treated [2]. The acute insult can be a drug, viral hepatitis, non-hepatotropic infections, alcoholic hepatitis, autoimmune hepatitis, sepsis, portal vein, or hepatic vein thrombosis [3].

Severe alcohol hepatitis (SAH)can trigger ACLF and is considered the most common cause of ACLF in India and 2nd most common in Asia [4]. Current management of SAH includes abstinence from alcohol, nutritional support, and oral corticosteroid therapy. STOPAH trial gives supportive evidence for survival benefits in severe alcoholic hepatitis [5]. Corticosteroids have been shown to reduce 28-day mortality without improving 90-day mortality. One of the commonest complications of prednisolone therapy is sepsis, hence sepsis screening before starting prednisolone therapy is essential. The APASL committee on its recommendations for the treatment of SAH-related ACLF, AARC score less than or equal to 10 without extra-hepatic organ failure suggests Specific medical therapy (SMT). SMT in SAH-ACLF includes corticosteroid therapy, Granulocyte colony-stimulating factor (GCSF) [6], and fecal microbial transfer (FMT)[7]. Except for corticosteroids the other modalities of treatment are still investigative.

The aim of the study is to determine the efficacy of prednisolone in reducing 28-day as well as 3-month mortality rate in SAH-related ACLF. Currently, Steroids remain the only proven option in SAH, and with add-on ACLF there have been Indian studies favouring the use of Low volume plasma exchange (LVPE) along with low-dose steroids to improve 1-year survival [8]. There are limited studies from India on the use of high-dose steroids in SAH-related ACLF and its outcome in survival. The study also aims to identify predictors of survival in SAH-related ACLF. AARC score has been recently well used for formulating treatment approaches in ACLF [9]. It has been found to be superior to MELD (model for end-stage liver disease) score as well as the CLIF-C ACLF score in predicting survival. This study uses the AARC score/grade in categorizing patients and calculating survival in each group.

MATERIALAND METHODS

Study Design

This is a prospective cohort study, and the study was done at the Department of Gastroenterology, Tirunelveli Medical College from July 2022 to July 2023. The institutional ethical committee approved the study and all patients gave informed consent to take part in the study.

Inclusion and Exclusion Criteria

All patients having ACLF according to APASL definition with significant alcohol intake were included. Only patients with Maddrey's discriminant function score(DF score) >32 were included in the study. Underlying chronic liver disease was diagnosed based on ultrasonogram abdomen showing features of chronic liver disease.

Exclusion criteria included patients with metabolic diseases like obesity, diabetes, coronary artery disease, and chronic kidney disease. Patients with other chronic liver diseases like chronic viral hepatitis, metabolic dysfunction associated fatty liver disease, Budd-Chiari syndrome, Wilson disease, and autoimmune hepatitis were excluded from the study. Patients with sepsis, variceal bleed, overt encephalopathy, and renal dysfunction defined as creatinine>1.4 were not given prednisolone, and any patients developing these complications were stopped prednisolone during the course of the study. Patients with sepsis were treated with broad-spectrum antibiotics.

27 patients, all males, were included in the study and 17 patients were initiated on prednisolone.

METHODOLOGY

Clinical examinations and laboratory investigations like complete hemogram(CBC), liver biochemistry (LFT), renal biochemistry (RFT), coagulation profile mainly prothrombin time and International normalization ratio (PT-INR), viral markers, ultrasonogram abdomen were done for all patients at baseline. CBC, LFT, RFT, and PT-INR were repeated at 1 week, 1 month, and 3 months after baseline. Sepsis screening was done at baseline, 1st week, and 1 month by blood cultures, urine cultures, ascitic fluid cell count and culture, and chest x-ray. Patients are kept close follow-up by twice weekly outpatient(OP) visits or in-patient care in 1st month followed by monthly visits to OP. Selected patients without the above-mentioned complications were treated with oral prednisolone 60mg once daily for 4 weeks and were tapered in the next 2 weeks. Lille's score was used to calculate the response to treatment at 1 week. All patients with Lille's score >0.45 were stopped prednisolone therapy. The quantitative data for DF score, Lille score, AARC score, and MELD score were made categorical for analysis

The primary outcome was 28 days survival in the prednisolone group compared with the prednisolone un-initiated group, and 3 months survival in the prednisolone completed group. The secondary outcomes were predictors of 3-month survival including sepsis, DF score, MELD score, AARC score, and Lille score.

Data Analysis

Data analysis was performed using SPSS version 24. Quantitative Variables were expressed as mean, standard deviation, median, and interquartile range. Qualitative variables were expressed as frequency and percentage. The association between categorical variables was analyzed by the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS:

The median age was 47 (42-56) in this study and all patients were males(100%). Only 17 out of 27 (62.9%) patients were eligible for prednisolone therapy and out of which only 12 patients (44.4%) completed prednisolone therapy. Sepsis was the most common complication in these SAH-ACLF patients (40.7%) and was significantly associated with poor 3-month survival (p=0.014). There was a survival benefit for the prednisolone group showing an improved survival rate both at the 28-day (p=0.08) and 3-month survival (p=0.004) compared to the non-prednisolone group. 3-month survival was reduced in patients with DF score >60 (p=0.06), significantly reduced in patients with MELD score >25 (p=0.001), Lille score>0.45 (p=0.005), and AARC grade 3 (p=0.031).

DISCUSSION

This study gives statistical support that prednisolone still has a role in SAH-related ACLF especially in prolonging survival rate. Prednisolone has survival benefits both at 28 days and 90 days. In a meta-analysis study by Alexandre et al, corticosteroids were associated with significant improvement in 28-day survival compared to both placebo and pentoxyphylline [10]. Only a handful of patients are eligible for prednisolone therapy. Sepsis remains the main adversary for the initiation and continuation of steroid therapy. There is a huge gap in treatment options for steroid-non-responsive and steroid-in-eligible patients [11]. G-CSF therapy and FMT are still approved only for therapeutic trials and Plasma exchange is showing varying results and is still investigational. A liver transplant is the only option in non-responsive patients to medical therapy, but multi-organ failure, sepsis, and lack of organ availability are major setbacks. Liver transplant in ACLF patients is known to be stormy with prolonged hospital stays and high mortality [12]. Although 62.9% patients were initiated on prednisolone therapy, only 44.4% of patients completed therapy but all these patients showed 100% response and improved survival rate. In a recent study by Shasthry et al, the steroid-eligible population was only 33% in their cohort of SAH but steroid response in these patients was 75% [13].

Sepsis was a significant factor in this study affecting steroid eligibility, steroid response, and survival. 40.7% had sepsis in the first 28 days and this was associated with poor 28-day as well as 90-day survival. In a study by Javier et al, 37% of ACLF patients had sepsis at presentation and 46% developed sepsis in due course of follow-up [14]. Whether sepsis is a triggering event for acute hepatic insult or whether it is a consequence is still debated, but most guidelines recommend empirical broad-spectrum antibiotics with or without antifungals as this has been shown to reduce ICU stay and reduce early mortality.

There are many prognostic scores in ACLF and the relatively new AARC score is easy and simple to calculate and has been found to correlate directly to survival. AARC grade 3 (score>10) are at high risk of death and in this study, AARC grade 3 patients had 75% 28-day mortality and 100% 3-month mortality. According to the AARC study group, AARC grade 1,2 and 3 patients had a mortality rate of 12.7%, 44.5 %, and 85.9%, respectively, and was found to be superior to CLIF-C score. AARC scores are dynamic and can be used as a guide for approach to therapy.

Limitations

The study had a low sample size and hence is underpowered. The study only has male population because males predominantly consume alcohol in this locality. The study did not utilize other treatment options like G-CSF and LVPE for non-steroid responders.

CONCLUSION

This study gives valuable information about the efficacy of prednisolone as a specific medical therapy drug in SAH-related ACLF. From the study, it is now understood that prednisolone improves both 28-day as well as 3-month survival in SAH-related ACLF. AARC score should be used to guide therapy as well as to prognosticate in ACLF.

Patient Baseline Characteristics (Table 1)

	N	mean ± sd	Range	Median	IQR
Age	27	48 ± 7.8	31 - 63	47	42 - 56
Bilirubin mg/dl	27	8.85 ± 5.35	5 - 27.9	7	5.6 - 9.48
Albumin g/dl	27	3 ± 0.72	1.6 - 4.5	3	2.5 - 3.5
Prothrombin (seconds)	27	27.6 ± 6.6	20.2-47.5	26.3	23.7 - 28.2
INR	27	2.26 ± 0.6	1.62 - 3.9	2.07	1.89 - 2.26
Serum creatinine mg/dl	27	1.2 ± 0.62	0.6 - 3.1	1	0.7 - 1.4
serum lactate mmol/lit	27	1.54 ± 0.77	0.5 - 3.3	1.4	0.8 - 2.1
DF score	27	75.8 ± 30.1	44.6-164.5	66.9	59 - 75.6
AARC score	27	8.67 ± 1.62	6 - 13	8	8 - 10
MELD score	27	25.7 ± 5.1	17 - 40	25	22 - 28
Bilirubin after 1 week mg/dl	27	8.84 ± 4.81	3.2 - 24.2	8.5	4.8 - 10.3
Lillie score	18	0.198 ± 0.204	0.038 - 0.888	0.153	0.081 - 0.208

Primary Outcome (Table 2)

	28 days survival				Total		χ^2	df	p
	Yes		No						
	N	%	N	%	N	%			
Prednisolone	16	94.1	1	5.9	17	100	2.902	1	0.088
Non-Prednisolone	7	70	3	30	10	100			
Total	23	85.2	4	14.8	27	100			
Prednisolone Initiated	3 months survival				Total		χ^2	df	p
	Yes		No						
	N	%	N	%	N	%			
Yes	13	76.5	4	23.5	17	100	8.13	1	0.004
No	2	20	8	80	10	100			
Total	15	55.6	12	44.4	27	100			

Secondary Outcomes (Table 3)

MELD	3 months survival				Total		χ^2	df	p
	Yes		No						
	N	%	N	%	N	%			
≤25	12	85.7	2	14.3	14	100	10.71	1	0.001
>25	3	23.1	10	76.9	13	100			
Total	15	55.6	12	44.4	27	100			
DF score	3 months survival				Total		χ^2	df	p
	Yes		No						
	N	%	N	%	N	%			
≤60	6	85.7	1	14.3	7	100	3.48	1	0.062
>60	9	45	11	55	20	100			
Total	15	55.6	12	44.4	27	100			

AARC grade	3 months survival				Total		χ^2	df	p
	Yes		No						
	N	%	N	%	N	%			
1	5	83.3	1	16.7	6	100	6.95	2	0.031
2	10	58.8	7	41.2	17	100			
3	0	0	4	100	4	100			
Total	15	55.6	12	44.4	27	100			
Lille prognosis	3 months survival				Total		χ^2	df	p
	Yes		No						
	N	%	N	%	N	%			
Good	14	87.5	2	12.5	16	100	7.88	1	0.005
Poor	0	0	2	100	2	100			
Total	14	77.8	4	22.2	18	100			
Sepsis	3 months survival				Total		χ^2	df	p
	Yes		No						
	N	%	N	%	N	%			
Yes	3	27.3	8	72.7	11	100	6.01	1	0.014
No	12	75	4	25	16	100			
Total	15	55.6	12	44.4	27	100			

REFERENCES

1. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Mahtab MA, Rahman S et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL): an update. Hepatology International 2019, 13(4), 353–390.
2. Arroyo V., Moreau R., Jalan R. (2020). Acute-on-Chronic liver failure. N. Engl. J. Med. 382 2137–2145.
3. Zaccherini G, Weiss E, Moreau R. Acute-on-chronic liver failure: Definitions, pathophysiology and principles of treatment. JHEP Rep. 2020 Sep 2;3(1):100176.
4. Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. Nat Rev Gastroenterol Hepatol 13, 131–149 (2016).
5. Thursz, M., Richardson, P., Allison, M., Austin, A., Bowers, M., Day, C. P.,(2015). Prednisolone or pentoxifylline for alcoholic hepatitis. The New England Journal of Medicine, 372(17), 1619–1628
6. Baig M, Walayat S, Dhillon S, Puli S. Efficacy of Granulocyte Colony Stimulating Factor in Severe Alcoholic Hepatitis: A Systematic Review and Meta-Analysis. Cureus. 2020 Sep 15;12(9):e10474
7. Pande A, Sharma S, Khillan V, Rastogi A, Arora V, Shasthry SM, et al. Fecal microbiota transplantation compared with prednisolone in severe alcoholic hepatitis patients: a randomized trial. Hepatol Int. 2023 Feb;17(1):249-261
8. Kumar SE, Goel A, Zachariah U, Nair SC, David VG, Varughese S, et al. Low Volume Plasma Exchange and Low Dose Steroid Improve Survival in Patients With Alcohol-Related Acute on Chronic Liver Failure and Severe Alcoholic Hepatitis - Preliminary Experience. J Clin Exp Hepatol. 2022 Mar-Apr;12(2):372-378
9. Maiwall R, Pasupuleti SSR, Choudhury A, Kim DJ, Sood A, Goyal O, et al. AARC score determines outcomes in patients with alcohol-associated hepatitis: a multinational study. Hepatol Int. 2023 Jun;17(3):662-675
10. Louvet A, Thursz MR, Kim DJ, Labreuche J, Atkinson SR, Sidhu SS,. Corticosteroids Reduce Risk of Death Within 28 Days for Patients With Severe Alcoholic Hepatitis, Compared With Pentoxifylline or Placebo-a Meta-analysis of Individual Data From Controlled Trials. Gastroenterology. 2018 Aug;155(2):458-468.e8
11. Ayares G, Idalsoaga F, Díaz LA, Arnold J, Arab JP. Current Medical Treatment for Alcohol-Associated Liver Disease. J Clin Exp Hepatol. 2022 Sep-Oct;12(5):1333-1348
12. Xia, L., Qiao, Z., Zhang, Z.-J., Zi-cheng Lv, Tong, H., Tong, Y., et al. (2022). Transplantation for EASL-CLIF and APASL acute-on-chronic liver failure (ACLF) patients: The TEA cohort to evaluate long-term post-Transplant outcomes. EClinicalMedicine, 49, 101476–101476.
13. Shasthry SM, Sharma MK, Shasthry V, Pande A, Sarin SK. Efficacy of granulocyte colony-stimulating factor in the management of steroid-nonresponsive severe alcoholic hepatitis: a double-blind randomized controlled trial. Hepatology 2019;70:802-811
14. Fernández, J., Acevedo, J., Wiest, R., Gustot, T., Amoros, A., Deulofeu, C., (2017). Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut, 67(10), 1870–1880.