



PROGRESS IN DRUG THERAPY FOR HEPATORENAL SYNDROME: A SYSTEMATIC REVIEW OF CLINICAL STUDIES IN THE LAST 3 YEARS.

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INTRODUCTION

Rapid deterioration of kidneys in patients with severe liver injury i.e., cirrhosis is termed a hepatorenal syndrome (HRS). Hemodynamic instability due to increased splanchnic blood flow, systemic vasodilation, and renal vasoconstriction might cause HRS, and the goal of the drug therapies is to improve systemic circulation. This article aims to review the efficacy and safety of drug therapies tested in the last 3 years in HRS patients

METHODS

- We searched PubMed, Embase, Cochrane, and WOS from 1/1/2019 till 05/15/2022. We screened 520 articles and included 3 clinical trials (N=462) and 5 observational studies (N=1,034) with >5 patients providing data about the safety and efficacy of drugs. All case reports, case series, review articles, meta-analyses, and clinical studies with irrelevant populations were excluded.

RESULTS

In 8 studies, 708 patients were treated with terlipressin +albumin, 73 with noradrenaline, 22 with midodrine + albumin, 28 with midodrine+ albumin+ octreotide, 82 with other vasoconstrictors, and 121 with albumin only. In two clinical studies (N=416), HRS patients treated with terlipressin + albumin had a reversal in 32%-39.7%, liver transplant (LT) in 12.5%-23%, and death in 51% (11% with respiratory failure) of the patients, versus a reversal in 17%, LT in 29% and death in 45% (2% with respiratory failure) with albumin. In three clinical studies (N=382), HRS patients with terlipressin + albumin had a reversal in 40%-50.2%, overall response (OR) in 41.7%-72.9%, and death in 51% versus a reversal in 16.7%-22.7%, OR in 20%-23% and death in 82% with noradrenaline/other vasoconstrictors. In a retrospective study (N=88), HRS patients treated with midodrine+ octreotide+ albumin had a reversal, LT, and death in 25%, 3.6%, and 39.2%, respectively, versus reversal, LT, and death in 10%, 23%, and 43%, respectively, with non-standard treatment. In a pilot study (N=42), recurrence of HRS was 18% with midodrine vs. 50% with albumin only.

DISCUSSION

Terlipressin with albumin significantly improved the reversal of HRS and transplants. However, mortality wasn't improved due to treatment-related adverse effects. Terlipressin with albumin significantly improved the outcomes in HRS patients as compared to noradrenaline with albumin. Standardized albumin + midodrine + octreotide was more effective than non-standardized treatment of HRS. Midodrine with albumin reduced the recurrence of HRS in HRS recovered patients as compared to albumin. More RCTs are needed to confirm these results.

Study	Phase	Treatment therapy	N	Outcomes
Trials				
Wong et al. 2021	III (RCT)	Terlipressin + Albumin (90 days)	199	Reversal of HRS (SCr <1.5mg/dl) =32%, Renal transplant=29% Liver transplant=23%, Death=51% (11% with respiratory failure)
		Placebo	101	Reversal of HRS (SCr <1.5mg/dl) =17%, Renal transplant=39%, Liver transplant=29%, Death=45% (2% with respiratory failure)
Sharma et al. 2021	Pilot study (on patients recovered with terlipressin + albumin)	Midodrine + albumin	22	Recurrence of HRS=18%, Mean ascitic tap in 2 months=1.9
		Albumin	20	Recurrence of HRS=50%, Mean ascitic tap in 2 months=2.6
Arora et al. 2020	RCT	Terlipressin + albumin	60	Reversal of HRS (SCr within 0.3mg/dl of baseline) = 40%, Any response (7-days) = 41.7% Survived patients=49%
		Noradrenaline+ albumin	60	Reversal of HRS (SCr within 0.3mg/dl of baseline) = 16.7%, Any response (7-days)=20%, Survived patients=18%
Observational studies				
Kulkarni et al. 2022	Prospective	Terlipressin + Albumin	116	Adverse effects leading to discontinuation=21%, Complete response (SCr within 0.3mg/dl of baseline) = 39.7%, Transplant free patient -at 90 days=57.8%, liver transplant=12.5%
Hiruy et al. 2021	Retrospective	Albumin+ midodrine+ octreotide (standardized)	28	Full response (SCr within 0.3mg/dl of baseline) =25%, renal replacement=21%, liver transplant=3.6%, 30-day mortality=39.2%
		Non-standardized treatment	60	Full response (SCr within 0.3mg/dl of baseline) = 10%, renal replacement=45%, liver transplant=23%, 30-day mortality=43%
Moore et al. 2020	Retrospective	Terlipressin+ albumin	203	Complete response (SCr <1.5mg/dl) =50.2%, overall response=72.9% Renal transplant=12%, liver transplant=2%,
		Other vasoconstrictors	22	Complete response (SCr <1.5mg/dl) =22.7%, overall response=59.1%
Givo et al. 2020	Retrospective	Terlipressin+ albumin	24	Response to treatment=67%
		Noradrenaline+ albumin	13	Response to treatment=23%
Nguyen-Tat et al. 2019	Retrospective	Terlipressin + albumin for HRS-1 patients	54	HRS reversal=48%, relapse=8%, median OS=89±53
		Terlipressin + albumin for HRS-2 patients	52	HRS reversal=46%, relapse=50%, mortality=20%, median OS=239±174

RCT= randomized clinical trial, HRS=Hepatorenal syndrome, SCr=serum creatinine,