Gastroenterology and Hepatology From Bed to Bench.
2024 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

BRIEF REPORT

p-ISSN: 2008-2258 e-ISSN: 2008-4234

Role of oral Midodrine in preventing hepatorenal syndrome in Child-Turcotte-Pugh class C cirrhotics: a pilot study

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ABSTRACT

Aim: The purpose of the study was to assess benefits of oral midodrine in the role of primary prevention of hepatorenal syndrome (HRS) in Child-Turcotte-Pugh Class C (CTP-C) cirrhotics.

Background: The present non-randomized pilot study was designed for primary prevention of HRS as there is absence of an effective and definite treatment for this complication of cirrhosis to date other than liver transplant (LT).

Methods: This study effectively involved 30 patients each enrolled in interventional and control arms suffering from liver cirrhosis CTP-C with normal renal function and having a mean arterial pressure (MAP) < 80 mmHg who were subjected to clinical examination and baseline blood investigations. The mean daily dosage of midodrine used across the study group was 16.75 mg.

Results: At the end of 4 months of study, 11 individuals completed the study without attaining any endpoints from the control group while 23 accomplished it from the interventional arm. Nearly 50 % patients required a midodrine dose of 7.5 mg 8th hourly while the rest attained the targeted MAP with lower doses. By increasing MAP, the rate of HRS development during the study period (i.e. 4 months) was found to be significantly reduced in patients from interventional arm. The number needed to treat (NNT) observed in survival analysis to prevent one death was found to be 7.6.

Conclusion: This study successfully established the role oral midodrine in primary prevention of HRS in cirrhotics at high risk. Midodrine was well tolerated with no significant adverse effects in patients under study.

Keywords: Midodrine, Hepatorenal syndrome, CTP-C cirrhotics.

(Please cite as: **Salim T, Maindad D. Role of oral Midodrine in preventing hepatorenal syndrome in Child-Turcotte-Pugh class C cirrhotics: a pilot study. Gastroenterol Hepatol Bed Bench 2024;17(4):438-449. https://doi.org/10.22037/ghfbb.v17i4.3019).**

Introduction

In liver cirrhosis, fibrotic tissues alter portal blood flow and resistance, leading to portal hypertension and activation of splanchnic arterial vasodilation (1). The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are closely linked to the hepatic vascular alterations and resulting portal hypertension (2).

Patients with advanced cirrhosis frequently develop the hepatorenal syndrome (HRS), a condition characterized by a marked reduction in renal blood flow and glomerular filtration rate (GFR) in the absence of significant histological abnormalities in the kidney and of other known causes of renal failure (3). HRS is a major clinical event during the course of decompensated cirrhosis. It usually develops in a close chronological relationship with a precipitating event, particularly severe bacterial infections, superimposed acute alcoholic, toxic, or viral hepatitis, or major surgical procedures, and is associated with a very poor prognosis (median survival <2 weeks and 6 months in Type 1 and Type 2 HRS respectively). Annual incidence of HRS in patients with ascites is reported to be approximately 8 % (4). Progression of the decompensated disease may be further accelerated by the development of other complications such as variceal bleeding, acute kidney injury (AKI), with or

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without the features of HRS, hepato pulmonary syndrome (HPS), portopulmonary hypertension (PPHT), cirrhotic cardiomyopathy (CCM), and bacterial infections. The maintenance of an adequate arterial pressure in cirrhosis with ascites is assured by the activation of endogenous vasoconstrictor systems.

The present study was designed for the primary prevention of HRS as there is absence of an effective and definite treatment for this complication of cirrhosis except liver transplant (LT) so far (5). Because of the bad prognosis of HRS, there is a pressing need to create evidence to support if any prophylactic agent attains enough relevance to conduct large scale trials and scientific studies. Low mean arterial pressure (MAP) is a valuable predictor of death in patients with liver cirrhosis and ascites (6). Therefore, this study was designed to test the hypothesis 'whether raising MAP prophylactically above a threshold of 80 mm Hg in Child C cirrhotics would result in a reduced incidence of HRS or improve survival'. In this context, the effect of midodrine, an α-adrenergic agonist vasoconstrictor drug, which is important in reducing the frequency and quantity of large volume paracentesis (LVP) over the study period was examined.

Methods

Study population

All patients with liver cirrhosis who would qualify as CTP-C Cirrhosis with normal renal function and having a mean arterial pressure (MAP) < 80 mmHg, attending OPD / IPD of the Bharati Hospital and Research Center, Pune, India from June 2021 to December 2022 within age group 18-65 years were included in study. Patients with active comorbid diseases suh as pulmonary, cardiac, renal disease, etc., HRS on presentation or acute kidney injury, hepatocellular carcinoma (HCC) and other malignancies, acute-on chronic liver failure, diabetics, and obstructive uropathy were excluded from study. Patients displaying baseline etiology, such as on-going liver insult or uncorrectable e.g. active alcoholic hepatitis were again not considered for study.

Study design, participants, and ethics approval

Study design was based on non-randomized experimental study where each subject was followed-up for 4 months, while data analysis and reporting were completed in a month. Patients of CTP-C cirrhosis who met the inclusion criteria were informed about possible beneficial effects of midodrine. Patients who provided the consent for being put on oral long-term midodrine in addition to standard of care were included in 'Interventional Group' (Group A or GrA). However, patients who opted out of midodrine therapy were continued on standard of care and constituted 'Control Group' (Group B or GrB). This study was approved by the Institutional Ethics Committee Board of Bharati Vidyapeeth University, Pune, India (REF NO: BVDUMC/IEC/10, Dated: 30/06/2021) and since it was a prospective interventional study and data were collected anonymously, waiver of written informed consent was also obtained.

Study variables

All patients included in study were subjected to clinical examination and baseline blood investigations. Baseline workup included LFTs, CBC, KFTs, BSL, Sr Na+, K+, Urine R/E, M/E Hepatitis Markers, Auto-immune profile (if indicated), USG abdomen and KUB for kidney size, echotexture or obstructive uropathy, CT abdomen (if indicated), C/S of blood, urine and ascitic fluid (as indicated), CXR-PA view as well as ECG and SOS 2D-ECHO.

Measurement of all basal parameters of all subjects

Diagnosed cases of cirrhosis based on clinical, radiological, or laboratory findings irrespective of the etiology were subjected to appropriate investigations to define CTP Class and MAP (measurement on presentation; average of three readings were recorded at 15 min interval). Patients were followed-up for 4 months after enrolling into the study.

Dosage of Midodrine

Oral midodrine administration was started at 2.5 mg 8th hourly after recording MAP < 80 mmHg (multiple readings). Re-assessment of MAP and titration of midodrine dosage to elevate MAP above 80 mmHg was undertaken on every 7th day. Drug administration was continued on the fixed dose until completion of study or reaching endpoints.

Follow-ups

Enrolled subjects were asked to follow-up weekly for MAP assessment for deciding the dose of midodrine

in respective groups. Compliance of experimental group associated with midodrine therapy (GrA) was ensured by cross-checking the consumption with blister packs. Subsequently, monthly clinical review and assessment of renal function plus serum Na+ was accomplished to monitor the effect of treatment in both study groups. The patients were instructed to report for review on SOS basis in case of any deterioration vis-a-vis febrile illness, abdomen pain, oliguria, altered sensorium, evidence of GI bleeding, progressive abdominal distension, etc. Patients requiring admission were hospitalized and complications were treated as per standard guidelines.

Paracentesis including LVP was carried out in patients according to clinical condition, and the need was assessed as per standard guidelines during the review as well as follow-up visits. LVP was defined as ≥ 5 liters of paracentesis in a single session. LVP was employed o in case of tense ascites causing respiratory discomfort, diuretic resistant ascites, and diuretic intractable ascites.

Outcomes

The primary outcome considered was development of HRS, while secondary outcomes included survival and LVP (frequency and volume during study period). Evaluations of study were conducted in a standardized way by trained gastroenterologists and physicians. Counselling of relatives of patients was accordingly conducted from time to time about salt-restricted diet, need for regular consumption of the prescribed medications and, in turn, preventing complications. Primary and secondary prophylaxis of variceal bleeding, colloid (albumin) administration targeting volume expansion in patients with a rising serum creatinine level following LVP, diuretic use or with spontaneous bacterial peritonitis (SBP), administration of antibiotics prophylactically to high-risk patients covering SBP or other infections, and those hospitalized for GI bleeding were followed as per standard guidelines. Standard baseline treatment pertaining to the cause of cirrhosis was continued according to guidelines.

Statistical analysis

Patient data were collected and entered in Microsoft Excel data sheet, which was subsequently analyzed using statistical product and service solutions (SPSS) software, version 28.0. Continuous variables were expressed as mean ± standard deviation (SD) and ranges. Categorical variables were expressed using numbers and percentages. All patients who were enrolled into both study groups (GrA) and (GrB) were

Table 1. Basic characteristics of enrolled patients of both respective study groups. NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; MELD-Na: model for end-stage liver disease-sodium; HB: haemoglobin.

	GrA			GrB		
	Number	Range	Mean ± Standard Deviation	Number	Range	Mean ± Standard Deviation
1st Month	30			30		
2nd Month	25			23		
3rd Month	24			15		
4th Month	23			11		
Age (Years)		32 – 75	47.87 ± 10.42		25 - 75	48.56 ± 11.51
Sex						
Male	26			25		
Female	4			5		
Etiology						
Alcohol	25			21		
Hepatitis B	3			3		
NASH	1			4		
AIH	1			3		
Crypt	1					
C BCS				1		
CTP Score		10 – 13	11.4 ± 0.34		10 - 13	11.13 ± 0.39
MELD-Na		15 – 37	24.97 ± 1.62		15 - 39	25.03 ± 1.85
Hb (gm%)		4.5 – 11	8.06 ± 1.62		4.5 - 15.1	8.73 ± 2.11
Na^+ (Mmol/L)		118 - 140	130.53 ± 6		118 to 140	130.56 ± 5.37

included in this study through non-randomized sampling. Survival analysis was done for both groups. Comparison of month-wise LVP with groups was assessed using chi-square test or fisher exact test as felt appropriate. Two-sample Z-test was conducted wherever proportion analysis was indicated. Comparison between two survival curves was assessed using log-rank test. Relative risk analysis was done whenever necessary. P value <0.05 was considered to be significant for the analysis.

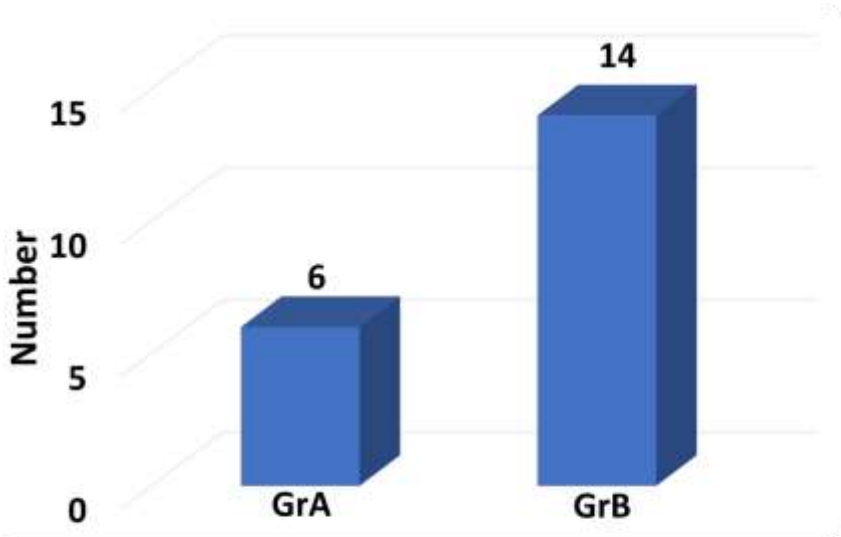
Results

Basic characteristics of study population

Out of 38 and 36 patients enrolled in GrA and GrB respectively, 8 and 6 were either lost to follow-up or were not adherent to consented instructions. Consequently, in each group, 30 patients were actively involved for the analysis. Basic characteristics of the study population are enlisted in Table 1; it could be inferred that the patients in both the arms were comparable regarding age, sex, etiology, and severity of liver disease. At the end of 4 months of the study, 11 individuals completed the study without attaining any endpoints from GrA, while 23 accomplished it from GrB. Out of the 60 patients enrolled, GrB contained 25 male and 5 female patients, while GrA involved 26 male and 4 female patients. The most common etiology for chronic liver disease was alcohol-related (76.6%) followed by Hepatitis-B related (10%) and NASH-induced (8.3%) in the study groups. As far as chronic liver disease (CLD) severity scores are concerned, mean CTP scores of enrolled patients were 11.4 ± 0.34 in GrA and 11.13 ± 0.39 in GrB. Mean MELD-Na scores in GrA and GrB were 24.97 ± 1.62 and 25.03 ± 1.85 respectively.

Hepatorenal syndrome (HRS)

Of the 30 patients who had completed follow-up, 6 and 14 were diagnosed with HRS in GrA and GrB respectively during the study duration (Figure 1). On administering drug, it was observed that there was a 57 % lower probability of being diagnosed with HRS as in GrA as compared to GrB. The analysis revealed a significantly lower cumulative incidence of HRS (relative risk [RR] = 0.43; 95% confidence interval [CI] = 0.19-0.96; P = 0.04) in patients of GrA as compared to those in GrB.



Arms	HRS		Total	RR (95%CI)	p-value
	Yes	No			
GrA	6	24	30	0.43 (0.19-0.96)	0.04
GrB	14	16	30	1	

Figure 1. Number of patients diagnosed with HRS.

The 4-month actuarial probability of remaining free of HRS was observed to be significantly higher in GrA than in GrB (absolute risk reduction (ARR) to 27 % and number needed to treat was 3.75 patients). This study presented a relative risk reduction (RRR) of 57% for HRS with the help of drug.

Evaluation of death as an endpoint

Two deaths from patients in GrA and six from GrB were reported during the study, highlighting significance of the present investigation in the use of midodrine, though the results were not statistically significant with P-value of 0.15. However, NNT of 7.69 to prevent one death is a favorable statistic and the study showed a relative risk reduction of 67% for death through using midodrine drug.

Need for large volume paracentesis (LVP) sessions

LVP was required in 12 patients (41%) of the 29 who underwent paracentesis inGrA in the first two month as compared to 8 and 9 in GrB in first and second months respectively. Need for LVP sessions kept diminishing as the study progressed monthly in both study groups. There was no contrasting difference in the intervals and number of sessions of LVP in both groups in third and fourth months of study. Use of midodrine did not show any significant reduction in the frequency for LVP in either arm. P-value derived from Mann-Whitney U-test was 0.54.

Complications other than HRS

Other complications of cirrhosis apart from HRS were also compared between the two study groups. The maximum number of complications were recorded in the 1st month of follow-up with 17 patients from the GrA and 15 from GrB (Figure 2). Among the complications recorded, spontaneous bacterial peritonitis (SBP) was noted to be the most common complication in both study groups, but its incidence progressively declined in follow-up visits, though slightly less significantly in GrB patients. Variceal bleed, which was not considered as an end point of the study, was found to occur in six patients from GrA and three patients in GrB. Two-sample Z-test was adopted to compare the incidence of other complications apart from HRS in patients from both study groups. Proportional analysis of complications other than HRS indicated that there was no statistically significant difference between both study groups ($p > 0.05$).

Evaluation of number of admissions required

The number of admissions recorded during the

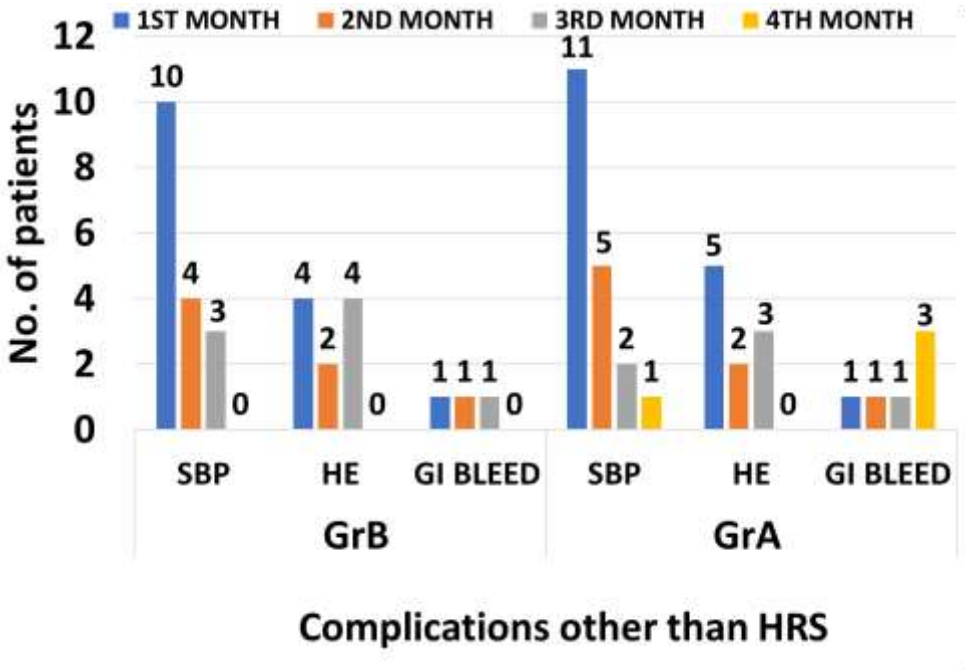


Figure 2. Monthly complication rates other than HRS during study durations.

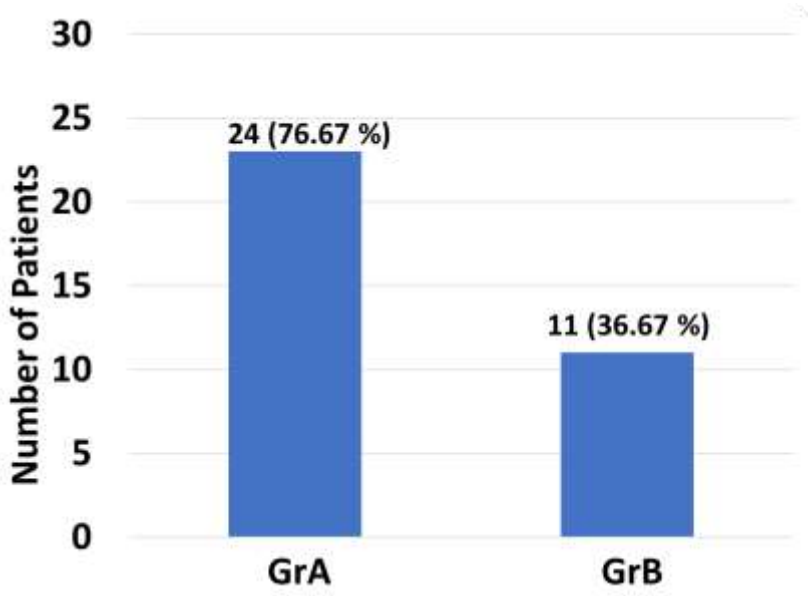


Figure 3. Survival rate without reaching an endpoint at the end of study duration.

study duration across both study groups kept on subsequently reducing along the period of observation. GrA exhibited the descending trend until the 4th month. Use of midodrine did not show any significant reduction in cumulative number of admissions based on results obtained from both groups. The p-value as per Mann-Whitney U test was calculated to be 0.95.

Number of subjects survived without reaching an event in each arm

GrA patients recorded significantly higher (76.6 %) HRS-free survival rate, which was more than twice as large as that of the GrB (only 36.6 %), as displayed in Figure 3.

Table 2. Data for 1st month follow-up. HE: hepatic encephalopathy, GI: gastrointestinal, SBP: spontaneous bacterial peritonitis, HRS: hepatorenal syndrome, TDS: three times daily.

		GrA (N = 30)		GrB (N = 30)		P-value
Parameters		Range	Mean	Range	Mean	
Sr Creat (mg/dl)		0.4 - 3.2	1.23	0.7 - 3.3	1.27	0.38
Paracentesis						
Patients required paracentesis		29		27		
Volume	≤5	17		19		
	>5	12		8		
No. of sessions		1-4	1.62	1-5	1.93	0.14
Total quantity		0.75 – 17	5.88	2-17	6.29	0.36
Mod-gross ascites		28		27		
No of admissions		0 – 3	0.86	0 - 3	0.9	0.43
Other complications						
HE		5		4		
GI Bleed		1		1		
SBP		11		10		
Total no. complications		(n=17) 17	5.66 ± 4.65	(n=14) 15	5 ± 4.23	0.5
HRS		0		0		
Death		0		0		
Midodrine dosage (TDS; mg)						
2.5		6				
5		11				
7.5		13				

Dosage of midodrine to achieve MAP > 80 mmHg

Majority patients among GrA were put on a midodrine dosage of 7.5 mg TDS (n=13) followed by the dosages of 5mg and 2.5 mg respectively. The mean daily dosage used across the study group was 16.75 mg.

Table 3. Data for 2nd month follow-up

		GrA (N = 30)		GrB (N = 30)		P-value
Parameters		Range	Mean	Range	Mean	
Sr Creat (mg/dl)		0.4 - 3.0	1.28	0.8 – 3.1	1.55	0.22
Paracentesis						
Patients required paracentesis		25		22		
Volume	≤5	15		13		
	>5	12		9		
No. of sessions		1-3	1.56	1-4	1.68	0.3
Total quantity		1-15	5.52	2-15	6.5	0.36
Mod-gross ascites		23		22		
No. of admissions		0 - 2	0.7	0 - 1	0.7	0.5
Other complications						
HE		2		2		
GI Bleed		1		1		
SBP		5		4		
Total no.		(n=6) 8	2.67 ± 1.92	(n=6) 7	2.3 ± 1.41	0.41
HRS		5		7		
Death		0		1		
Midodrine Dosage (TDS; mg)						
2.5		6				
5		11				
7.5		13				

Table 4. Data for 3rd month follow-up

		GrA (N = 25)		GrB (N = 23)		P-value
Parameters		Range	Mean	Range	Mean	
Sr Creat (mg/dl)		0.5 - 1.9	1.27	1-2	1.5	0.00023
Paracentesis						
Patients required paracentesis		17		15		
Volume (in L)	≤5	11		7		
	>5	6		8		
No. of sessions		1-4	1.59	1-4	2.13	0.08
Total quantity		0.75 - 16	5.8	2-17	7.7	0.13
Mod-gross ascites		17		15		
No. of admissions		0 – 2	0.52	0 - 2	0.52	0.49
Other Complications						
HE		3		4		
GI Bleed		1		0		
SBP		2		3		
Total No.		(n=5) 6	2 ± 0.92	(n=4) 7	2.33 ±1.92	0.45
HRS		1		7		
Death		1		2		
Midodrine Dosage (TDS; mg)						
2.5		6				
5		11				
7.5		13				

Month-wise analysis charts

During the 1st month, none of the patients from either study groups reached endpoint (Table 2). However, the maximum number of complications (17 in GrA & 15 in GrB) in patients was reported in this month.

At the end of 2nd month, 5 and 7 events of HRS were reported in GrA and GrB, respectively (Table 3). Additionally, 1 death was reported in GrB. Eight patients from GrA and 7 from GrB reported complications during this month and SBP cases were reported in the maximum number of patients just as in cumulative analysis.

In the 3rd month, only one case of HRS was recorded in GrA patients and 7 in GrB (Table 4). One patient from GrA and two from GrB died during this period. The mean creatinine recorded in patients from GrA was considerably lower than in GrB with a statistical significance ($p<0.001$). However, the number of overall complications in patients exhibited a downward trend as compared to previous months. The number of performed paracentesis sessions dropped on average in the monthly follow-up.

The 4th month recorded 4 deaths across the study groups with one from GrA and three from GrB with zero and two cases of HRS respectively (Table 5). In this month, death of 2 patients from GrA and 6 deaths from GrB were recorded.

Side effects of Midodrine

Minor side effects (such as nausea, vomiting and tremors, which did not require any dose modifications) were observed in GrA patients during the study period.

Discussion

Hepatorenal syndrome is potentially a reversible form of renal failure occurring in cirrhosis with ascites, acute liver failure, or acute on-chronic liver failure (ACLF) (1). Contemporary first-line therapies recommended for HRS are vasoconstrictors coupled with albumin; among them, terlipressin is suggested in clinical practice guidelines as first-line therapy for HRS, wherever it is available (7). Either of the different forms of HRS increases mortality, i.e. median survival of < 2 weeks for HRS-acute kidney disease (HRS-AKI) and 3-6 months for HRS-non-AKI (HRS-NAKI) (4). HRS reversibility by improvement in effective arterial blood volume results in suppression of the overactivity of vasoconstrictor systems and increase in renal perfusion.

Observed increases of baseline of MAP with terlipressin treatment are consistent with published findings of vasoconstrictor therapy in HRS in which

Table 5. Data for 4th month follow-up

		GrA (N = 24)		GrB (N = 14)		P-value
Parameters		Range	Mean	Range	Mean	
Sr Creat (mg/dl)		0.4 - 1.8	1.19	0.9 - 3	1.57	0.0014
Paracentesis						
Patients required paracentesis		11		7		
Volume	≤5	7		4		
(in L)	>5	4		3		
No. of sessions		1-3	1.54	1-5	2.28	0.11
Total Quantity						
Mod-gross ascites		11		7		
No. of admissions		0 - 1	0.39	0 - 2	0.68	0.099
Other complications						
HE		0		0		
GI Bleed		3		0		
SBP		1		0		
Total No:		(n=4)	1.33 ± 1.41	(n=0)	0	
		4		0		
HRS		0		2		
Death		1		3		
Midodrine dosage (TDS; mg)						
2.5		6				
5		11				
7.5		13				

elevations in MAP have been associated with improved clinical outcomes (8). Owing to poor prognosis of HRS, there is urgent need to provide evidence to support if any prophylactic agent attains enough relevance to conduct large scale research and scientific studies. Vasopressor therapies, based on the findings of earlier overall observational studies, are reported to be beneficial in reversing HRS. Considering this mechanism, our aim was to prevent HRS as lack of an effect of vascoconstrictors on survival was established with pooled analysis in the past (8). Low MAP was a valuable prognosticator of death in patients suffering from liver cirrhosis and ascites (6). Thus, this study was designed to test the hypothesis whether raising MAP prophylactically above a threshold of 80 mm Hg in CTP-C would result in a reduced incidence of HRS or improve survival. In this context, efficacy of midodrine, an α-agonist, in CTP-C patients with MAP below 80 mm Hg who stood clearly at high risk of developing HRS, was studied.

A lower MAP is often tolerated in compensated and stable patients through compensatory mechanisms, which allow end-organ perfusion to be maintained (9). Such compensatory mechanisms can be affected by any degree of insult to cause clinical or sub-clinical complications, namely, refractory ascites, as well as significant hypotension and decompensation. Fragility of the system that maintains MAP may not only be secondary to circulatory abnormalities but also to cirrhotic cardiomyopathy. Previous studies have established that for HRS reversal to occur, a rise in MAP in response to treatment is required, which was the sole mechanism to create the hypothesis of preventing HRS with oral vasoconstrictors beforehand (10). Maintenance of circulatory function by targeting a higher MAP, albeit through a surrogate marker, is recommended to improve renal outcome in cirrhosis by ameliorating endothelial dysfunction and restoring microcirculation (10).

In the present study, midodrine was employed to increase MAP > 80 mm Hg by titrating the dose individually in the selected patients during successive review visits. It was observed that nearly 50 % of the patients required a midodrine dose of 7.5 mg 8th hourly, while the rest attained the targeted MAP with lower doses. Specifically, 13 of them were put on a dose of 22.5 mg of midodrine daily, while 11 of them were put on 15 mg and 6 of them on 7.5 mg daily doses respectively. In a study conducted by Paolo A et al, midodrine was used at a dose of 15 mg orally daily (11). The 7.5-mg daily dose of midodrine was established based on a pilot study conducted by the same authors where it was found to be the minimum dose capable of elevating MAP by at least 5 mm Hg in almost 80% of cirrhotic patients (11). Maiwall (2021), in his study, concluded that targeting a higher MAP, 80 - 85 vs 60 - 65 mmHg in critically ill patients with cirrhosis and septic shock was associated with better tolerance of dialysis, as well as better recovery of AKI, supporting our theory (10).

Although there is no definitive treatment modality for decompensated liver diseases other than liver transplantation (LT), it raises the questions due to major shortcomings such as the paucity of organs in any country, cost and allocation of livers to increasing numbers of critically ill patients without setting objective or consensual limits on how sick the patients can become when they receive an organ (acceptability by the body). Although LT benefits these patients individually, high post-transplant mortality rate of this population has raised concerns and consensus against their transplantation (12). Patients diagnosed with decompensated cirrhosis or end-stage liver disease (ESLD) have reportedly a poor median survival of about 2 years without transplantation (13). Midodrine can offer benefits to the patients awaiting transplant to prevent pre-transplant renal dysfunction during the bridging time (14). Non-affordability to liver transplantation is a serious problem in developing and under-developed countries as a majority of them are self-funded unlike the established programs in the west, merits need for preventing complications such as HRS to prolong their survival and the complications of decompensated liver disease gains utmost prognostic value.

Incidence of HRS in patients with decompensated liver disease is approximately 4%. Cumulative probability of developing HRS at 1st year is 18% and at 5th year is 39% in patients with decompensated liver diseases. One third of patients suffering from SBP can gradually develop HRS (15). Such staggering numbers suggest that HRS is a major, frequent and dreaded complication in patients with liver cirrhosis. Midodrine elevates the MAP by directly acting on the peripheral α-receptor, and therefore, is widely used in the

treatment of hypotensive disorders (11). Midodrine is believed to help in reducing the progression of liver disease by causing a significant reduction of serum metabolites of nitric oxide, which is thought to be one of the most important factors in the pathogenesis of arterial vasodilation in cirrhosis.

By elevating MAP, the rate of HRS development during the study period (i.e. 4 months) was found to be significantly reduced in patients from GrA as compared to the patients from the GrB. The number of patients who developed HRS was 6 from GrA while being 14 from GrB. A statistically significant difference was noted in the incidence of HRS (p-value of 0.04) between the two groups. The results indicated that there is a promising role for midodrine in preventing renal failure in CTP Class C cirrhotics.

The study closest to our design was a single center prospective analysis published in 2021 by Parikh (2021), where 50 consecutive patients were enrolled into two groups after complete resolution of HRS (serum creatinine within 0.3 mg/dL of baseline) with administration of albumin (40 grams per day) plus terlipressin (2-4 mg per day) (16). In his study, Group A patients were continued on standard of care (SOC) medication while Group B patients were administered midodrine with fixed doses of 22.5mg per day in addition. The primary outcome was the recurrence of AKI within 12 weeks. Four patients in each group were lost to follow-up, while 2 patients in Group A and 3 patients in Group B died. The recurrence of AKI within 12 weeks was higher in Group A patients as compared to Group B (5/19 versus 2/18 respectively) patients. At 12 weeks, 3 patients from Group A and 10 patients from Group B could tolerate diuretics. With this small study, Parikh (2021) concluded that midodrine served as an effective drug for the secondary prevention of HRS. Herein, we emphasize the role of midodrine as sole vasoconstrictor in primary prevention in a subgroup of cirrhotics who were at high risk of developing HRS. Our study included slightly increased number of enrolled study subjects (n=60) and more encouraging HRS incidence (6/30 in GrA versus 14/30 in GrB) results were obtained. To the best of our knowledge, this prospective experimental study is the only study of its kind where midodrine administration exhibited promising results for primary prevention of HRS (16).

The NNT for prevention of HRS was 3.75 as per our analysis. ARR and RRR for development of HRS were 27 % and 57 % respectively. Low NNT to prevent one episode of HRS is a promising feature of this study. Secondary outcomes evaluated in our pilot study were the occurrence of complications, need (frequency and quantity) for LVP, and survival analysis across the groups. The number of patients who died in GrA was 2 while 6 deaths were recorded in GrB. However, statistical significance could not be achieved, possibly due to recruitment of a lower number of patients. NNT observed in survival analysis to prevent one death was 7.6. ARR and RRR were estimated to be 0.13 and 0.67 for risk reduction for death, respectively. Although the relative analysis for death as an event did not reach statistical significance, reasonably small (7.6) NNT value establishes prominence of midodrine in prolonging survival. Nevertheless, this hypothesis can only be proved with a larger study and longer period of observation. Even though survival benefit is modest, increased bridging time to LT could be advantageous. Midodrine can be used for all stable CTP-C cirrhotics patients enrolled in a transplant program to prevent renal derangement. Our results suggested a clear trend in survival benefit established in GrA. Reduced renal complication rates observed in our drug trial demonstrated adequacy towards a positive outcome for future researchers. Although the required number of LVP sessions was reduced by midodrine administration, no statistical significance could be achieved in the cumulative 4 months analysis (P-value of 0.54). Based on the above numbers, it is evident that midodrine plays a significant role in preventing HRS and possibly increases survival. Taking into account other complications that may contribute to the all-cause mortality, incidences of complications such as SBP, HE and GI bleed in the two groups were also analyzed. However, there was no difference in non-HRS complication rates ($p > 0.05$). Decline in complications over 4-month duration in both study groups could be attributed to standard of care. Since the statistical analysis showed that there was no difference in the incidence of other complications in either group, the beneficial effects could not be ascribed to midodrine only.

Midodrine has been reported to be included in around 15 studies in cirrhotics in the last two and a half decades. Almost all of them were randomized controlled trials (RCTs) conducted to assess and create

evidence for its various potential benefits by its effect on circulatory hemodynamics. Few studies used midodrine at higher dosages as compared to our study to assess improvements in clinical parameters in cirrhotic ascites. We could efficaciously demonstrate desired prevention potential of midodrine at lower dosages. The mean daily dosage of midodrine used across the study group was 16.75 mg and yet we could achieve the target MAP of 80 mmHg and complete the analysis with such a comparatively lower dose than the similar study earlier conducted by Parikh (2021) (16). V. Singh et. al. (2012) presented their randomized pilot study wherein they concluded that midodrine plus standard medical therapy improved systemic hemodynamics without any renal or hepatic dysfunction in the patients and was superior to standard medical therapy for the control of ascites (17). However, we could not reproduce similar results to support this conclusion in the present study. Shortcomings associated with the study are its non-randomized pilot study nature, limited number of recruited patients due to time constraints and short period of observation (4 months).

Based on occurrence of few minimal side effects not requiring any dose modifications during the 4 month of evaluation and being tolerated fairly even at 22.5 mg daily dosage, it could be emphasized that midodrine possessed a good safety profile. As far as the potential effectiveness of midodrine in CTP Class C cirrhotics is concerned, it should be stressed to evaluate its role in prevention of HRS with experimental data on a larger scale. To the best of our knowledge, this is the only study wherein midodrine has been evaluated for primary prevention of HRS in high-risk cirrhotics. Follow-up was done very meticulously and drop–out rate was zero after the 1st month follow-up visit. Two compared groups were evenly matched in terms of demographics and severity of liver disease. However, the proposed beneficial effect of midodrine needs to be replicated in larger studies with longer observation period.

Conclusion

Our study successfully established the role oral midodrine in generating a significant beneficial effect in the primary prevention of HRS in cirrhotic patients at high risk whose baseline MAP was less than 80 mm Hg. In this study, oral midodrine could not exhibit a statistically significant survival benefit. However, a clear trend to improved survival given the acceptable NNT of 7.6 could be established. Midodrine did not impact the frequency of LVP in either group. Non–HRS complications rates were similar in both study groups. Midodrine was well tolerated with no significant adverse effects in the experimental subjects.

Conflict of interests

The authors declare that they have no competing interests.

Acknowledgement

Authors thank the management of Bharati Vidyapeeth University Medical College, Pune – 411043, India for support in the development of this project.

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