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Midodrine versus Albumin to Prevent Paracentesis Induced Circulatory Dysfunction in Acute on Chronic Liver Failure Patients in the Outpatient Clinic–a Randomized Controlled Trial☆,☆☆,☆☆☆

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Background: **Paracentesis-induced circulatory disturbance (PICD) occurs in 12–20% of patients receiving human albumin for large-volume paracentesis, and can occur at lower than five liter paracentesis in acute-on-chronic liver failure (ACLF). Albumin infusions are associated with higher costs and more prolonged daycare admissions. The aim of the study was to determine if oral midodrine-hydrochloride can prevent PICD in these patients by increasing the mean arterial pressure (MAP).** ***Methods:*** **This open-labeled randomized controlled trial included ACLF patients undergoing paracentesis between 3 and 5 L, who were randomized to receive either 20% human albumin or midodrine hydrochloride 7.5 mg thrice daily for three days, 2 h before paracentesis. MAP was recorded daily. The primary outcome was the plasma renin activity (PRA) on day six, and a 50% increase from baseline was considered PICD.** ***Results:*** **183 consecutive patients of ACLF were screened, and 50 patients were randomized to either arms. Alcohol was the most common underlying cause of cirrhosis. Day 6, PRA was non-significantly ($P = 0.056$) higher in the midodrine group. The absolute change of PRA between the two groups was not significant ($P = 0.093$). Four (16%) patients in the albumin group and five (20%) in the midodrine group developed PICD. MAP increase was not different between the albumin and midodrine arms ($P = 0.851$). Midodrine was found to be more cost-effective.** ***Conclusions:*** **Three days of oral midodrine is as effective as a human-albumin infusion in preventing PICD in ACLF patients undergoing paracentesis lesser than that done in large volume paracentesis. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Ascites is the most common form of decompensation in patients with liver cirrhosis.[1] Many patients with ascites require repeated large-volume paracentesis (LVP). To prevent paracentesis-induced circulatory disturbance (PICD), a human albumin infusion is commonly used during paracentesis.[2,3] PICD is a significant cause of morbidity and mortality, and can go unrecognized.[4] PICD is defined as an increase in plasma renin activity (PRA) on the sixth day after the paracentesis of more than 50% of the pre-treatment value.[5] The incidence of PICD after LVP varies between 12 and 20% in patients receiving albumin.[6] PICD may be caused due to fluid shifts during paracentesis, leading to a decrease in an effective, circulating blood volume. Increased PRA is considered the hallmark of PICD associated with hypo responsiveness to vasoconstrictors.[7]

Albumin use has been associated with a reduction of PICD by 60%, and is superior to other volume expanders.[8] However, there is a paucity of data on PICD in patients with ACLF. The basic pathophysiology of portal hypertension and increased intestinal permeability and associated altered hemodynamics differs in severity between patients of decompensated chronic liver disease and ACLF.[9] Patients of ACLF can develop PICD even with paracentesis of less than 5 L (which defines large volume paracentesis). The same has been defined in a previous study as modest

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☆☆The manuscript is submitted on behalf of all authors, and they have all participated in the work to be published.

☆☆☆This study was approved by the institutional review board and ethical committee of the institute and registered with clinicaltrials.gov. (NCT05240391).

Abbreviations: AARC: APASL Asia Research Consortium ACLF Score; ACLF: Acute-on-chronic liver failure; APASL: Asia Pacific Association of Study of Liver Disease; HE: hepatic encephalopathy; MAP: Mean arterial pressure; PRA: Plasma renin activity; PICD: Paracentesis-induced circulatory disturbance

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volume paracentesis, though the terminology is still not widely accepted. Albumin infusions have been shown to reduce PICD and mortality in these subgroups of patients.[10]

The major deterrents to using albumin are the cost, the prolongation of day-care admission, and the adverse effects like volume overload and transfusion-related reactions.[11,12] Lower dose administration of albumin has been tried and found to be adequate to prevent PICD.[13,14] Though the use of an oral drug like midodrine has been used to prevent PICD in patients with decompensated cirrhosis, the results are conflicting. [15 16 17]

We hypothesized that in patients with ACLF undergoing paracentesis of less than 5 L, oral midodrine hydrochloride could prevent PICD by increasing the mean arterial pressure (MAP). The study aimed to determine if midodrine can prevent the development of PICD when compared to intravenous 20% human albumin infusions in patients of ACLF undergoing paracentesis for recurrent ascites.

MATERIALS AND METHODS

Study Design

This study was a prospective, single-center, randomized controlled trial conducted at the Asian Institute of Gastroenterology Hospitals, India, between February 2022 and May 2022. The local institutional ethics committee approved the study (AIG/IEC-Post BH &R −02.12.2109/ER-16), and the study was registered at clinicaltrials.gov.in (NCT05240391). All consecutive patients who fulfilled the Asia Pacific Association of Study of Liver Disease (APASL) criteria for ACLF and required therapeutic paracentesis for recurrent ascites were prospectively enrolled for the study and underwent randomization to receive either human albumin 20% or midodrine hydrochloride 7.5 mg thrice daily for three days. Due to the different nature of the administration of both the study arms, there was no blinding.

Patients Screening and Eligibility Criteria

All consecutive patients with recurrent ascites and older than 18 years with ACLF as per the APASL criteria were screened for possible inclusion in the study. Patients with acute kidney injury defined as serum creatine of >0.3 mg/dl above the baseline, severe cardiovascular disease, history of urinary retention, pheochromocytoma, thyrotoxicosis, persistent and excessive supine hypertension defined by systolic blood pressure >170/90 mm Hg, patients on non-selective beta blockers, pregnant patients, and those who were unable to give informed consent were excluded before randomization. All patients of ACLF had cirrhosis, as was defined by evidence from imaging, laboratory, and endoscopic findings. The indication of doing paracentesis was based on the patient's complaint of shortness of breath or inability to lie down on the bed, which was attributable to ascites. None of the patients were on any other vasoconstrictors like terlipressin or octreotide.

Randomization and Intervention

The patients included in the study were allocated to either intravenous 20% human albumin or oral midodrine hydrochloride in a ratio of 1:1 using block randomization, each block consisting of 10 patients. The study coordinator, BAG, generated the randomization sequence. MS, PNR, RG, AK, and NG enrolled study participants after screening for inclusion and exclusion criteria. Each investigator received a block randomization sequence as eight sealed, opaque envelopes labeled as block identifiers (1–5) and a sequence within the block (1–10). These envelopes were prepared by BAG. The investigators narrated the study protocol to the patients at the time of written informed consent. The assignment of the patient was sealed in an opaque envelope that was opened after obtaining written informed consent.

The patients assigned to the albumin arm received 100 ml of a human albumin infusion 20% intravenously over 4 h, starting towards the end of the paracentesis. The patients assigned to the midodrine arm received oral midodrine hydrochloride 7.5 mg thrice daily for three days, starting 2 h before paracentesis. Paracentesis was done in the day-care department of the institute.

Follow up

The baseline characteristics of the patients, along with the etiologies of the acute and chronic components of ACLF, were recorded. A PRA blood sample was taken after overnight fasting and after at least 1 h of bed rest on the day of paracentesis and the sixth day. MAP was recorded daily twice, and the average was taken. Renal function tests and serum electrolytes tests were performed on day 3 and day 6.

Study Endpoints

The Primary Outcome was the occurrence of PICD on day six, defined by a 50% increase in the PRA from the baseline.

Secondary Outcomes were changes in serum creatinine and sodium values on day 6, change in the MAP, the incidence of post-paracentesis hepatic encephalopathy, and mortality on day 28.

Definitions

ACLF

ACLF was defined as per the APASL criteria as "acute hepatic insult manifesting as jaundice [serum bilirubin

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≥5 mg/dL (85 μmol/L) and coagulopathy (international normalized ratio (INR) ≥ 1.5) or prothrombin activity <40%] complicated within four weeks by clinical ascites and encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis".[18]

PICD

PICD was defined as a 50% increase in PRA over the baseline on the sixth day after paracentesis.[16]

Statistical Analysis

This is a pilot study, so sample size calculation was not considered. The data were collected using a study proforma and entered into Microsoft Excel for analysis. The continuous variables were expressed as a mean and standard deviation for parametric data and as a median and interquartile range for non-parametric data. The categorical data were expressed as percentage. The continuous variables were compared using a student's t-test and paired t-test, wherever appropriate. The change in parameters at the end of the follow-up compared to the baseline was compared using an independent sample t-test. Categorical variables were compared using a chi-squared test and Fisher's exact test, wherever appropriate. The presence of hepatic encephalopathy in both groups at the end of the follow-up was analyzed using the McNamar's test. A *P*-value of <0.05 was considered statistically significant. The statistical analysis was performed using SPSS (v 25, IBM).

RESULTS AND OBSERVATIONS

One hundred and thirty-eight consecutive ACLF patients requiring paracentesis, presenting to the hepatology clinic of the institute were screened. Seventy-eight patients were excluded for not meeting the inclusion criteria, as shown in Figure 1, and finally, fifty patients were randomized to receive either midodrine or 20% human albumin during paracentesis.

Both groups' baseline demographic, clinic, and laboratory parameters were similar (Table 1), including the median number of admissions prior to enrollment in the study. The use of diuretics, a combination of spironolactone (50–100 mg) and/or frusemide (40–80 mg), was similar in both groups. 75% of patients were on a combination dose of 100mg/40 mg of spironolactone and frusemide.

Alcohol use disorder-related liver disease was the most common etiology of chronic liver disease in both the groups. The acute insult for ACLF has been shown in Table 2. Two patients in the albumin arm had possible

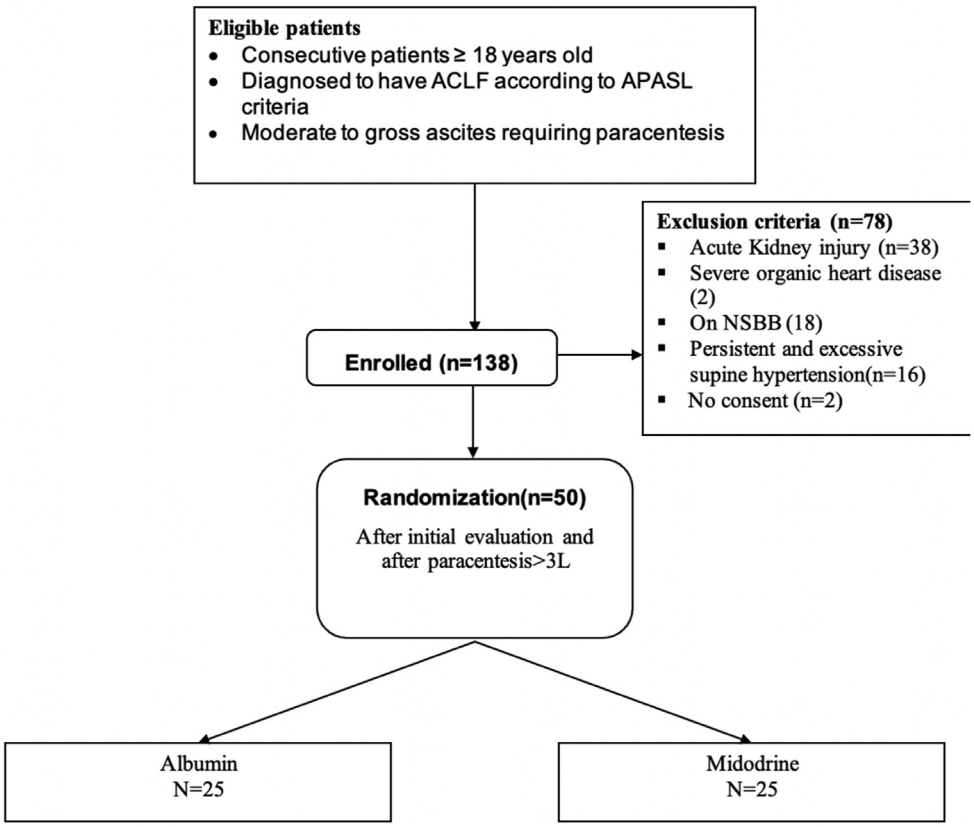

Figure 1 A consort diagram showing a screening of patients and randomization. NSBB: non-selective beta-blockers, ACLF: Acute-on chronic liver failure; APASL: Asia Pacific Association for Study of Liver Diseases; N = number of patients.

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Table 1 Table Showing Baseline Characteristics of Both the Groups Before Paracentesis.

Variable	Albumin group	Midodrine group	*P* value
Age in years	53.2 ± 11.1	58.5 ± 10.3	0.085
Male: Female (n,%)	17(68%):8 (32%)	19(76%):6(24%)	0.54
Etiology			
AUD related	13 (52%)	10 (40%)	0.283
NASH	8 (32%)	10 (40%)	
HBV	2 (8%)	2 (8%)	
HCV	0 (0%)	1 (4%)	
AIH	0 (0%)	1 (4%)	
Cryptogenic	2 (8%)	1 (4%)	
MAP	76.8 ± 3.46	76.1 ± 3.51	0.601
Serum bilirubin	15.95 ± 4.75	19.73 ± 9.93	0.201
Lactate (mmol/dl)	1.2 ± 0.3	1.1 ± 0.21	0.43
MELD Na	28.68 ± 4.75	30.5 ± 4.74	0.168
Serum sodium mg/dl	130.2 ± 4.0	128.4 ± 4.8	0.156
Serum creatinine mg/dl	1.2 ± 0.24	1.08 ± 0.36	0.171
Blood urea	18.4 ± 8.2	19.6 + 6.4	0.57
Paracentesis in previous 3 months	3.92 ± 1.12	3.72 ± 0.94	0.497
Volume of paracentesis in L	4.72 ± 0.92	4.72 ± 0.84	1.00
h/o variceal bleed in last 28 days	0	0	
AARC Score			
Grade I/II	22	23	
Grade III	3	2	
PRA	19.96 ± 7.35	22.56 ± 8.21	0.243
h/o hospitalization within last 3 months (Median, Range)	1 (0–2)	1 (0–3)	

AUD, alcohol use disorder; NASH, non-alcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; AIH, autoimmune hepatitis; MAP, mean arterial pressure; MELD Na, Model for end-stage liver disease – sodium; L, liters; n, number; %, percentage; PRA, plasma renin activity; AARC, APASL Asia Research Consortium ACLF Score.

superimposed alcoholic hepatitis as per the AASLD definition[19], and were managed conservatively with no use of steroids or pentoxifylline. The history of infection, including spontaneous bacterial peritonitis (one patient in the albumin arm) one month before enrollment in the study was similar between both the albumin and midodrine groups [15 (60%) vs. 11 (44%), $P = 0.34$]. There was no report of SBP in the 28-day follow-up period. Urinary tract infection was the most common form of infection [in both the groups (24% in the albumin and 16% in midodrine group)]

Table 2 Characteristics of Acute Insults and Pre-Enrollment Insults.

	Albumin Group N = 25	Midodrine group N = 25	*P* value
Acute insult:			
Hepatic	17 (68%)	17 (68%)	1.0
Non-hepatic	14 (56%)	12 (48%)	0.78
Both	06 (24%)	03 (12%)	
h/o Infection in last 1 month	15 (60%)	11 (44%)	0.34
UTI	24%	16%	
Pneumonia	12%	8%	
SSTI	9%	12%	
h/o HE 28 days before enrollment	4 (16%)	3 (12%)	
Spontaneous bacterial peritonitis at enrollment	0	0	

UTI, Urinary Tract Infection; HE, hepatic encephalopathy; SSTI, skin and soft tissue infection; N, number of patients.

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Table 3 Delta Change of Laboratory Parameters Between Day 0 and Day 6.

	Albumin group	Midodrine group	*P* value
PRA (mean ± SD)	2.9 ± 7.28	2.82 ± 4.68	0.963
Serum creatinine (mean ± SD)	0.15 ± 0.71	0.02 ± 0.175	0.372
Serum sodium (mean ± SD)	1.2 ± 3.81	0.0 ± 2.73	0.225
MAP (mean ± SD) Day 3	2.0 ± 1.8	2.8 ± 2.1	0.154
MAP (mean ± SD) Day 6	2.3 ± 3.12	3.1 ± 2.89	0.851

MAP, mean arterial pressure; SD, standard deviation; PRA, plasma renin activity.

followed by pneumonia in the albumin group (12%) and skin and soft tissue infection in the midodrine group (12%). Hepatic encephalopathy was noted in four patients (16%) in the albumin group and three (12%) in the midodrine groups in the month preceding enrollment, and the patients were on rifaximin prophylaxis at a dose of 550 mg twice daily. All patients were on Norfloxacin prophylaxis at a dose of 400 mg/day.

The delta change in the MAP was not different between the albumin and midodrine groups at either on day 3 (2.0 ± 1.8 vs 2.8 ± 2.1 mm Hg, P = 0.154) or at day 6 (2.3 ± 3.12 vs 3.1 ± 2.89, P = 0.851) (Table 3).

The PRA measured on day six was non-significantly higher (P = 0.056) in the midodrine group than the values noted in the albumin group. Furthermore, a significant rise in the absolute PRA value from the baseline was recorded in the midodrine group (P = 0.006). This increased value, however, did not fulfill the criteria of PICD.

The absolute change in the PRA between the two groups did not show any statistical significance (P = 0.963) (Figures 2 and 3).

Four (16%) patients had an increase in PRA of more than 50% from baseline in the albumin group, and five (20%) patients in the midodrine group (Figure 2), suggesting PICD.

Secondary Endpoints

One patient in the midodrine group (serum sodium 123.2) developed hyponatremia, defined as a serum sodium value of less than 125 mg/dl, while the lowest sodium recorded in the albumin arm was 126.2 mg/dl. However, both the groups had no statistically significant change in serum sodium or serum creatinine values. Changes in MAPs also did not differ between the two groups (P = 0.851). The absolute difference in laboratory parameters from baseline and at day six is shown in Table 3. Three (12%) patients in the albumin group and four (16%) in the midodrine group died (P = 0.60) within 28 days of admission, the most common cause of death being multi-organ failure due to sepsis in six patients and upper gastrointestinal bleed in one patient (Table 4).

One patient (4%) developed fluid overload in the albumin group. The other adverse events were not significantly different between the two groups. Three patients (12%) in the albumin group and two (8%) in the midodrine groups developed grade I–II hepatic encephalopathy on day two

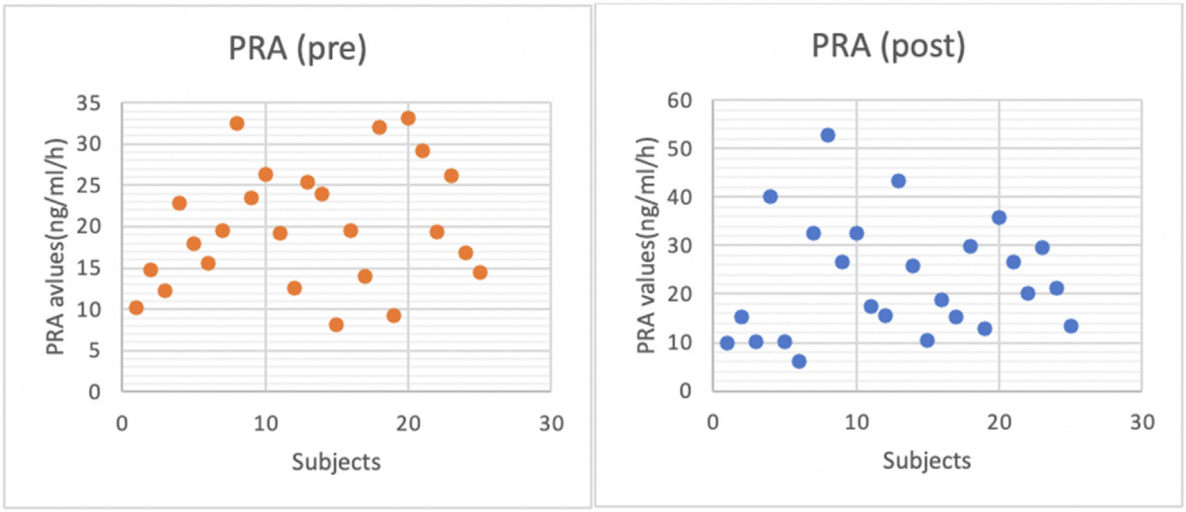

Figure 2 A scatter plot showing the mean plasma renin activity pre-paracentesis at baseline and day 6 post-paracentesis in the albumin group.

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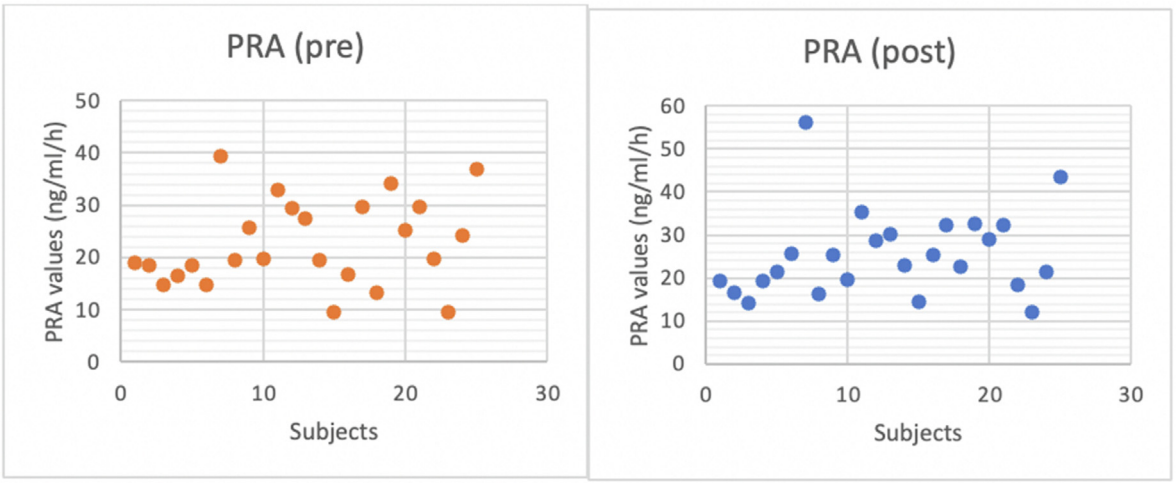

Figure 3 A scatter plot showing the mean plasma renin activity pre-paracentesis at baseline and day 6 post-paracentesis in the midodrine group.

post-paracentesis. Only three (12%) patients in the albumin group and one (4%) in the midodrine group developed acute kidney injury, defined as a rise in serum creatinine by >0.3 mg/dl from baseline within the first six days of paracentesis. All nine patients in the study who developed AKI had a rise in creatinine on the second assessment of creatinine on day 6. These patients were started on a standard volume expansion, with the withdrawal of diuretics on the diagnosis of acute kidney injury.

For the patients who required repeated paracentesis during the follow-up period of 28 days, which was similar in the albumin and midodrine arm [2.2 ± 0.96 vs. 2.3 ± 1.10. (P = 0.73)], received the same intervention that was administered during study randomization and at the same dosage.

In the follow-up analysis on day 28, two patients in the albumin arm and one in the midodrine arm progressed from AARC (APASL Asia Research Consortium ACLF Score) grade 1 to grade 2, while one patient each progressed from AARC grade 2 to grade 3. No patient showed regression of the AARC score.

Among the three patients who progressed from AARC grade 1 to 2, one (in albumin arm) developed a lung infection (pneumonia) and was admitted to the intensive care unit and succumbed. The second patient in the albumin arm had worsening ascites and acute kidney injury and was managed conservatively. The third patient (in the midodrine arm) developed sepsis and was listed for living donor liver transplantation but succumbed to the disease.

One of the two patients who progressed from AARC grade 2 to 3 was taken up for liver transplantation on day 28. The other patient (in the albumin arm) developed sepsis and multi-organ failure and died on day 24.

Table 4 Table Showing Adverse Events and Study Outcome in Both the Groups.

	Albumin Group (n = 25)	Midodrine Group (n = 25)
Fluid overload	1/25 (4%)	0/0 (0%)
Hypertension	0/0 (0%)	0/0 (0%)
Urinary retention	0/0 (0%)	0/0 (0%)
Grade I/II HE day2–3 paracentesis	3 (12%)	2 (8%)
Acute kidney injury	3 (12%)	1 (4%)
Mortality at day 28 - Cause of death	3 (12%) Multi-organ failure – Sepsis-3	4 (16%) Multi-organ failure – Sepsis-3 UGI Bleed: 1
PICD	4 (16%)	5 (20%)
Underwent transplantation	2 (day 28)	1 (day 30)
Paracentesis requirement in the 28 day follow up period	2.2 ± 0.96	2.3 ± 1.10. (P = 0.73)

HE, Hepatic encephalopathy; PICD, paracentesis induced circulatory difference; UGI, upper gastro-intestinal.

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The need for hospitalization was similar in both the arms–six in the midodrine arm and five in the albumin arm. The most common reasons for admissions include hepatic encephalopathy, acute kidney injury, and sepsis, as shown in Table 4. These included three patients who underwent transplantation.

When the cost-effective analysis was done between the albumin and midodrine groups, midodrine was found to be a significantly cost-effective model in preventing PICD (6082 vs. 1012 INR; $P = 0.0001$) (Figure 4).

DISCUSSION

PICD is an often overlooked complication after paracentesis. The dynamics, which involve alteration of the renin-angiotensin-aldosterone system associated with a reduction in cardiac output, start within the first 12 h of paracentesis.[20] These alterations are more marked in patients with ACLF. They can occur with a moderate volume of paracentesis involving the fluid removal of the fluid of approximately four liters, where even albumin is not routinely recommended for decompensated cirrhosis.[10] This is due to an exaggerated inflammatory response with a higher inducible nitric-oxide production, micro-circulatory disturbances, and a lower MAP in patients with ACLF.[10]Albumin use in these ACLF patients has been effective in the prevention of PICD.

Human Albumin infusions have been used extensively for the prevention of PICD in patients of decompensated cirrhosis undergoing LVP.[21] However, albumin infusions need extra duration of day-care hospitalization as they usually start towards the end of paracentesis and lead to additional costs. Further, as an intravenous drug, reactions to albumin, like acute lung injury, fluid overload, etc., are observed in clinical practice.[22,23]

Midodrine is a drug that is approved for dysautonomia and orthostatic hypotension. Its active metabolite, desglymidodrine acts via alpha-one receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure.[24] The use of midodrine in hepatorenal syndrome has shown improvement in the renal plasma flow, glomerular filtration rate, and urinary sodium excretion and a significant concomitant reduction in PRA, plasma vasopressin, and plasma glucagon; thereby, improving hemodynamic.[25] The increase in hemodynamic and MAP could be beneficial in preventing PICD in ACLF patients undergoing paracentesis.

A pilot study that compared midodrine at a dose of 5–10 mg every 8 h to maintain a MAP of ten mmHg above the baseline for 72 h versus albumin to prevent PICD in decompensated cirrhosis patients showed that midodrine was equal to albumin at a lower cost.[17] However, a similar study involving 24 patients found that midodrine used at a dose of 12.5 mg every 8 h for two days following 8 L of paracentesis was ineffective in preventing PICD (60% vs. 31%).[16] A third study which involved patients with hepatocellular carcinoma did not show a beneficial effect of midodrine used at a dose of 12.5 mg every 8 h for three days over 20% human albumin used at a dose of 8 g/L of the fluid removed in patients with decompensated cirrhosis.[15] However, our study is the first randomized trial in patients with ACLF comparing midodrine versus albumin to prevent PICD. Our study found midodrine to be as effective as albumin infusions despite not showing a significant rise in MAP. It was possible that midodrine maintained the MAP in paracentesis, and the same would have translated into a beneficial effect. The non-increase in the MAP could be secondary to the volume loss during paracentesis, and incremental or longer duration of midodrine use may have exerted a further beneficial effect.

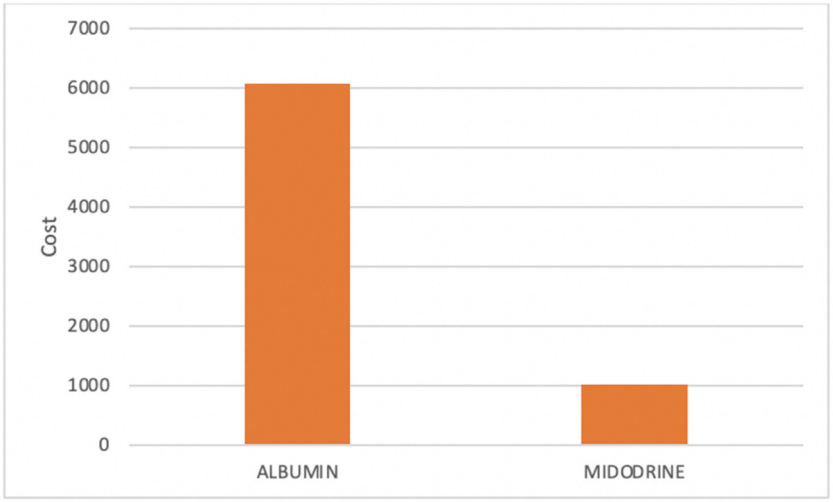

Figure 4 A bar diagram showing the cost-effectiveness of midodrine over albumin infusions in Indian rupees.

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There has been a wide variation in the mean baseline PRA values among various studies. The mean values of baseline PRA obtained in our study population are similar to the findings in another study from India.[17] A study done on ACLF involving 80 patients, which reported a mean PRA value of 21.95 ± 7.01 ng/mL/h, was comparable to our study (19.96 ± 7.35 in the albumin group vs. 22.5 ± 8.21 in the midodrine group, $P = 0.243$).[10] This contrasts significantly with the reported PRA levels in patients with decompensated cirrhosis (1.6–13 ng/mL/h).[26] Some studies have calculated direct plasma renin concentration (PRC) rather than PRA in decompensated chronic liver disease; therefore, the data is heterogeneous.[16] PRA was calculated in our study rather than a direct plasma renin values estimation, as it was proven in multiple studies to be a better marker for assessing PICD. We noted significant rise in the absolute value of PRA levels in the midodrine group on the sixth day ($P = 0.003$). However, the rise was not significant enough to fulfill the definition of PICD.

In our study, alcohol was the most common etiology of chronic liver disease. Hepatic precipitants for ACLF were noted in 68%, and 52% had non-hepatic precipitants. The prevalence of triggers of decompensation in ACLF varies by the area of the world. In the CANONIC study, bacterial infections and alcoholism are the two major identifiable factors compared with China, where a hepatitis B relapse was more predominant, followed by bacterial infections.[27,28] In our study, alcohol was found to be the most common hepatic precipitant cause (40%), followed by a history of the use of complementary and alternative medicines and hepatotropic viral infections, respectively. Among the non-hepatic precipitants, infections were the most noted trigger, and urosepsis was the most prevalent (20%). SARS-2 Covid-19 infection was the trigger in 6% of the study subjects.

The mean value of the amount of fluid removed during paracentesis in our study was 4.72 L. All the previous studies considered 5–6 L as the cut-off for the risk of PICD. We did paracentesis of fewer than five liters based on the finding of a recent study by Vinod Arora *et al.*, where with a paracentesis of less than five liters, PICD was more prevalent in the study group receiving no albumin group (70% vs. 30%), with a higher incidence of hepatic encephalopathy, AKI, and in house mortality.[10] Our study showed that PICD is common in ACLF, and develops even with paracentesis of fewer than 5 L. In our study, among the nine patients who developed PICD, four patients (16%) received intravenous albumin infusions.

Hyponatremia has been reported after LVP.[29] In our study, though there was a trend towards lower serum sodium in the albumin group compared with the baseline, it was not of statistical significance ($P = 0.129$). Midodrine has been evaluated in studies in combination with octreotide to prevent hyponatremia in decompensated cirrhosis without much success.[30]Post-paracentesis acute kidney injury developed post-paracentesis in four (8%) cases (three in the albumin group & one in the midodrine group), out of which three subjects died. There was a rise in the model for end-stage liver disease (MELD) score in those patients who developed AKI and was secondary to the rise in the creatinine value. The median delta change in the MELD score was 3 (range −1 to 5). Worsening of the Child-Turcotte-Pugh score was noted in 3/25 (12%) cases in the midodrine arm, while it was in 4/25 (16%) in the albumin arm. No patient showed improvement in the Child-Turcotte-Pugh score.

High PRA is a marker of severe circulatory dysfunction. The majority of the patients in our study was very sick, with a mean MELD Na score of 28.68 ± 4.75 in the albumin group and 30.5 ± 4.74 in the midodrine group ($P = 0.168$). The mean bilirubin was 15.95 ± 4.75 in the albumin group and 19.73 ± 9.93 ($P = 0.201$). A recent study has shown that PRC was higher in ACLF patients 134 (36–378) mmol/L when compared to those without ACLF 65 (17–242) mmol/L and in healthy controls 8 (6–17) mmol/L. PRC is a direct measure of plasma renin, and the conversion factor of PRA (nanograms per milliliter per hour) to direct renin concentration (milliunits per liter) is 8–12, depending on the assay used.[31]

A cost-effective analysis was done in our study, and the cost of midodrine treatment was significantly lower as compared with that of albumin in Indian rupees (mean:6082 vs. 1012 INR; $P = 0.0001$) The cost of therapy in the albumin group included the price of day-care admission, and the patient can save significant resources if an oral drug can be used.

The study had some limitations. The midodrine dose was constant and not titrated based on the MAP. In addition, using midodrine for three days was based on previous studies, while the PRA was measured on the 6th day. Whether continuing midodrine for six days would be better than three days of treatment needs to be explored. In addition, 28 day mortality in our study was lower possibly due to significantly more patients in the lower AARC grade I/II and the exclusion of patients with organ failure, mainly AKI, which corelates with mortality.[32] Previous studies have shown a cumulative mortality of 12.7% in patients with AARC grade I patients.[33]

The results of this pilot study of the use of midodrine to prevent PICD in patients with ACLF suggest that three days of oral midodrine is as effective as intravenous albumin in preventing PICD at a much lesser cost. However, more extensive multicenter studies in a uniform cohort of patients are required to validate the same.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Mithun Sharma: Conceptualization, Formal analysis, Methodology, Validation, and Original draft; **N Jaya Sai**

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Sujith Reddy: Data curation, formal analysis, and visualization; **Rakesh Kalpala:** Project administration, review, and editing; **Nitin Jagtap**: Methodology, software, and validation; **Anand V Kulkarni:** resources, validation, and review and editing; **Rajesh Gupta:** Editing and reviewing; **Padaki Nagaraja Rao**: Supervision and review and editing; **Sowmya TR:** Data curation, and visualization; **Manasa Alla**: Review and editing; **Duvvur Nageshwar Reddy**: Review and editing, and project administration.

CONFLICTS OF INTEREST

All authors have none to declare.

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