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The effects of midodrine on patients with liver cirrhosis and refractory ascites: a randomized controlled trial

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Abstract

Background: Splanchnic vasodilation is a significant contributor to the development of ascites in cirrhotic patients. So, midodrine, an alpha-one agonist, may improve circulatory abnormality in cirrhotic patients via its vasoconstrictive action, thus lessening refractory ascites.

Aim: To assess the efficacy and the safety of midodrine (alpha adrenergic agonist) on patients with liver cirrhosis and refractory ascites.

Patients and Methods: 80 cirrhotic patients with refractory ascites were enrolled in this prospective study. The patients consisted of 40 patients receiving standard medical therapy (SMT) (dietary salt restriction and diuretics) and 40 patients receiving standard medical therapy +midodrine in a dose of (7.5 mg /8 hours) for one month. Body weight, abdominal circumference, complete blood count, liver and renal function tests, serum electrolytes and 24-hour urine volume, and Na level were obtained at the study's start and end.

Results: Body weight and abdominal circumference significantly decreased in midodrine group patients compared to the control group (p <0.001). Also, 24-hour urinary volume and Na excretion were substantially higher in midodrine group patients at the study's end than in SMT patients (p <0.001). Additionally, both systolic and diastolic blood pressure were higher in midodrine patients at the end of the study(P<0.001).

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Conclusions: Midodrine could be used safely as an adjuvant to SMT in cirrhotic patients with refractory ascites, with better outcomes evidenced by reduced body weight and increased Na excretion in urine.

Keywords: cirrhosis, refractory ascites, midodrine.

Introduction

Cirrhosis is a chronic liver disease that causes damage to liver tissue scarring of the liver (fibrosis - nodular regeneration) [1]

Ascites is a common complication of liver cirrhosis. About 20% of patients with cirrhosis have ascites at their first presentation, and 20% of those presenting with ascites die in the first year of the diagnosis [2].

According to the criteria of the International Ascites Club, refractory ascites is defined as ''ascites that cannot be mobilized or the early recurrence of which (i.e., after large-volume paracentesis) cannot be satisfactorily prevented by medical therapy [3].

Evidence demonstrates that renal sodium retention in patients with cirrhosis and ascites is mainly due to increased proximal and distal tubular sodium reabsorption rather than a decreased filtered sodium load. The mediators of sodium's enhanced proximal tubular reabsorption have not been elucidated completely. In contrast, the increased reabsorption of sodium along the distal tubule is related chiefly to hyperaldosteronism secondary to Portal hypertension and splanchnic vasodilatation [4].

Patients with cirrhosis and ascites should have a moderately salt-restricted diet with a daily salt intake of no more than 5–6.5 g (87 mmol–113 mmol sodium). A more severe reduction in dietary sodium content is considered unnecessary; on the contrary, it can result in complications, including hyponatremia, reduced caloric intake, higher risk of renal impairment (0% vs. 14%), hepatic encephalopathy (HE), hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP) and mortality, additionally, such diets are challenging to comply with [5].

The approach to therapy is either aldosterone antagonists in a stepwise increase every seven days (100–400 mg/day in 100 mg/day steps) with furosemide (40–160 mg/day, in 40 mg/day steps) added only in patients not responding to high doses of aldosterone antagonists or combined therapy of aldosterone antagonists and furosemide from the beginning of treatment (100 and 40 mg/day increased in a stepwise manner every seven days in case of no response up to 400 and 160 mg/day). All patients initiating diuretics should be monitored for adverse events, such as renal failure, hepatic encephalopathy, electrolyte disorders, gynecomastia, and muscle cramps. Almost half of adverse events require diuretic discontinuation or dose reduction [6].

Large volume paracentesis (LVP) is the standard of care for managing significant volume ascites both in conjunction with diuresis to relieve symptoms of a tense abdomen, as well as in the management of refractory ascites when diuretics become ineffective, or the side effects preclude their continued use [7].

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Midodrine hydrochloride forms an active metabolite of desglymidodrine that is an alpha1- agonist and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure [8].

Vasopressors, such as midodrine, have been used in non-azotemic patients with ascites, resulting in conflicting results about increasing mean arterial pressure and urine sodium excretion and significant decreases in plasma renin and aldosterone [9].

The study aims to assess the efficacy and the safety of midodrine (alpha adrenergic agonist) in patients with liver cirrhosis and refractory ascites.

Patients and methods

Study design and patients: This study was a prospective study during the period from April 2021 to March 2022

Eighty people, either in or out-patients, participated in the study. They enrolled in Tanta University Hospital's Tropical Medicine and Infectious Diseases Department. Forty patients with cirrhosis and refractory ascites were randomly assigned to receive either conventional medical treatment (SMT) as a control or SMT + midodrine 2.5 mg (3 pills / 8 hours) for a month. Diuretics such as spironolactone up to 400 mg /day and furosemide up to 160 mg /day, as well as a daily salt intake of less than 90 mmol, constituted the standard therapy or as tolerated provided that no complications as hepatic encephalopathy, hypokalemia, hyponatremia, impaired renal functions had occurred. Plus, large volume paracentesis (LVP).

Randomization procedures were automated, using centrally allocated computer-generated random numbers.

Participants were randomized to either the intervention (midodrine) or the control group. Thus, there was no possibility of any trial team influencing the allocation of participants.

The inclusion criteria were cirrhotic patients older than 18, regardless of cause, with refractory ascites defined by the European Association for the Study of the Liver [3].

The exclusion criteria were: (1) acute or chronic renal disease patients. (2) Patients with cardiac disease such as coronary heart disease, abnormal blood pressure, and congestive heart failure. (3) Hepatocellular carcinoma. (4) Portal vein thrombosis. (5) Patient with non-refractory ascites (6) Patient unwilling to participate in the study.

The study's primary outcome is to assess midodrine's effect on body weight, abdominal circumference, and urine volume. (At least mean weight loss >0.8 kg per day)

The secondary outcome is to assess the safety of midodrine as a treatment for refractory ascites.

All participants gave their informed written consents, and the study was approved by the Research Ethics Committee of the Faculty of Medicine, Tanta University, Tanta, Egypt (**approval number 34461/2/2021**).

Methods: All participants in the study were subjected to the following:

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Complete medical history, including Personal data like age, residence, sex, particular habits (e.g., Smoking), occupation, and phone number. History of present illness, asking the patient about the frequency of tapping, diuretic intake, compliance with salt restriction, cause of cirrhosis if available (HCV or others), and upper endoscopy. History of diabetes, hypertension, heart disease, and other medical conditions or operations.

Through clinical examination, including frequency of tapping, body weight, and abdominal girth measurement. Also, general and local examinations evaluate the patient for hepatic encephalopathy, pallor, jaundice, pleural effusion, and lower limb edema. Abdominal examination for abdominal distension, tenderness, rigidity, palpable mass or organomegaly, or degree of ascites.

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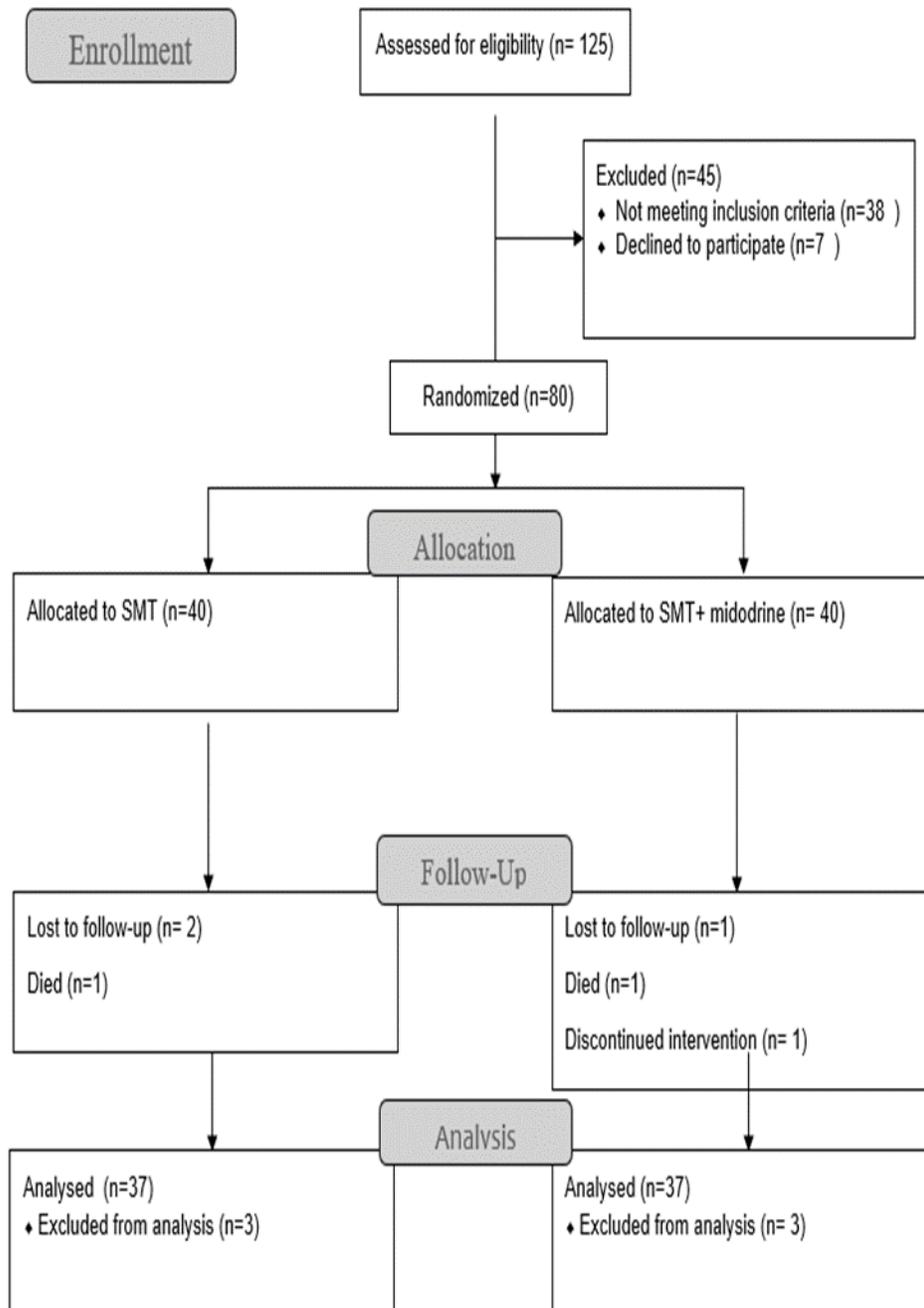
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Fig. 1. **Flowchart showing the disposition of the patients included in the study.**

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Laboratory tests, such as a complete blood count, liver panel, kidney panel, serum electrolyte profile, and 24-hour urine volume and Na excretion, as shown in table (1) - Child-Pugh score was assessed for all cirrhotic patients. Abdominal ultrasonography and triphasic CT were also performed.

*Tab 1. **Baseline characteristics in each group.***

Baseline characteristics	Group I (n= 40)	Group II (n= 40)
Body weight (Kg)		
Min. – Max.	70.0 – 120.0	66.0 – 117.0
Mean ± SD.	92.13 ± 12.17	89.10 ± 13.04
Median (IQR)	92.0(85.0 – 101.0)	88.50(77.0 – 96.0)
Abdominal circumference (cm)		
Min. – Max.	86.0 – 139.0	89.0 – 149.0
Mean ± SD.	109.18 ± 16.79	120.4 ± 16.05
Median (IQR)	105.5(95.0 – 125.0)	121.5(108.5 – 134.0)
Systolic blood pressure		
Min. – Max.	90.0 – 120.0	90.0 – 120.0
Mean ± SD.	99.50 ± 8.15	99.0 ± 9.28
Median (IQR)	100.0(90.0 – 105.0)	100.0(90.0 – 110.0)
Diastolic blood pressure		
Min. – Max.	60.0 – 80.0	60.0 – 80.0
Mean ± SD.	68.0 ± 5.16	67.0 ± 5.64
Median (IQR)	70.0(65.0 – 70.0)	70.0(60.0 – 70.0)
Hemoglobin		
Min. – Max.	6.90 – 12.00	7.80 – 13.70
Mean ± SD.	9.54 ± 1.13	10.0 ± 1.27
Median (IQR)	9.60(8.9 – 10.2)	9.70(9.4 – 10.2)
Platelets (150-400 PLT/mm^3)		
Min. – Max.	46.0 – 160.0	40.0 – 492.0
Mean ± SD.	90.65 ± 22.40	128.5 ± 94.06
Median (IQR)	88.0(75.5 – 105.0)	105.0(74.5 – 141.5)
Total leucocytic count		
Min. – Max.	2.30 – 12.0	2.0 – 19.50
Mean ± SD.	6.64 ± 2.61	6.88 ± 3.74
Median (IQR)	6.20(4.7 – 8.0)	6.20(3.9 – 9.3)
24-hour urine volume		
Min. – Max.	800.0 – 1600.0	800.0 – 2500.0
Mean ± SD.	1142.50 ± 246.92	1230.0 ± 350.24
Median (IQR)	1200.0(1000.0 – 1200.0)	1200.0(1000.0 – 1400.0)
Serum Na		
Min. – Max.	116.0 – 137.0	117.5 – 138.0
Mean ± SD.	128.2 ± 5.60	126.7 ± 5.87
Median (IQR)	128.5(125.5 – 132.0)	128.0(122.0 – 130.5)
Serum K		
Min. – Max.	3.0 – 5.50	2.70 – 5.90
Mean ± SD.	4.16 ± 0.59	4.10 ± 0.74
Median (IQR)	4.0(3.8 – 4.5)	3.90(3.5 – 4.5)
Urinary Na		
Min. – Max.	10.50 – 90.0	10.50 – 315.0
Mean ± SD.	24.98 ± 17.23	42.23 ± 53.75
Median (IQR)	22.0(13.3 – 26.0)	26.0(13.8 – 41.5)
Total Bilirubin		
Min. – Max.	0.90 – 9.0	0.60 – 19.0
Mean ± SD.	3.40 ± 2.08	3.48 ± 3.49
Median (IQR)	2.30(1.8 – 4.8)	2.10(1.8 – 3.9)
Serum creatinine		
Min. – Max.	0.80 – 1.60	0.70 – 2.0

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Mean ± SD.	1.14 ± 0.24	1.14 ± 0.28
Median (IQR)	1.20(1.0 – 1.3)	1.15(1.0 – 1.3)
Urea (5-20 mg/dL)		
Min. – Max.	2.40 – 135.0	22.0 – 120.0
Mean ± SD.	54.74 ± 23.60	60.43 ± 28.99
Median (IQR)	46.50(42.0 – 65.0)	54.50(39.0 – 87.5)
Albumin (3.5–5.0 g/dL)		
Min. – Max.	1.80 – 3.20	1.80 – 3.30
Mean ± SD.	2.66 ± 0.31	2.58 ± 0.36
Median (IQR)	2.70(2.4 – 2.8)	2.55(2.3 – 2.8)
ALT (3-36 units/L)		
Min. – Max.	12.0 – 112.0	10.0 – 112.0
Mean ± SD.	36.33 ± 20.85	35.70 ± 22.97
Median (IQR)	33.0(22.0 – 44.5)	29.50(20.5 – 48.0)
AST (8-33units/L)		
Min. – Max.	18.0 – 125.0	18.0 – 138.0
Mean ± SD.	52.80 ± 25.92	55.45 ± 29.84
Median (IQR)	45.0(37.5 – 68.5)	45.0(36.0 – 72.0)
INR (1.1)		
Min. – Max.	1.20 – 2.0	1.0 – 2.10
Mean ± SD.	1.61 ± 0.21	1.59 ± 0.26
Median (IQR)	1.60(1.5 – 1.8)	1.60(1.4 – 1.8)

INR= International normalized ratio. Aspartate transaminase= AST. Alanine transaminase= ALT, Hemoglobin level (13.8-17.2 gm/dl) in males and (12.1-15.1 gm/dl) in females, Total leucocytic count (4-11*10^9/L), 24-hour urine volume (800-2000ml/day), Serum Na (135-145mmol/L), Serum K (3.5-5.5mEq/L), Urinary Na (40-220mEq/day), Total Bilirubin (0.1-1.2mg/dL), Serum creatinine (0.7-1.3mg/dL).

The physical and laboratory examinations were repeated one month later to evaluate the impact of midodrine on the severity of ascites and any potential adverse effects it may have had on the study participants.

The risks to participants and the drug's safety were assessed by follow-up visits, blood pressure measurements, and asking about side effects such as epistaxis and headache.

Any hospital admission during the study was recorded.

Statistical analysis: IBM's statistical program, SPSS, version 20.0, was used to process and analyze the data. IBM Corp., Armonk, New York. Quantitative and qualitative information was presented in the same way. Normality was determined with the use of the Shapiro-Wilk test. The minimum and maximum values and the mean, standard deviation, median, and interquartile range (IQR) were used to characterize the quantitative data. The 5% significance threshold was used to evaluate the results. The tests included: (1) Chi-square to make group comparisons using categorical variables. When more than 20% of the cells have an anticipated count of less than 5, use either Fisher's Exact or Monte Carlo to adjust the chi-square. (3) T-test for students When comparing two groups using quantitative variables with a normal distribution, (4) Comparing two groups using the Mann-Whitney U When comparing two groups based on quantitative variables that have an irregular distribution, Method 5: The McNamara and Marginal Homogeneity Test Used to evaluate the relative importance of each step When comparing two time periods using quantitative variables with a normal distribution, the paired t-test is the method of choice. Wilcoxon signed-ranks test (7th version) When comparing two time periods using quantitative data with an irregular distribution.

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Results: 80 cirrhotic patients with refractory ascites were enrolled in this prospective study. Patients consisted of 40 patients received standard medical therapy (SMT), and 40 received SMT + midodrine. The studied groups' demographic, baseline clinical, and laboratory findings were summarized in **(Tab 1).**

Only 37 patients completed the study to its end in each group. In the control group, two patients did not adhere to the follow-up, and one patient died due to hepatorenal syndrome. In group II, one patient stopped the drug after the development of epistaxis, another did not complete follow-up, and another patient also died due to the development of hepatorenal syndrome, as shown in **Fig (1).**

There were no significant differences between the studied groups regarding age and gender. As regards the etiology of cirrhosis, we found that the primary etiology of cirrhosis is hepatitis C in both groups.
It was found that there was no difference between the two studied groups as regards the etiology of cirrhosis. As regards diuretic intake, it was found that there was no significance between the two studied groups as regards furosemide intake. There was a significant difference between the two groups regarding spironolactone intake at baseline, with 38 patients in group I and 34 patients in group II, which was attributed to the randomization of the patients.
Regarding tapping, it was found that there was no significance between the two studied groups at baseline. Still, there was a significant decrease in the frequency of tapping among midodrine group patients, which was not found in the control group at the end of the study (P value =0.021) **(tab 3).** Regarding the occurrence of hepatic encephalopathy, there was a significant difference between the two groups at the end of the study, where two patients developed hepatic encephalopathy in group II. In contrast, eight patients developed hepatic encephalopathy in group I before the end of the study(P<0.001) **(tab 2).**

Tab2. Comparison between the two groups according to general examination at the end of the study.

General examination at the end	Group I (n = 37)		Group II (n = 37)		χ^2	P
	No.	%	No.	%		
Conscious level						
Conscious	29	57.5	35	94.6		
Hepatic encephalopathy	8	24.3	2	5.4		
Frequency of tapping (months)						
Min. – Max.	0.0 – 2.0		0.0 – 2.0		U= 498.50[*]	0.021[*]
Mean ± SD.	0.92 ± 0.60		0.59 ± 0.55			
Median (IQR)	1.0(1.0 – 2.0)		1.0(1.0 – 2.0)			
Body weight						
Min. – Max.	63.0 – 120.0		65.0 – 116.0		t= 1.879	0.064
Mean ± SD.	91.65 ± 12.82		86.0 ± 13.04			
Median (IQR)	92.0(86.0 – 101.0)		86.0(77.0 – 91.0)			

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Abdominal girth						
Min. – Max.		84.0 – 138.0		84.0 – 145.0	t=	0.041*
Mean ± SD.		109.2 ± 16.11		117.0 ± 15.94	2.082*	
Median (IQR)		105.0(95.0 – 126.0)		116.0(106.0 – 128.0)		
Lower limb edema						
No	1	2.6	0	0.0		
Mild	4	10.5	19	51.4	χ^2=	MCp
Moderate	29	76.3	15	40.5	15.671*	<0.001*
Marked	4	10.5	3	8.1		

IQR: Inter quartile range.SD: Standard deviation. t: Student t-test, χ^2: Chi-square test. MC: Monte Carlo. U: Mann Whitney test, p: p-value for comparing the studied groups: Statistically significant at $p \leq 0.05$, Group I: Refractory ascites on standard treatment, Group II: refractory ascites on standard treatment plus Midodrine.*

Regarding body weight, there was no significant difference between the two studied groups at baseline. Still, there was a substantial decrease in average body weight among midodrine group patients, which did not happen in control patients(P<0.001) **(Tab 3).**

As regards abdominal circumference, it was found that there was a significant difference between the two groups, with more reduction in average abdominal girth in midodrine patients than in control patients(P<0.001) **(Tab 3).**

As regards lower limb edema, there was a significant decrease in both groups at the end of the study compared to baseline (P<0.001) **(Tab 2).** However, this decrease was significantly apparent in midodrine patients than in control patients **(Tab 3).**

Table 3. Comparison between the study's start and end according to general examination in groups I and II.

	Group I					
	The start (n = 37)		The end (n = 37)		Test of Sig.	p
General examination	No.	%	No.	%		
Conscious level						
No hepatic encephalopathy	31	83.8	35	94.6		
Hepatic encephalopathy	6	16.2	2	5.4		
Frequency of tapping (month)						
Min. – Max.	0.0 – 3.0		0.0 – 2.0		Z=	0.002*
Mean ± SD.	1.49 ± 0.77		0.92 ± 0.60		3.084*	
Median (IQR)	1.0(1.0 – 2.0)		1.0(1.0 – 2.0)			
Body weight						
Min. – Max.	70.0 – 120.0		63.0 – 120.0			
Mean ± SD.	92.51 ± 12.09		91.65 ± 12.82		t=	0.234
Median (IQR)			92.0(86.0 – 101.0)		1.210	
	92.0 (86.0 – 100.0)					

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Abdominal girth

Min. – Max.	86.0 – 139.0		84.0 – 138.0		t= 1.182	0.245
Mean ± SD.	109.70 ± 16.73		109.2 ± 16.11			
Median (IQR)	106.0 (95.0 – 125.0)		105.0(95.0 – 126.0)			

Lower limb edema

No	0	0.0	1	2.6		
Mild	0	0.0	4	10.5		
Moderate	22	59.5	29	76.3	MH= 40.0[*]	<0.001[*]
Marked	15	40.5	4	10.5		

	Group II					
	The start		The end			
General examination	(n = 37)		(n = 37)		Test of Sig.	P
	No.	%	No.	%		
Conscious level						
No hepatic encephalopathy	29	78.4	35	49.6		
Hepatic encephalopathy	8	21.6	2	5.4		
Frequency of tapping (month)						
Min. – Max.	0.0 – 4.0		0.0 – 2.0			
Mean ± SD.	1.81 ± 1.20		0.59 ± 0.55		Z=4.542[*]	<0.001[*]
Median (IQR)	2.0(1.0 – 2.0)		1.0(0.0 – 1.0)			
Body weight						
Min. – Max.	66.0 – 117.0		65.0 – 116.0			
Mean ± SD.	88.54 ± 13.36		86.0 ± 13.04		t= 5.946[*]	<0.001[*]
Median (IQR)	88.0 (77.0 – 95.0)		86.0(77.0 – 91.0)			
Abdominal girth						
Min. – Max.	89.0 – 149.0		84.0 – 145.0			
Mean ± SD.	119.57 ± 16.40		117.0 ± 15.94		t= 6.274[*]	<0.001[*]
Median (IQR)	118.0(106.0 – 134.0)		116.0(106.0 – 128.0)			
Lower limb edema						
No	0	0.0	0	0.0		
Mild	0	0.0	19	51.4	MH= 50.0[*]	<0.001[*]
Moderate	23	62.2	15	40.5		
Marked	14	37.8	3	8.1		

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Regarding blood pressure, it was found that both systolic and diastolic blood pressure were higher in midodrine patients at the end of the study(P<0.001).

There was no significant difference between the two studied groups either at baseline or at the end of the study regarding hemoglobin level, total leucocytic count, serum Na level, serum K level, total bilirubin, serum creatinine, blood urea, and serum albumin, ALT, AST and INR (**Tab 4**).

Tab 4. Comparison between the two groups according to the laboratory data at the end of the study.

Lab (at the end)	Group I (n = 37)	Group II (n = 37)	Test of Sig.	P
Serum creatinine				
Min. – Max.	0.80 – 2.0	0.60 – 2.30	U= 618.50	0.472
Mean ± SD.	1.24 ± 0.30	1.20 ± 0.40		
Median (IQR)	1.20(1.0 – 1.4)	1.10(1.0 – 1.3)		
Urea				
Min. – Max.	26.0 – 170.0	16.0 – 200.0	U= 618.00	0.472
Mean ± SD.	56.94 ± 24.93	68.16 ± 40.30		
Median (IQR)	48.0(44.0 – 65.0)	53.0(40.0 – 98.0)		
Albumin				
Min. – Max.	2.20 – 3.20	2.0 – 3.50	U= 669.00	0.866
Mean ± SD.	2.61 ± 0.27	2.63 ± 0.33		
Median (IQR)	2.50(2.4 – 2.8)	2.50(2.4 – 2.7)		
Alanine transaminase				
Min. – Max.	12.0 – 150.0	12.0 – 88.0	U= 572.50	0.225
Mean ± SD.	41.73 ± 26.84	34.68 ± 17.77		
Median (IQR)	36.0(24.0 – 45.0)	28.0(22.0 – 43.0)		
Aspartate transaminase				
Min. – Max.	15.0 – 450.0	16.0 – 164.0	U= 628.50	0.544
Mean ± SD.	66.86 ± 74.22	54.11 ± 28.52		
Median (IQR)	45.0(38.0 – 66.0)	44.0(38.0 – 64.0)		
International normalized ratio				
Min. – Max.	1.0 – 1.90	1.20 – 2.50	t= 0.762	0.449
Mean ± SD.	1.56 ± 0.22	1.61 ± 0.26		
Median (IQR)	1.60(1.5 – 1.8)	1.60(1.4 – 1.7)		
Hemoglobin				
Min. – Max.	7.90 – 12.80	8.0 – 13.0	U= 1.752	0.085
Mean ± SD.	9.49 ± 0.90	9.95 ± 1.32		
Median (IQR)	9.50(9.0 – 10.0)	9.50(9.2 – 10.7)		
Platelets				
Min. – Max.	42.0 – 126.0	44.0 – 442.0	t= 2.079	0.044*
Mean ± SD.	90.62 ± 19.48	122.0 ± 89.73		
Median (IQR)	89.0(75.0 – 105.0)	92.0(82.0 – 108.0)		
Total leucocytic count				
Min. – Max.	1.90 – 12.0	2.80 – 10.80	U= 678.50	0.948
Mean ± SD.	6.74 ± 2.87	6.49 ± 2.44		
Median (IQR)	6.50(4.4 – 9.2)	5.30(4.8 – 8.2)		
24-hour urine volume				
Min. – Max.	800.0 – 1900.0	1000.0 – 2500.0	U= 421.50	0.004*
Mean ± SD.	1264.9 ± 311.1	1527.0 ± 384.2		
Median (IQR)	1200.0 (1000.0 – 1500.0)	1500.0 (1200.0 – 1600.0)		
Serum Na				

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Min. – Max.	118.0 – 137.50	116.0 – 137.0	t= 0.011	0.992
Mean ± SD.	127.0 ± 5.25	127.0 ± 5.72		
Median (IQR)	128.0(122.0 – 130.0)	128.0(125.0 – 130.0)		
Serum K				
Min. – Max.	2.80 – 5.60	3.20 – 5.80	t= 1.678	0.098
Mean ± SD.	4.05 ± 0.67	4.31 ± 0.68		
Median (IQR)	4.0(3.7 – 4.2)	4.40(3.7 – 4.9)		
Urinary Na				
Min. – Max.	12.0 – 112.0	16.0 – 360.0	U= 278.00*	<0.001*
Mean ± SD.	31.73 ± 22.90	82.70 ± 68.12		
Median (IQR)	22.50(18.0 – 35.0)	72.0(32.5 – 125.0)		
Total Bilirubin				
Min. – Max.	1.20 – 7.50	0.80 – 10.70	U= 528.500	0.091
Mean ± SD.	3.26 ± 1.66	2.82 ± 2.17		
Median (IQR)	2.50(2.0 – 4.5)	2.10(1.8 – 3.0)		

*IQR: Inter quartile range. SD: Standard deviation, t: Student t-test. U: Mann Whitney test, p: p-value for comparing the studied groups *: Statistically significant at p ≤ 0.05.*

There was no significant difference between groups as regards urine volume and urinary Na level at baseline **(Tab 1)**. Still, there was a substantial increase in both values in midodrine group patients than in control group patients at the end of the month of the study (P<0.001) **(Tab 5).**

Tab 5. Comparison between the study's start and end in groups I and II according to laboratory data.

	Group I			
Lab	**The start** **(n = 37)**	**The end** **(n = 37)**	**Test of Sig.**	**p**
Serum creatinine				
Min. – Max.	0.80 – 1.60	0.80 – 2.0	Z= 2.310*	0.021*
Mean ± SD.	1.12 ± 0.23	1.24 ± 0.30		
Median (IQR)	1.10 (1.0 – 1.20)	1.20(1.0 – 1.4)		
Urea				
Min. – Max.	2.40 – 135.0	26.0 – 170.0	Z= 0.752	0.452
Mean ± SD.	53.96 ± 24.04	56.94 ± 24.93		
Median (IQR)	45.0 (42.0 – 65.0)	48.0(44.0 – 65.0)		
Albumin				
Min. – Max.	1.80 – 3.20	2.20 – 3.20	Z= 1.007	0.314
Mean ± SD.	2.65 ± 0.31	2.61 ± 0.27		
Median (IQR)	2.70 (2.40 – 2.80)	2.50(2.4 – 2.8)		
Alanine transaminase				
Min. – Max.	12.0 – 112.0	12.0 – 150.0	Z= 1.319	0.187
Mean ± SD.	37.46 ± 21.15	41.73 ± 26.84		
Median (IQR)	33.0 (22.0 – 45.0)	36.0(24.0 – 45.0)		
Aspartate transaminase				
Min. – Max.	18.0 – 125.0	15.0 – 450.0	Z= 0.327	0.743
Mean ± SD.	53.57 ± 26.30	66.86 ± 74.22		
Median (IQR)	45.0 (39.0 – 72.0)	45.0(38.0 – 66.0)		
International normalized ratio				
Min. – Max.	1.20 – 2.0	1.0 – 1.90	t= 0.687	0.496
Mean ± SD.	1.59 ± 0.21	1.56 ± 0.22		
Median (IQR)	1.60 (1.40 – 1.80)	1.60(1.5 – 1.8)		
Hemoglobin				
Min. – Max.	6.90 – 12.0	7.90 – 12.80	t= 0.475	0.638
Mean ± SD.	9.58 ± 1.09	9.49 ± 0.90		

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Lab			Test of Sig.	p
Median (IQR)	9.60 (8.90 – 10.20)	9.50(9.0 – 10.0)		
Platelets				
Min. – Max.	46.0 – 160.0	42.0 – 126.0	t=	0.737
Mean ± SD.	89.24 ± 22.34	90.62 ± 19.48	0.338	
Median (IQR)	85.0 (75.0 – 104.0)	89.0(75.0 – 105.0)		
Total leucocytic count				
Min. – Max.	2.30 – 11.0	1.90 – 12.0	Z=	0.838
Mean ± SD.	6.56 ± 2.54	6.74 ± 2.87	0.204	
Median (IQR)	6.20 (4.70 – 8.0)	6.50(4.4 – 9.2)		
24-hour urine volume				
Min. – Max.	800.0 – 1600.0	800.0 – 1900.0	Z=	0.054
Mean ± SD.	1137.84 ± 256.42	1264.9 ± 311.1	1.924	
Median (IQR)	1200.0 (1000.0 – 1200.0)	1200.0 (1000.0 – 1500.0)		
Serum Na				
Min. – Max.	116.0 – 137.0	118.0 – 137.50	t=	0.142
Mean ± SD.	128.59 ± 5.18	127.0 ± 5.25	1.500	
Median (IQR)	129.0 (126.0 – 132.0)	128.0(122.0 – 130.0)		
Serum K				
Min. – Max.	3.0 – 5.50	2.80 – 5.60	t=	0.675
Mean ± SD.	4.11 ± 0.57	4.05 ± 0.67	0.423	
Median (IQR)	4.0 (3.70 – 4.50)	4.0(3.7 – 4.2)		
Urinary Na				
Min. – Max.	10.50 – 90.0	12.0 – 112.0	Z=	0.053
Mean ± SD.	25.61 ± 17.69	31.73 ± 22.90	1.936	
Median (IQR)	22.0 (15.0 – 26.0)	22.50(18.0 – 35.0)		
Total Bilirubin				
Min. – Max.	0.90 – 8.0	1.20 – 7.50	Z= 0.707	0.480

	Group II			
Lab	**The start (n = 37)**	**The end (n = 37)**	**Test of Sig.**	**p**
Hemoglobin				
Min. – Max.	7.80 – 13.70	8.0 – 13.0	t=	0.486
Mean ± SD.	10.06 ± 1.31	9.95 ± 1.32	0.704	
Median (IQR)	9.80 (9.40 – 10.20)	9.50(9.2 – 10.7)		
Platelets				
Min. – Max.	40.0 – 492.0	44.0 – 442.0	t=	0.359
Mean ± SD.	130.27 ± 97.41	122.0 ± 89.73	0.928	
Median (IQR)	105.0 (73.0 – 143.0)	92.0 (82.0 – 108.0)		
Total leucocytic count				
Min. – Max.	2.0 – 19.50	2.80 – 10.80	Z=	0.264
Mean ± SD.	7.12 ± 3.79	6.49 ± 2.44	1.117	
Median (IQR)	6.30 (4.30 – 9.50)	5.30(4.8 – 8.2)		
24-hour urine volume				
Min. – Max.	800.0 – 2500.0	1000.0 – 2500.0	Z=	<0.001*
Mean ± SD.	1227.03 ± 350.91	1527.0 ± 384.2	4.643*	
Median (IQR)	1200.0 (1000.0 – 1400.0)	1500.0 (1200.0 – 1600.0)		
Serum Na				
Min. – Max.	117.50 – 138.0	116.0 – 137.0	t=	0.968
Mean ± SD.	126.99 ± 5.88	127.0 ± 5.72	0.040	
Median (IQR)	128.0 (122.0 – 131.0)	128.0(125.0 – 130.0)		
Serum K				
Min. – Max.	2.70 – 5.90	3.20 – 5.80	t=	0.124
Mean ± SD.	4.13 ± 0.76	4.31 ± 0.68	1.574	
Median (IQR)	3.90 (3.50 – 4.50)	4.40(3.7 – 4.9)		
Urinary Na				

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Min. – Max.	10.50 – 315.0	16.0 – 360.0	Z=	<0.001[*]
Mean ± SD.	42.97 ± 55.21	82.70 ± 68.12	4.156[*]	
Median (IQR)	29.0 (15.0 – 38.0)	72.0(32.5 – 125.0)		
Total Bilirubin				
Min. – Max.	0.60 – 19.0	0.80 – 10.70	Z=	0.466
Mean ± SD.	3.42 ± 3.59	2.82 ± 2.17	0.729	
Median (IQR)	2.10 (1.80 – 3.50)	2.10(1.8 – 3.0)		
Mean ± SD.	3.27 ± 1.94	3.26 ± 1.66		
Median (IQR)	2.30 (1.80 – 4.80)	2.50(2.0 – 4.5)		
Serum creatinine				
Min. – Max.	0.70 – 2.0	0.60 – 2.30	Z=	0.260
Mean ± SD.	1.14 ± 0.29	1.20 ± 0.40	1.127	
Median (IQR)	1.10 (1.0 – 1.30)	1.10(1.0 – 1.3)		
Urea				
Min. – Max.	22.0 – 120.0	0.60 – 2.30	Z=	0.208
Mean ± SD.	61.16 ± 30.01	1.20 ± 0.40	1.260	
Median (IQR)	54.0 (38.0 – 90.0)	1.10(40.0 – 98.0)		
Albumin				
Min. – Max.	1.80 – 3.30	2.0 – 3.50	Z=	0.612
Mean ± SD.	2.58 ± 0.37	2.63 ± 0.33	0.507	
Median (IQR)	2.50 (2.30 – 2.80)	2.50(2.4 – 2.7)		
Alanine transaminase				
Min. – Max.	10.0 – 112.0	12.0 – 88.0	Z=	0.441
Mean ± SD.	36.65 ± 23.57	34.68 ± 17.77	0.771	
Median (IQR)	31.0 (22.0 – 51.0)	28.0(22.0 – 43.0)		
Aspartate transaminase				
Min. – Max.	18.0 – 138.0	16.0 – 164.0	Z=	0.528
Mean ± SD.	56.16 ± 30.30	54.11 ± 28.52	0.632	
Median (IQR)	45.0 (37.0 – 72.0)	44.0(38.0 – 64.0)		
International normalized ratio				
Min. – Max.	1.0 – 2.10	1.20 – 2.50	t=	0.607
Mean ± SD.	1.59 ± 0.25	1.61 ± 0.26	0.519	
Median (IQR)	1.60 (1.40 – 1.80)	1.60(1.4 – 1.7)		

*IQR: **Inter quartile range.** SD: **Standard deviation, t: Paired t-test.** Z: **Wilcoxon signed ranks test,** p: p-value for comparing **Start** and **End** *: Statistically significant at p ≤ 0.05.*

Discussion:

The pathophysiology of cirrhotic ascites is that vasodilatation and hyperdynamic circulatory dysfunction induce the non-osmotic release of antidiuretic hormone, reflex activation of neurohormonal systems, and activation of the renin-angiotensin-aldosterone system (RAAS) with sodium and water retention. Large-volume paracentesis (LVP) is used in patients with cirrhosis and tense ascites. This leads to a decrease in adequate arterial blood volume and systemic vasodilation, and it is associated with impaired renal function and increased activity of the RAAS in approximately 80% of cases [4]. Previous studies demonstrated that using a vasoconstrictor may effectively prevent the hemodynamic changes caused by paracentesis-induced circulatory dysfunction (PICD). [10,11]

Midodrine hydrochloride, an α1-agonist, increases effective circulating blood volume and renal perfusion by increasing systemic and splanchnic blood pressure. [10]

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In the present study, both systolic and diastolic blood pressure were found to be higher on average in group II compared to group I at the end of the study, and this is attributed to vasoconstrictor effects of midodrine.

These results were supported by Rai et al., 2017[12], which used midodrine and tolvaptan on different groups. Also, the same results appeared in another study by Angeli et al., 1998[13], but it studied the acute effects of oral midodrine on the hemodynamics of cirrhotic patients. Another study by Tandon et al., 2009[10] showed the same results but used different doses of Midodrine.

Regarding body weight, it significantly decreased in the midodrine group at the end of the study.

Singh et al.,2012[14], Ali et al., 2014[15] and Obiedallah et al., 2017[16] agreed with our results.

 Other results appeared in another study, Kalambokis et al., 2007[11]; though the reduction in body weight was not statistically significant, the study was only for seven days.

There was a marked decline in tapping frequency in the midodrine group than in the control group. These findings contrast with those of similar research. Obiedallah et al., 2017[16] found no significant improvement in both frequency and volume of ascetic fluid drained after one month of use of midodrine plus standard medical therapy.

In our study, there was no discernible difference between the two groups regarding serum sodium and potassium at the end of the study. This agrees with Ali et al., 2016[17]and Obiedallah et al., 2017[16]. On the contrary, Singh et al., 2012[14] found that serum sodium reduced dramatically in the group receiving standard medical care. Serum sodium levels did not alter much in the midodrine group following therapy.

It also observed that hyponatremia is a frequent complication of diuretic therapy in these patients, which was also noted in our study, where the baseline serum sodium in both groups was 128.2 and 126.7, respectively. Patel et al., 2017[18] showed different results. They found that oral midodrine improves serum hyponatremia in cirrhotic patients, but this study was for only 72 hours, along with albumin infusion.

As regard urinary sodium levels showed clinical significance between the two studied groups, where it was higher in group II than in group I

Also, urinary sodium levels significantly increased in midodrine group patients between the study's start and end.

Our results agreed with Rai et al., 2017[12], which was conducted for a longer duration.

Also, Singh et al., 2012[14] revealed that midodrine considerably increased urinary sodium excretion After 1 and 3 months of therapy, but this effect was no longer seen after six months.

The same results appeared in Tandon et al., 2009[10], where there was only an increase in urine sodium level in the spot test at the middle of the study with no further increase toward its end. Angeli et al., 1998[19] studied the acute effects of midodrine on renal hemodynamics and agreed with our study. Although it studied the acute effects, it suggested that the natriuretic effects of midodrine reach a plateau after a period.

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The natriuretic effects of midodrine may be attributed to the suppression of the renin-angiotensin system (RAAS), as in Tandon et al., 2009[10].

On the other hand, natriuretic response to furosemide in patients with cirrhosis and ascites: effects of midodrine, which was discussed by Misra et al., 2010[20], disagreed with our results, claimed that there was no effect of midodrine in urine sodium level, but it was studying the acute effects of midodrine on IV furosemide for 6 hours only.

24-hour urine output was higher in the midodrine group than in the placebo group. Furthermore, it increased in the midodrine group from baseline to endpoint but remained stable in the control group throughout the study.

These results disagree with Ali et al., 2014[15], who found no difference in urine output in the midodrine and the placebo groups. However, it should be noted that this study was conducted for a shorter duration using smaller doses of midodrine. On the other hand, Singh et al., 2013[21], Obiedallah et al., 2017[16], and Rai et al., 2017[12] agreed with our results as regards the increase in urine output after the use of Midodrine.

We found no statistically significant difference in total bilirubin levels between the two groups from the study's beginning to end. Total bilirubin levels in the midodrine and control groups were also similar from the beginning to the completion of the research. Similar findings were seen for total bilirubin in studies by Kalambokis et al., 2007[11], Singh et al., 2012[14], and Obiedallah et al., 2017[16]. However, Tandon et al., 2009[10] reported that total bilirubin considerably rose after one month of therapy with midodrine, octreotide-LAR, and albumin but then recovered to baseline following one month of discontinuation of the medication.

Kalil et al., 2018[23] found that using midodrine was associated with worsening INR and total bilirubin, unlike our study. It should be noted that this study included patients waiting for only liver transplants.

There was no statistically significant difference between the groups regarding albumin level. Either at the beginning or the conclusion of the investigation. There was also no variation between the two groups during the study's duration. These results were supported by Kalambokis et al., 2007[11], Oda et al., 2011[24], Singh et al., 2013[21] and Ali et al., 2014[15].

On the contrary, Tandon et al., 2009[10] found that synthetic functions of the liver, including albumin, have been impaired with the use of midodrine despite using albumin infusion.

Nevertheless, this may be attributed to the addition of octreotide, which causes splanchnic vasoconstriction, reducing the portal pressure and hepatic perfusion.

Regarding serum creatinine statistically, we identified no distinguishing features between both groups at baseline and the end of the study. However, there was a slight increase in serum creatinine in the control group, unlike in the midodrine group.

This was the case, according to the research conducted by Kalambokis et al., 2005[25], Tandon et al., 2009[10], and Singh et al., 2012[14] where systemic hemodynamics improved, but renal function did not alter after treatment and the adequate circulating volume. On the other hand, Krag et al., 2007[26] suggested more improvement in renal functions using vasopressors such as

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terlipressin, considering that it assessed renal functions by GFR, which may be more accurate than serum creatinine.

Oda et al., 2011[24] looked at the effects of midodrine on blood flow in cirrhotic patients with and without ascites. They found that the drug improved renal hemodynamics in non-ascetic patients but did not affect patients with refractory ascites. However, a significant rebound in plasma renin activity was found after treatment with midodrine was discontinued. That is why an increase in renal vascular resistance, a decrease in renal blood flow, and a modest drop in glomerular filtration rate explain this. During this period, the sympathetic nervous system and the renin-angiotensin-aldosterone system are heavily activated.

Except for one incidence of severe epistaxis in which the patient stopped using midodrine, no adverse events related to the drug have been reported. In contrast, six patients out of 59 reported stomach pain when taking midodrine for six months Singh et al., 2012[14]. However, they were all relatively minor and did not necessitate a break in treatment. Similar findings were seen in a study by Rai et al., 2017[12], in which only 2 of 13 individuals experienced moderate stomach discomfort that did not necessitate therapy termination.

One of the limitations was the small sample size of our investigation, short duration, and the dosage form (3 tablets /8 hours), which was an obstacle to the compliance of many patients.

Conclusion: The addition of midodrine to SMT is linked to more effective therapeutic management of ascites (reduction of body weight, abdominal circumference) as well as lower limb edema and laboratory (increase of urine volume and urine Na level), and it is considered safe for patients with liver cirrhosis with little side effects.

Footnotes.

Peer-Reviewers: Amr Shaaban Hanafy (professor of internal medicine), Nabila Hassan (professor of tropical medicine), Mohamed Emara (professor of gastroenterology, hepatology, and infectious diseases).

E- Editor: Salem Youssef Mohamed, Osama Ahmed Khalil.

Ethics Approval and Consent to Participate: All procedures followed were by the ethical standards of the responsible committee on human experimentation (Institutional

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Review Board (IRB)" (34461/2/2021) of Tanta University and with the Helsinki Declaration of 1964 and later versions.

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