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ORIGINAL ARTICLE

Value of Midodrine in Management of Refractory Ascites due to Liver Cirrhosis

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ABSTRACT

Background: Patients with ascites, hepatorenal syndrome, or both who have reduced plasma renin activity can benefit from midodrine, which is an α1-adrenergic agonist, by increasing the effective arterial blood volume by splanchnic vasoconstriction and decreasing nitrite as well as nitrate activity. This study aimed to assess the efficacy of midodrine in management of refractory ascites due to liver cirrhosis.

Methods: The present case-control study included 100 patients who had refractory ascites due to liver cirrhosis. They were divided into 2 groups (50 each): The control group who received standard medical treatment (SMT), and the midodrine group who received SMT in addition to midodrine. Ascitic fluid study for calculation of SAAG and exclusion of spontaneous bacterial peritonitis was done for all participants. Patients were followed up one month of treatment.

Results: After 1-month, mean values of body weight, paracentesis frequency, furosemide and spironolactone doses, S.creatinine were decreased significantly, mean arterial blood pressure and eGFR was significantly increased, among midodrine group (P<0.001). At cutoff value equal to 15 mg/ day, midodrine played a role in protection against hepatorenal syndrome. After 1 week a statistically significant positive correlation was revealed between midodrine dose and mean arterial blood pressure (p<0.001), After 1 month, statistically significant negative correlations were revealed between midodrine dose and body weight, paracentesis frequency and diuretic doses (p<0.001). Also, a statistically significant positive correlation was found between midodrine dose and mean arterial blood pressure (p<0.05).

Conclusions: The addition of midodrine to standard medical treatment (salt restriction and diuretics) has an important role in managing the refractory ascites with protection against hepatorenal syndrome at dose 15mg/day. So, it is considered safe adjuvant treatment for patients who had refractory ascites due to liver cirrhosis with little side effects.

Keywords: Midodrine; Refractory ascites; liver cirrhosis.

INTRODUCTION

Fibrogenesis and angiogenesis are correlated with liver cirrhosis, a significant outcome of chronic liver disease (CLD). Ascites and other consequences of liver cirrhosis are caused by portal hypertension (PHT) and impaired hepatocyte activity [1].

Within a decade of a cirrhosis diagnosis, ascites develops in around half of all patients, making it the most common complication of the disease. When other treatment options fail or

are not feasible, some cases with tense ascites need large-volume paracentesis (LVP) to alleviate their symptoms [2].

Refractory ascites is defined as ascites that is resistant to high-dose diuretic treatment and/or sodium restriction or redevelops rapidly after paracentesis. A failure of diuretic treatment is when the patient is unable to excrete enough salt in their urine (<78 mmol per day) or when diuretic problems such as hepatic encephalopathy, renal failure, or hyponatremia occur [3].

A wide variety of treatment options are available for refractory ascites, including medicinal management, transjugular intrahepatic portosystemic shunts, implanted drainage devices, serial large volume paracenteses, and others [4].

Major contributors to ascites development include portal hypertension and splanchnic vasodilatation. Vasodilation of the splanchnic arteries leads to more pronounced arterial underfilling and the permanent activation of the sodium-retaining mechanisms [5].

Hepatorenal syndrome patients may benefit from vasopressors. The use of vasopressors to avoid circulatory dysfunction after paracentesis has also been attempted, with varying degrees of success. The use of different vasoconstrictors has recently been demonstrated to improve renal function, salt excretion, and circulatory function in non-azotemic cirrhotic patients with ascites [6].

Midodrine enhances the effective arterial blood volume through splanchnic vasoconstriction, and it enhances renal perfusion and glomerular filtration. It is an α1-adrenergic agonist. In patients with ascites and reduced plasma renin activity and antidiuretic hormone levels, midodrine reduced nitrite and nitrate activity. This effect was observed in patients without hepatorenal syndrome as well, this mechanism could be the cause for decreasing both portal pressure and the ascitic fluid accumulation [7].

For this debate about, we did this research to assess the efficacy of midodrine in management of refractory ascites due to liver cirrhosis.

METHODS

This case-control study was done in Tropical Medicine Department at Zagazig University Hospitals and El Ahrar Teaching Hospital on 100 patients with refractory ascites due to liver cirrhosis for 6 months, during the period from June 2023 to December 2023. It has been approved from our Institutional Research Board – (IRB#9068/15-11-2021). Moreover, patients' written consent was obtained.

Inclusion criteria: Patients who had refractory ascites due to liver cirrhosis. They were diagnosed according to clinical, lab and ultrasonographic finding of cirrhosis. Refractory ascites is characterized by the inability to mobilize the ascites or by its early recurrence after therapeutic paracentesis and cannot be satisfactorily prevented by medical therapy [3].

The 100 patients were divided into two equal groups (50 subjects in each): Control Group: patients on standard medical treatment and large volume paracentesis as needed. Midodrine Group: patients who received standard medical treatment in addition to the midodrine tolerable dose 5–10 mg every 8 hours to keep the average blood pressure 10 mm Hg higher than the baseline [8].

***Exclusion criteria*:** Ascites of non-hepatic causes, Spontaneous bacterial peritonitis or other infection before the study, hepatic encephalopathy grade 2 or more before the study, as well as of patients who had hepatocellular carcinoma (HCC) or other malignancies, portal vein thrombosis, Hepatorenal syndrome before the study, cardiovascular disease or systemic hypertension or diabetes, and those who were on treatment with drug known with effects on systemic and renal hemodynamics within 7 days before inclusion as prostaglandins inhibitors as NSAIDs (non-steroidal anti-inflammatory drugs), beta blockers and angiotensin converting enzyme Inhibitors.

All the included patients were subjected to full history taking, dose of midodrine in group 2

and frequency of indicated paracentesis and general and local examination was done on all participants. Complete physical examination: Mean arterial blood pressure which is calculated through this equation: 1/3(SBP)+2/3(DBP) Diastolic blood pressure (DBP) and systolic blood pressure (SDP) values [9]. Glomerular filtration rate was assessed using Modification of Diet in Renal disease (MDRD) equation [10].

Laboratory investigations were done (Complete blood count, Coagulation profile, INR, Liver, and kidney function test, Ascetic fluid study for calculation of SAAG and exclusion of spontaneous bacterial peritonitis, Serum creatinine, MELD-Na score, and Urine analysis).

Ultrasonographic examination of abdomen and pelvis was done for diagnosis of cirrhosis, ascites and exclusion of HCC, portal vein thrombosis and chronic medical diseases of kidney.

Statistical Analysis

Version 26 of SPSS was used for tabulating the data. We used percentages and numbers to represent our categorical data. Mean +/- standard deviation (SD) was used to display continuous, normally distributed data. Median and range were used to express data that did not follow a normal distribution. Statistical tests were employed that were suitable for the type of data: When comparing two groups' regularly distributed data, we utilized the Student t-test, and when comparing categorical data, we used the chi-square test. ANOVA test was utilized for continuous data at different time points. The diagnostic accuracy of midodrine dosages was evaluated using a receiver operator characteristics test. For the purpose of multivariate analysis, Binary Logistic regression was employed.

RESULTS

Non statistically significant differences were revealed between both groups as regards age, sex distribution, body weight, mean arterial blood pressure, paracentesis frequency, and furosemide, spironolactone doses at baseline, baseline investigations and ultrasonographic findings (Table 1).

After 1 week, mean arterial blood pressure was increased significantly among study group with significant lowering of Spironolactone and furosemide dose when compared with control group ($p<0.001$) (Table 2).

After 1-month, mean values of body weight, paracentesis frequency, furosemide and spironolactone doses were decreased significantly and mean arterial blood pressure was significantly increased among midodrine group ($p<0.05$), S. creatinine was significantly lower and eGFR was significantly higher among the midodrine group ($p=0.003$) Statistically significant difference between both groups were revealed regarding hepatorenal syndrome was statistically lower in midodrine group ($p=0.03$). Statistically significant difference was revealed between both groups regarding ascites with higher frequency of marked ascites among control group than midodrine group ($p<0.001$)(Table 3).

In the midodrine group**,** statistically significant difference was revealed in clinical data over one month, where there were significant increases in mean arterial blood pressure while there were significant decreases in paracentesis frequency, doses of diuretics and midodrine dose ($p<0.001$) (Table 4).

At cutoff value equal to 15 mg/ day after 1 week, midodrine played a role in protection against hepatorenal syndrome**.** Also, at cutoff value equal to 15 mg/ day after 1 month (Figure 1A, B). Analysis of risk factors for SBP showed that rise of serum bilirubin increased the odds for SBP with odd ratio (OR) of 2.43, 95% Confidence interval (CI) of -1.47 to -0.19, p value of 0.010. Other factors did not show statistically significant effect, Analysis of risk factors for hepatic encephalopathy showed that rise of total leucocyte count in ascitic fluid increased odds for hepatic encephalopathy (OR=1.010, 95% CI=1.15-4 to 0.0201 , p=0.047) (Table 5).

After 1 week statistically significant positive correlation was revealed between midodrine

dose and mean arterial blood pressure ($p<0.05$). After 1 month, statistically significant negative correlations were found between midodrine dose and body weight, paracentesis frequency *and* diuretic doses ($p<0.05$) (Table 6).

Table (1): Comparison between the 2 groups regarding demographics characteristics, baseline clinical data, Ascitic fluid, baseline investigations, and baseline ultrasonography findings of studied group.

	Control group	Midodrine group	Test of significance	P value
Age (years) Mean ± SD	63.38 ± 9.7	65.32 ± 10.3	(t) 0.31	0.45
Sex No. (%) - Male - Female	38 (76%) 12 (24%)	35(70%) 15 (30%)	X^2= 0.1	0.3
Body weight (Kg)	82.59 ± 5.5	83.1 ± 4.98	-0.5	0.69
Mean arterial blood pressure (mmHg)	63.6 ± 4.85	64.2 ± 7.5	-1.4	0.37
Number of paracentesis/ weeks	0.6 ± 0.23	0.6 ± 0.33	0.01	0.54
Furosemide dose (mg)	88.8 ± 36.4	96 ± 19.8	1.23	0.22
Spironolactone dose (mg)	212 ± 91.8	221.6 ± 76.1	0.57	0.57
Total leucocytic count (cell/ mm^3)	166.2 ± 79.1	174.5 ± 80.1	0.02	0.5
Total protein (g/dL)	1.76 ± 0.62	1.68 ± 0.65	0.613	0.54
Serum ascites albumin gradient (SAAG)	1.87 ± 0.36	1.86 ± 0.3	0.001	0.99
WBC($10^3/mm^3$)	6.7 ± 1.64	6.8 ± 1.5	(t) -0.39	0.69
Platelets ($10^3/mm^3$)	60.9 ± 13.29	62.4 ± 13.68	(t) -0.56	0.58
Hemoglobin (g/dL)	8.3 ± 0.93	8.4 ± 0.98	(t) -0.21	0.83
S. creatinine (mg/dL)	1.08 ± 0.19	1.1 ± 0.75	(t) -0.62	0.53
eGFR	49.79 ± 27.9	48.53 ± 26.8	(t) 0.23	0.82
ALT(IU/L)	15.13 ± 5.8	17.16 ± 4.9	(t) 0.001	0.85
AST(IU/L)	33.3 ± 10.34	32.05 ± 8.9	(t) 0.001	0.85
S. bilirubin (mg/dL)	3.08 ± 1.23	3.17 ± 0.95	(t) 0.38	0.7
S. albumin (g/dL)	2.39 ± 0.39	2.4 ± 0.38	(t) -0.18	0.85
INR	1.64 ± 0.2	1.67 ± 0.24	(t) 1.48	0.14
Sodium (mEq/L)	127.2 ±1.67	128.3 ±1.89	(t) 0.30	0.38
Potassium (mEq/L)	3.8 ± 0.49	3.86 ± 0.43	(t) -0.64	0.52
Hematuria	0 (0%)	0 (0%)	X^2= 0.7	0.99
Proteinuria	0 (0%)	0 (0%)	X^2=0.7	0.99
MELD. Na	20.56 ± 2.4	19.74 ± 2.66	(t) 1.65	0.1
ECG -Normal	50 (100%)	50 (100%)	X^2= 0.001	0.85
Baseline ultrasonography findings				
Liver				
Shrunken Cirrhotic	50 (100%)	50 (100%)	$X^{2=}$ 0.001	0.85
Spleen				
- Splenomegaly - Splenectomy	45 (90%) 5 (10%)	46 (92%) 4 (8%)	$X^{2=}$ 0.1	0.33
Ascites				
- Moderate - Marked	5 (10%) 45 (90%)	8 (16%) 42 (84%)	$X^{2=}$ 1.23	0.7
Renal US				
Normal	50 (100%)	50 (100%)	$X^{2=}$ 0.001	0.85
Portal vein diameter (mm)	15± 2.1	14± 1.1	(t) 0.87	0.33

(t) Student t- test; (X^2) Chi- square test

Table (2): Clinical data, Laboratory investigations, after 1 week.

	Control group Mean ± Sd	Midodrine group Mean ± SD	(t)	P value
Body weight (Kg)	81.7 ± 5.49	82.1 ± 4.9	-0.4	0.69
Mean arterial blood pressure (mmHg)	58.6 ± 4.8	74.2 ± 7.5	-12.33	*<0.001*
Number of paracentesis/ weeks	0.59 ± 0.13	0.62 ± 0.24	-0.47	0.64
Furosemide dose (mg)	98.8 ± 26.4	91 ± 16.7	-4.6	*<0.001*
Spironolactone dose (mg)	218 ± 89.78	201.7 ± 76	-3.5	*<0.001*
WBC ($10^3/mm^3$)	7.58 ± 1.5	7.6 ± 1.6	0.001	0.85
Platelets ($10^3/mm^3$)	73.8 ± 12.3	73.9 ± 12.1	0.001	0.85
Hemoglobin (g/dL)	8.8± 0.93	8.8 ± 0.98	-0.209	0.83
S. creatinine (mg/dL)	1.3 ± 0.7	1.2 ± 0.82	-0.86	0.39
eGFR	44.79 ± 27.9	43.5 ± 26.5	0.23	0.818
AST (IU/L)	22.1 ± 5.8	22.6 ± 4.9	0.001	0.85
ALT (IU/L)	36.7 ± 8.5	35.9 ± 7.4	0.001	0.85
S. bilirubin (g/dL)	3.64± 0.74	3.5 ± 0.62	0.96	0.34
S. albumin (g/dL)	2.58 ± 0.39	2.6± 0.38	-0.17	0.86
INR	1.29 ± 0.37	1.18 ± 0.32	1.58	0.12
Sodium (mEq/L)	127 ± 2.5	128 ± 2.6	1.13	0.33
Potassium (mEq/L)	3.7 ± 0.4	3.82 ± 0.38	-1.3	0.19
MELD. Na	20.69± 2.14	19.8± 2.6	1.06	0.3

(t) Student t- test

Table (3): Clinical data, Laboratory investigations and Ultrasonography after 1 month.

	Control group Mean ± Sd	Midodrine group Mean ± SD	(t)	P value
Body weight (Kg)	80.65 ± 6.027	78.8 ± 5.13	2.1	*0.04*
Mean arterial blood pressure (mmHg)…	62.1 ± 5.05	87.1 ± 5.57	-20.79	*<0.001*
Number of paracentesis / weeks	0.58 ± 0.25	0.4 ± 0.19	2.69	*0.008*
Furosemide dose (mg)	94.2 ± 36.4	82 ± 19.62	8.054	*<0.001*
Spironolactone dose (mg)	220 ± 91.78	170.3 ± 76.01	6.5	*<0.001*
WBC($10^3/mm^3$)	8.2 ± 3.4	8.18 ± 3.1	0.073	0.942
Platelets ($10^3/mm^3$)	58.8 ± 12.25	59.32 ± 12.3	-0.2	0.839
Hemoglobin (g/dL)	8.3± 0.98	8.3± 0.93	0.209	0.835
S. creatinine (mg/dL)	1.8± 1.2	1.4 ± 1.28	-6.728	0.003
eGFR	41.29 ± 3.8	49.2 ± 4.3	1.39	0.03
ALT (IU/L)	17.16 ± 5.8	17.2 ± 5.7	0.001	0.85
AST(IU/L)	31.7 ± 8.5	31.2 ± 8.6	0.001	0.85
S. bilirubin (g/dL)	3.4 ± 0.61	3.35 ± 0.62	0.704	0.48
S. albumin (g/dL)	2.4± 0.38	2.38 ± 0.39	0.179	0.86
INR	1.83 ± 0.4	1.98 ± 0.6	0.11	0.906
Sodium (mEq/L)	126.5 ±2.05	128.8 ± 3.18	-1.8	*0.3*
Potassium (mEq/L)	3.8 ± 0.37	3.86 ± 0.43	-0.44	0.65
MELD. Na.	21.1 ± 2.035	20± 2.33	1.09	0.8
Spontaneous bacterial peritonitis	10 (20%)	7 (14%)	0.64	0.4
Hepatorenal syndrome	11 (22%)	3 (6%)	2.87	0.03
Hepatic encephalopathy	5 (10%)	7 (14%)	0.38	0.54

Ultrasonographic findings				
Ascites (X^2)				
- Moderate - Marked	10 (20%) 40 (80%)	22 (44%) 23 (56%)	14.06	<0.001
1. Portal vein diameter (mm) (t)	16± 1.1	13±0.9	0.89	*0.30*

(t) Student t- test; (X2) Chi- square test

Table (4): Clinical data and Laboratory investigations changes over 1 month in midodrine group.

	baseline	After 1 week	After 1 month	P value
Body weight (Kg)	83.1 ± 4.98	82.1 ± 4.9	78.8 ± 5.13 [a, b]	<0.001
Mean arterial blood pressure (mmHg)	64.2±7.5	74.2 ± 7.5 [a]	87.1 ± 5.57 [a, b]	<0.001
Paracentesis frequency (/ week)	0.62±0.33	0.62 ± 0.24	0.4 ± 0.19 [a, b]	<0.001
Furosemide dose (mg)	96 ± 19.79	91 ± 16.7 [a]	82 ± 19.62 [a, b]	<0.001
Spironolactone (mg)	221.6 ± 76.1	201.7 ± 76 [a]	170.3 ± 76.01 [a, b]	<0.001
Midodrine (mg)	15.6 ± 5.6	13.5 ± 6.8	10.1 ± 4.18 [a, b]	<0.001
WBC ($10^3/mm^3$)	6.8 ± 1.5	7.6 ± 1.6	8.18 ± 3.1	0.16
Platelets ($10^3/mm^3$)	62.4 ± 13.68	73.9 ± 12.1	59.32 ± 12.3	0.09
Hemoglobin (g/dL)	8.4 ± 0.98	8.8 ± 0.98	8.3 ± 0.93	0.45
s. creatinine (mg/dL)	1.1 ± 0.75	1.2± 0.82	1.4± 1.28	0.06
eGFR	48.53 ± 26.8	43.5± 26.5	49.2± 4.3	0.7
Alanine aminotransferase (IU/L)	17.16 ± 4.9	22.6 ± 4.9	17.2 ± 5.7	0.7
Aspartate aminotransferase (IU/L)	32.05 ± 8.9	35.9 ± 7.4	31.2 ± 8.6	0.45
S. bilirubin (g/dL)	3.17 ± 0.95	3.5± 0.62	3.35 ± 0.62	0.33
S. albumin (g/dL)	2.4 ± 0.38	2.5 ± 0.38	2.38 ± 0.39	0.36
INR	1.67 ± 0.24	1.18± 0.32	1.33± 0.6	0.4
Sodium (mEq/L)	128.3± 1.89	128± 2.6	127.2± 3.18	*0.34*
Potassium (mEq/L)	3.8 ± 0.49	3.82 ± 0.38	3.86 ± 0.43	0.3
MELD. Na	19.74 ± 2.66	19.8± 2.6	20.35± 1.89	0.087

(F) Analysis of variance (ANOVA) test; level of significance (a, b) post- hoc analysis; (a) Significance against baseline (b) Significance against after 1 week

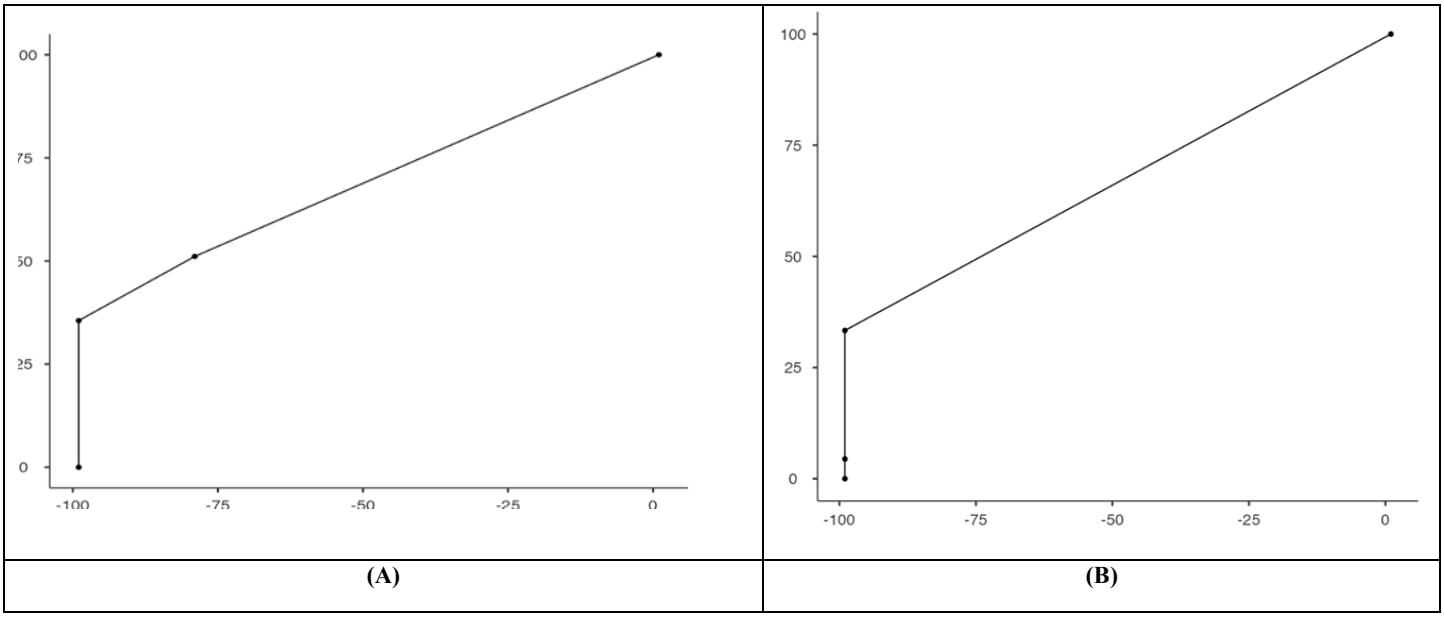
Table (5): Multivariate analysis to detect predictors for hepatorenal syndrome, spontaneous bacterial peritonitis, hepatic encephalopathy.

predictors for hepatorenal syndrome					
Predictor	Estimate	95% confidence interval		Odds ratio	P value
		Lower	Upper		
MAP	-0.08	-0.23	0.065	1.08	0.270
Paracentesis.frequecny	34.6	-9544.42	9613.77	8.7	0.994
Sodium	0.79	-1.7	3.27	0.45	0.534
Total leucocytic count	-1.036	-2.07	0.002	2.82	*0.050*
serum.bilirubin	2.67	0.83	4.51	1.9	*0.004*
TLC in ascites	0.017	-2.99	0.035	0.98	0.054
Midodrine dose	0.26	0.056	0.47	0.77	*0.013*
Furosemide dose	-0.26	-0.63	0.11	1.3	0.167
Spironolactone dose	0.077	-0.06	0.22	0.93	0.290

Predictors for spontaneous bacterial peritonitis					
Predictor	**Estimate**	**95% confidence interval**		**Odds ratio**	**P value**
		Lower	**Upper**		
MAP	**-0.11**	**-0.23**	**0.013**	**0.89**	**0.08**
Paracentesis.frequecny	**-0.89**	**-3.19**	**1.39**	**0.41**	**0.44**
Total leucocytic count	**0.02**	**-0.39**	**0.43**	**1.02**	**0.92**
serum.bilirubin	**-0.83**	**-1.47**	**-0.19**	**2.43**	***0.010***
TLC in ascites	**0.003**	**-0.004**	**0.019**	**1.004**	**0.36**
Midodrine dose	**0.017**	**-0.05**	**0.09**	**1.018**	**0.64**
Furosemide dose	**-0.42**	**-81.04**	**80.19**	**0.65**	**0.99**
Spironolactone dose	**0.162**	**-32.08**	**32.41**	**1.176**	**0.99**
predictors for hepatic encephalopathy					
Predictor	**Estimate**	**95% confidence interval**		**Odds ratio**	**P value**
		Lower	**Upper**		
MAP	**0.10446**	**0.00216**	**0.2068**	**1.110**	**0.045**
Paracentesis.frequecny	**-34.57760**	**-6733.60130**	**6664.4461**	**1.3**	**0.992**
Potassium	**-0.08441**	**-1.58868**	**1.4199**	**0.919**	**0.912**
Total leucocytic count	**-0.04560**	**-0.49794**	**0.4067**	**0.955**	**0.843**
serum.bilirubin	**0.53334**	**-0.22145**	**1.2881**	**1.705**	**0.166**
TLC in ascites	**0.01010**	**1.15-4**	**0.0201**	**1.010**	***0.047***

Table (6): Correlation analysis of midodrine dose and other parameters.

	Correlation coefficient	**P value**
After 1 week		
Body weight	**-0.13**	**0.36**
Mean arterial blood pressure	**0.889**	***<0.001***
Paracentesis frequency	**0.13**	**0.34**
Furosemide dose	**0.26**	**0.12**
Spironolactone dose	**0.19**	**0.18**
After 1 month		
Body weight	**-0.52**	***0.02***
Mean arterial blood pressure	**0.75**	***<0.001***
Paracentesis frequency	**-0.61**	***0.03***
Furosemide dose	**-0.3**	***0.01***
Spironolactone dose	**-03**	***0.01***



(A) **(B)**

Figure (1): (A): Receiver operator characteristics (ROC) curve in prediction of midodrine dose cutoff value after 1 week in protection of hepatorenal syndrome, (B): Receiver operator characteristics (ROC) curve in prediction of midodrine dose cutoff value after 1 month in protection of hepatorenal syndrome.

DISCUSSION

This research was conducted to assess the efficacy of midodrine in management of refractory ascites due to liver cirrhosis. In this study all patients were matched regarding baseline clinical data which includes body weight, mean arterial blood pressure, paracentesis frequency, doses of diuretics, ascitic fluid analysis, other laboratory investigations, ultrasonography findings and ECG.

The patients were divided into 2 groups, control group who received the standard medical treatment with therapeutic paracentesis, and midodrine group who received midodrine in addition to standard medical treatment and therapeutic paracentesis. They were followed up for one month and the baseline data were repeated after 1week and 1 month from the start of the study.

In this study, mean arterial blood pressure was higher significantly among study group than control group after 1 week and after 1 month of follow up ($p<0.05$). The result after 1 week was in accordance with Angeli *et al.* [11] and Kalambokis *et al.* [12] who reported that midodrine intake for 1 week was associated with lower heart rates and cardiac output, together with significant increases in systemic vascular resistance and mean arterial pressure.

Moreover, Tandon *et al.* [13] reported a significant increase in arterial blood pressure after one month. They added octreotide-LAR (long-acting release) and 50 gm albumin three times per week to midodrine for 1 month($p<0.05$).

In contrast, Rai *et al.* [14] didn't find a significant increase in mean arterial blood pressure with adding midodrine to standard medical therapy only, but the increase was significant with addition of tolvaptan ($p>0.05$).

In the present study, regarding body weight, after one week, no statistically significant differences were found between both groups. Also, Kalambokis *et al.* [12] reported the same result when they studied the natriuretic effect of midodrine in ascitic and non-ascitic cirrhotic patients for 7 days. But after one month in the present study, the study group showed a significant decrease in body weight ($p=0.04$). This agreed with Essam *et al.* [15]

Regarding paracentesis frequency, after one week there were no statistically significant differences between both groups (p=0.64), while after one month a significant decrease appeared in the midodrine group (p=0.008). This finding was in agreement with Sourianarayanane *et al.* [16] who reported the advantage of midodrine in treating ascites even when administered alone, in the absence of any other vasoconstrictors. Also, Essam *et al.* [15] showed the same result, in a prospective study to assess the natriuretic effect of midodrine.

These findings were in contrast with those of similar research conducted by Gomaa *et al.* [17] who found non statistically significant improvement in both frequency and volume of ascetic fluid drained after 1 month of use of midodrine plus standard medical therapy (p>0.05). They didn't exclude patients with hepatocellular carcinoma (who were 12 out of 40), a situation that could be considered as a cause of the poor outcome in their study.

In the present study, furosemide and spironolactone doses were significantly decreased in midodrine group both after one week and 1 month when compared with control group. The vasoconstricting effect of midodrine may be able to reverse a part of the pathologic processes that lead to elevated renal sodium retention and diuretic resistance. This agreed with the findings of Singh *et al.* [6] who revealed that furosemide and spironolactone doses were significantly decreased among the midodrine group (p<0.05).

In the current study, regarding laboratory investigations non statistically significant differences were revealed between both groups after one week and one month of treatment except serum creatinine and GFR which were significantly improved after one month among study group. The same results were reported by Oda *et al.* [18], Singh *et al.* [6], Ali *et al.* [19], Obiedallah *et al.* [5] and Essam *et al.* [15] in their previous studies.

On the other hand, some researchers disagreed regarding some laboratory parameters as Tandon *et al.* [13] who reported significant increase in total bilirubin, and non-significant decrease in albumin after using midodrine, octreotide LAR, and albumin infusion for one month, but during follow up, they returned to baseline within one month.

They explained that by the vasoconstrictor effect of octreotide on splanchnic vessels, decreasing portal pressure and hepatic perfusion and leading to deterioration of hepatic functions. Midodrine could also add on the vasoconstrictor effect of octreotide. Also, Kasiske *et al.* [20] found that the usage of midodrine was associated with deterioration in total bilirubin and INR. It should be stressed that their study only included critically ill patients, waiting for a liver transplant.

In the current study, serum creatinine was significantly lower and eGFR was significantly higher in the midodrine group compared to the control group after one month of midodrine therapy. This was in agreement with Krag *et al.* [21].

On the other hand, the studies conducted by Kalambokis *et al.* [12], Tandon *et al.* [13] and Essam *et al.* [15] showed that the effective circulatory volume and systemic hemodynamics improved but renal function remained unchanged during midodrine treatment. Another possible explanation is that serum creatinine, rather than GFR, was used to evaluate renal function [22].

Along the follow up period in this study, patients in control group showed increase in serum creatinine and decrease in GFR. Multiple factors can contribute to an elevated serum creatinine level in cirrhosis. One of these is a change in kidney perfusion caused by splanchnic vasodilation in portal hypertension, which can lead to hepatorenal syndrome (HRS). Another factor is specific kidney damage linked with the etiology of cirrhosis [23].

In midodrine group, despite of absence of significant changes in serum creatinine and eGFR, diuresis was enhanced which was expressed by significant decrease in body weight and significant decrease in frequency of paracentesis, and doses of diuretics. This result was also reported by Lin *et al.* [7] who found that midodrine reduced nitrite and nitrate

activity, decrease plasma renin activity and antidiuretic hormone level in patients with ascites, with or without HRS.

In contrast to absence of significant changes in serum sodium and potassium along this study in both groups, Tandon *et al.* [13] found that the group receiving standard medical care showed significant decrease in serum sodium which was not affected in midodrine group. In contrast, Rai *et al.* [14] showed significant increase in serum sodium only in patients received tolvaptan with midodrine. Furthermore, Patel *et al.* [24] disagreed with our findings as they found that oral midodrine improved serum hyponatremia in cirrhotic patients, but their study only lasted for two weeks, and included an albumin infusion.

Regarding MELD-Na score in this study, no significant differences observed between both groups along the study. Singh *et al.* [6] followed-up their patients for 6 months and reported a significant deterioration in the MELD score in the standard medical therapy group but not in the midodrine group. However, Tandon *et al.* [13] reported deterioration in the MELD score during midodrine treatment due to increase in INR and bilirubin which were returned to baseline levels after therapy discontinuation suggesting a direct treatment-related effect.

In this study, at the end of follow up period, a significant higher frequency of marked ascites among control group than study group was observed. The same finding was encountered by Ali *et al.* [19] who conducted their two-weeks study using midodrine in non-azotemic cirrhotics with ascites. They found that the degree of ascites assessed clinically by abdominal girth and radiologically by ultrasonography has decreased at the end of the study.

In this study, there was no statistically significant difference between both groups regarding portal vein diameter all over the study, a result that agreed with that of Ali *et al.* [19]

Regarding the correlation between midodrine dose and other parameters, after one week, there was a statistically significant positive correlation between midodrine dose and mean arterial blood pressure. The effect of midodrine on body weight, paracentesis frequency and diuretics doses doesn't appear during first week but become evident after one month and presented as significant negative correlation.

At the end of this study, the occurrence of HRS in midodrine group is significantly lower than control group; 3 (6%) vs 11 (22%). This may be due to vasoconstrictive action of midodrine on splanchnic circulation with subsequent increase in renal blood flow. This explanation was confirmed previously by Moreau *et al.* [25], Duvoux *et al.* [26] and Singh *et al.* [8] who reported improvement in systemic hemodynamics due to suppression in activity of the renin-angiotensin aldosterone system with midodrine therapy in cirrhotic patients with ascites.

Other complications that were reported during the study were spontaneous bacterial peritonitis and hepatic encephalopathy but without significant difference between control and midodrine group. This result was in agreement with Singh *et al.* [6].

In general, no serious side effects occurred in patients who received midodrine were observed during the study. The same was reported by Angeli *et al.* [27], Kalambokis *et al.* [12], Singh *et al.* [8] and Solà *et al.* [28]

In this study, it was found that midodrine in a dose of 15 mg/day is significantly protective against HRS but not significantly protective against SBP and hepatic encephalopathy. This could be explained by the multifactorial pathogenesis of SBP and HE.

With analysis of risk factors, it was found that rise of serum bilirubin was associated with increased probability for hepatorenal syndrome and spontaneous bacterial peritonitis. Hyperbilirubinemia is one of serum abnormalities that reflect the severity of the liver disease and elevates Child Pugh score. Montoliu *et al.* [29] found that a high Child Pugh score were independent predictors for HRS on multivariate analysis.

The same situation was reported by Ullah [30] who conducted his study to know the association of serum bilirubin level with SBP in hepatic encephalopathy patients and concluded that hyperbilirubinemia is directly related to the occurrence of SBP and may be used as a predictor of SBP in patients with ascites.

Also, in this study, the rise of total leucocyte count in ascitic fluid was associated with increased probability for hepatic encephalopathy.

Limitations of this study include a small sample size (total of 100 subjects) and it was done in single center so generalization of our findings need more validated larger sample and multicenter studies.

CONCLUSIONS

The addition of midodrine to standard medical treatment (salt restriction and diuretics) has an important role in managing the refractory ascites with protection against hepatorenal syndrome at dose 15mg/day. So, it is considered safe adjuvant treatment for patients who had refractory ascites due to liver cirrhosis with little side effects.

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