THE NATURETIC EFFECTS OF LONG-TERM USE of MIDODRINE ON PATIENTS WITH LIVER CIRRHOSIS AND REFRACTORY ASCITES

Abstract

Background: splanchnic vasodilatation is a major contributor to development of ascites n cirrhotic patients and associated with poor sodium excretion. SO MIDODRINE which is, alpha 1 agonist, may improve circulatory abnormality in cirrhotic patients via its vaso-constrictive action thus leading to better natriuresis.

Aim: to assess the efficacy and the safety of midodrine (alpha adrenergic agonist) on patients with liver cirrhosis as regard sodium excretion.

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

Results: Body weight and abdominal girth significantly decreased in midodrine group patients compared to control group ($p < 0.001$). Also, 24-h urinary volume and Na excretion were significantly higher in midodrine group patients at the end of the study compared to SMT patients ($p < 0.001$).

Conclusions: MIDODRINE could be used safely as an adjuvant to SMT (salt restriction and diuretics) in cirrhotic patients with refractory ascites in a dose of 7.5 mg TDS with better outcomes evidenced by reduced body weight and increase Na excretion in urine

Keywords: cirrhosis, ascites, MIDODRINE, natriuresis

Introduction

Ascites is a common, serious consequence of cirrhosis and the patient becomes susceptible to complications [(1).]

Hemodynamic compensation mechanisms include RAAS system and sympathetic nervous system activation and ADH release in response to systemic hypotension caused by splanchnic and systemic vasodilatation due to excess nitric oxide with subsequent dilutional hyponatremia associated with poor urinary sodium excretion. [(2).]

Patients with cirrhosis and ascites should have a moderately salt restricted diet with daily salt intake of no more than 5–6.5 g (87 mmol–113 mmol sodium) [(3)]

The best approach to therapy, either aldosterone antagonists in a stepwise increase every 7 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 7 days in case of no response up to 400 and 160 mg/day)[4].

Large volume paracentesis (LVP) is the standard of care for managing large 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 [5]

Midodrine, an alpha-1 agonist, has been prescribed for various etiologies of symptomatic hypotension. These comprise neurocardiogenic syncope, including vasovagal syncope, orthostatic hypotension in the elderly.It decreases nitrite and nitrate activity in ascetic patients with HRS and plasma renin activity along with antidiuretic hormone levels also decline. Midodrine has been shown to better control of ascites in a short-term pilot study in patients with refractory ascites but more studies are needed to confirm these findings [6]

Patients and methods

Study design and patients: This study was a prospective study during the period from April 2021 to March 2022. (Approval number 34461/2/2021).

A total of 80 patients either as an inpatient or outpatient were enrolled in this study. They were collected from the Department of Tropical medicine and infectious diseases, Tanta university hospital, Egypt. Patients were divided into 40 cirrhotic patients with refractory ascites receiving standard medical therapy (SMT) as a control group and 40 cirrhotic patients with refractory ascites receiving SMT+ MIDODRINE 2.5 mg (3 tablets / 8 hours) for 1 month. Traditional treatment included salt restriction to less than 90 mmol/day and diuretics spironolactone up to 400 mg /day and furosemide up to 160 mg /day or as tolerated provided that no complications as hepatic encephalopathy, hypokalemia, hyponatremia, impaired renal functions had occurred. Plus, large volume paracentesis (LVP).

The inclusion criteria were cirrhotic patients more than 18 years of age of any etiology and refractory ascites as defined according to European Association for the study of the liver [7]

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

All authors hadetical access to the study data and reviewed and approved the final manuscript.

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

1- Full history taking and through clinical examination including frequency of tapping, body weight and abdominal girth measurement. 2- Laboratory investigations including complete blood

count, liver function tests, renal function tests, serum electrolytes and 24-hour urine volume and Na excretion. 3- Child-Pugh score was assessed for all cirrhotic patients. 4- Abdominal ultrasonography.

Participants were randomized to either the intervention (midodrine) or the control group and the physical examination and the laboratory investigations were repeated after one month of the study to assess the effect of midodrine in the degree of ascites as well as its possible side effects

Statistical analysis:

With the use of the IBM SPSS software package version 20.0, data were input into the computer (Armonk, NY: IBM Corp) and Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. The used tests were (1)Chi-square test For categorical variables, to compare between different groups (2) Fisher's Exact or Monte Carlo correction for correction of chi-square when more than 20% of the cells have expected count less than 5(3) Student t-test For normally distributed quantitative variables, to compare between two studied groups (4) Mann Whitney test For abnormally distributed quantitative variables, to compare between two studied group (5) McNamar and Marginal Homogeneity Test Used to analyze the significance between the different stages (6) Paired t-test For normally distributed quantitative variables, to compare between two periods (7)Wilcoxon signed ranks test For abnormally distributed quantitative variables, to compare between two periods.

Results: A total of 80 cirrhotic patients with refractory ascites were enrolled in this prospective study. Patients consisted of 40 patients receiving standard medical therapy (SMT) and 40 patients receiving SMT +MIDODRINE. The demographic, baseline clinical and laboratory findings of the studied groups were summarized in **(Table 1).**

Only 37 patients completed the study to its end in each group. In control group there were 2 patients who did not adhere for follow up and 1 patient who died of hepatorenal syndrome. While in group II, there was 1 patient stopped the drug after development of epistaxis, another did not show for follow up and another patient died also due to development of hepatorenal syndrome as shown in **figure (1)**

There were no significant differences between the studied groups as regards age and gender. As regard the etiology of cirrhosis, we found that the main etiology of cirrhosis is hepatitis C in both groups then comes bilharziasis.

It was found that there was no difference between the two studied groups as regard the etiology of cirrhosis. As regard diuretic intake it was found that there was no significance between the two studied groups as regard furosemide intake. While there was significant difference between the two groups as regard spironolactone intake at baseline.

As regard to tapping, it was found that there was no significance between the two studied groups at baseline but there was significant decrease in frequency of tapping among midodrine group patients which was not found in control group (P value =0.021) **(table 3)**

As regard occurrence of hepatic encephalopathy, there was significant difference between the two studied groups at the end of the study where there were 2 patients developed hepatic encephalopathy in group II while 8 patients developed hepatic encephalopathy in group I before the end of the study($P<0.001$) **(table 2)**

As regard body weight, there was no significant difference between two studied groups at baseline but there was significant decrease in average body weight among midodrine group patients which did not happen in control patients($P<0.001$) **(Table 3)**

As regard abdominal girth, it was found that there was significant difference between the two groups with more reduction in average abdominal girth in midodrine patients than in control patients($P<0.001$) **(Table 3)**

As regard lower limb edema, there was significant decrease in both groups at the end of the study compared to baseline ($P<0.001$) **(table 2).** But this decrease was much marked in midodrine patients than in control patients **(Table 3)**

As regard blood pressure, it was found that both systolic and diastolic blood pressure 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 as regard hemoglobin level, total leucocytic count, serum Na level, serum K level, total bilirubin, serum creatinine, blood urea, and serum albumin, ALT, AST and INR (**Table 4).** There was no significant difference between both groups as regard urine volume and urinary Na level at baseline **(Table 1)** but there was significant increase in both values in midodrine group patients than in control group patients at the end of the month of the study ($P<0.001$) **(Table 5)**

Discussion:

The distinction between the two studied groups as regard the etiology of cirrhosis. Consistent with the findings of (Obiedallah et al., 2017)[8], another study which was conducted in 2017 and both studies were done in Egypt where liver cirrhosis is mostly caused by HCV. (Gomaa et al., 2017)[9]. There was significant difference between the two groups as regard spironolactone intake with 38 patients in group I and 34 patients in group II Which was attributed to randomization of the patients and side effects of diuretics in which spironolactone induced hyperkalemia is the most prominent as shown at (Angeli et al., 2010)[10]. Hepatic encephalopathy occurred in just 2 of group II's patients, compared to 8 of group I's patients. during the study. In another similar study (Singh et al., 2012)[11] 4 patients of 20 developed hepatic encephalopathy while receiving standard medical treatment while 3 patients of 20 developed HE in the midodrine group but this study was for longer duration for 3 months.

Regarding tapping, no significant difference was identified between the groups at baseline, however there was a marked decline in tapping frequency across the board for everyone. This decline, however, was noticeably more pronounced in the midodrine group than in the control group. These findings contrast with those of a similar research. (Obiedallah et al., 2017)[9] which found no significant improvement in both frequency and volume of ascetic fluid drained after 1 month of use of midodrine plus standard medical therapy. Regarding body weight, it was found that mean body weight in group I was less than group II due to randomization. And it significantly decreased in midodrine group at the end of the study which did not happen in control group. other results appeared in another study (Kalambokis et al., 2007)[12], though the reduction in the body weight was not statistically significant but the study was only for 7 days. Also, Singh et al.,2012[11], Ali et al., 2014[13] and Obiedallah et al., 2017[9] agreed with our results.

Regarding abdominal girth, before the study began, there was a large gap between the two groups of the study due to randomization and the average abdominal girth in midodrine group has significantly decreased but still higher than that of group I in which there was no significant reduction. The findings were backed up by the results of (Ali et al., 2014)[13] where the reduction in abdominal girths detected in midodrine group after 2 weeks of Midodrine therapy. Regarding blood pressure, 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)[14] which used midodrine and tolvaptan on different groups. Also, same results appeared in another study (Angeli et al., 1998)[15] but it studied the acute effects of oral midodrine on hemodynamics of cirrhotic patients.

Another study showed the same results (Tandon et al., 2009)[16] but it used different doses of Midodrine. Regarding serum sodium and potassium, at the end of the experiment, there was no discernible difference between the two groups.

(Singh et al., 2012)[11] Demonstrated, contrary to our findings, that serum sodium reduced dramatically in the group receiving normal medical care. Serum sodium levels did not alter much in the midodrine group following therapy.

Also, Ali et al., 2017[17] and Obiedallah et al., 2017[10] agreed with our study that was on significant change in both serum sodium and potassium with the use of midodrine

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 where it found that oral midodrine improve serum hyponatremia in cirrhotic patients but this study was for only 72 hours along with albumin infusion.

(Rai et al., 2017)[14] showed significant increase in serum sodium only with addition of tolvaptan. As regard urinary sodium level showed clinical significance between the two studied groups where it was higher in group II than in group I

Also, urinary sodium level significantly increased in midodrine group patients between the start and the end of the study which did not appear in control group.

Our results agreed with (Rai et al., 2017)[14] which was conducted for longer duration.

Also, (Singh et al., 2012)[11] revealed that After 1 and 3 months of therapy, midodrine considerably increased urinary sodium excretion, but this effect was no longer seen after 6 months.

mostly same results appeared in (Tandon et al., 2009)[16] where there was increase in urine sodium level only in spot test at the middle of the study with no further increase toward its end. (Angeli et al., 1998)[15] studied the acute effects of midodrine on renal hemodynamics agreed with our study although it studied the acute effects it suggested that natriuretic effects of midodrine reach plateau after a period of time.

The natriuretic effects of midodrine may be attributed to the suppression of renin angiotensin system (RAAS) as in (Tandon et al., 2009)[16]

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)[19] disagreed with our results, where it claimed that there was no effect of midodrine in urine sodium level but it was only studying the acute effects of midodrine on IV furosemide for 6 hours only.

As regard 24-hour urine volume, At the study's conclusion, it was shown to be greater in the midodrine group than in the control group. Furthermore, it rose in the midodrine group from the beginning to the end of the research, whereas the control group saw no change.

These results disagree with those of (Ali et al., 2014)[13] which found that there no difference in urine output in both midodrine group and placebo group. However, it should be noted that this

study was conducted for shorter duration using smaller doses of Midodrine. On the other hand, (Singh et al., 2013)[20], (Obiedallah et al., 2017)[8] and (Rai et al., 2017)[14] and agreed with our results as regard the increase in urine output after the use of Midodrine. Regarding liver enzymes, at whatever point in the trial, neither group differed significantly from the other.

Regarding total bilirubin, we discovered no statistically significant difference between the both groups at baseline and the conclusion of the research. Also, there was no difference in total bilirubin between the start and the end of the study in both midodrine and control groups. (Kalambokis et al., 2007)[12], (Singh et al., 2012)[11] and (Obiedallah et al., 2017)[8] found the same results as regard total bilirubin. In conflict with these results, (Tandon et al., 2009)[16] found that total bilirubin significantly increased at 1 month of use of midodrine, octreotide-LAR and albumin but it returned to baseline level after 1-month post-treatment.

As regard INR, according to our research, there is no discernible distinction between the two categories at the base lines as well as at the end of the study. Also, there was no difference in INR between the start and the end of the study in both midodrine and control groups.

(Kalambokis et al., 2007)[12], (Singh et al., 2012)[11] and (Obiedallah et al., 2017)[8] were also similar to our results as regard INR. (Kalil et al., 2018)[21] found that the use of midodrine was associated with more worsening of INR and total bilirubin unlike our study. It should be noted that this study included patients waiting for liver transplant only.

As regard albumin level, no significant difference was found between groups either at the beginning or the conclusion of the investigation. There was also no variation between the two groups during the course of the study's duration. These results were supported (Kalambokis et al., 2007)[12], (Oda et al., 2011)[22], (Singh et al., 2013)[21] and (Ali et al., 2014)[13]

To the contrary, (Tandon et al., 2009)[16] found that synthetic functions of liver including albumin have been impaired with the use of midodrine despite using albumin infusion.

But this may be attributed to addition of octreotide which cause splanchnic vasoconstriction reducing the portal pressure and hepatic perfusion.

As regard serum creatinine, we found that there was no significant difference between the both groups at baseline as well as at the end of the study. However, there was slight increase in serum creatinine in control group unlike in midodrine group.

This was the case, according to the research conducted by (Kalambokis et al., 2005)[23], (Tandon et al., 2009)[16] and (Singh et al., 2012)[11] where systemic hemodynamics improved but renal function did not alter after treatment and the effective circulating volume. on the other hand (Krag et al., 2007)[24] suggested more improve in renal functions with the use of vasopressors as terlipressin taking in consideration that it assessed renal functions by GFR which may be more accurate than serum creatinine

(Oda et al., 2011)[22] which studied the hemodynamic effects of midodrine in cirrhotic patients with ascites and without ascites found that there was improvement of renal hemodynamics in non-ascetic patients but it was not found in patients without refractory ascites, however it found noticeable rebound in the level of plasma renin activity after stoppage of midodrine. This was This can be explained by the massive activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, the increase in renal vascular resistance, the decrease in renal blood flow, and the relatively mild decrease in glomerular filtration rate that characterize this phase.

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, 6 patients out of 59 reported stomach pain when taking midodrine for 6 months (Singh et al., 2012)[11]. However, they were all rather minor and did not necessitate a break in treatment. Similar findings were seen in a study by (Rai et al., 2017)[14], in which only 2 of 13 individuals experienced moderate stomach discomfort that did not necessitate therapy termination.

In conclusion: The addition of midodrine to SMT (salt restriction and diuretics) is associated with increase of urine volume and urine Na level associated with more wight reduction which considered an improvement of naturetic response to diuretics and it is considered safe for patients with liver cirrhosis with little side effects

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

Consent :

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).

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Table (1): Baseline characteristics in each group

Baseline characteristics	Group I (n= 40)	Group II (n= 40)
Body weight		
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 girth		
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		
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
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		
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		
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)
Alanine transaminase		
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)
Aspartate transaminase		
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)
International normalized ratio		
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)

Table (2): Comparison between the two studied 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=	0.021*

Mean ± SD.	0.92 ± 0.60		0.59 ± 0.55		498.50*	
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)			
Abdominal girth						
Min. – Max.	84.0 – 138.0		84.0 – 145.0		t= 2.082*	0.041*
Mean ± SD.	109.2 ± 16.11		117.0 ± 15.94			
Median (IQR)	105.0(95.0 – 126.0)		116.0(106.0 – 128.0)			
Lower limb odema						
No	1	2.6	0	0.0	χ^2= 15.671*	MCp <0.001*
Mild	4	10.5	19	51.4		
Moderate	29	76.3	15	40.5		
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 between the studied groups*: Statistically significant at p ≤ 0.05

Group I: refractory ascites on traditional treatment

Group II: refractory ascites on traditional treatment plus Midodrine

Table (3): Comparison between the start and the end of the study according to general examination in group I and II

Group I						
General examination	**The start (n = 37)**		**The end (n = 37)**		**Test of Sig.**	**p**
	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= 3.084*	0.002*
Mean ± SD.	1.49 ± 0.77		0.92 ± 0.60			
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		t= 1.210	0.234
Mean ± SD.	92.51 ± 12.09		91.65 ± 12.82			
Median (IQR)	92.0 (86.0 – 100.0)		92.0(86.0 – 101.0)			
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 odema						
No	0	0.0	1	2.6	MH= 40.0*	<0.001*
Mild	0	0.0	4	10.5		
Moderate	22	59.5	29	76.3		
Marked	15	40.5	4	10.5		

Group II

General examination	**The start (n = 37)**		**The end (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		Z=4.542*	<0.001*
Mean ± SD.	1.81 ± 1.20		0.59 ± 0.55			
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		t= 5.946*	<0.001*
Mean ± SD.	88.54 ± 13.36		86.0 ± 13.04			
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		t=	<0.001*

Mean ± SD.	119.57 ± 16.40		117.0 ± 15.94		6.274*	
Median (IQR)	118.0(106.0 – 134.0)		116.0(106.0 – 128.0)			
Lower limb odema						
No	0	0.0	0	0.0	MH= 50.0*	<0.001*
Mild	0	0.0	19	51.4		
Moderate	23	62.2	15	40.5		
Marked	14	37.8	3	8.1		

IQR: **Inter quartile range** SD: **Standard deviation**

t: Paired t-test **MH: Marginal Homogeneity Test**

p: p value for comparing between **Start** and **End** *: Statistically significant at $p \leq 0.05$

Group I: refractory ascites on traditional treatment

Group II: refractory ascites on traditional treatment plus Midodrine

Table (4): Comparison between the two studied 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				
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 between the studied groups *: Statistically significant at p ≤ 0.05

Table (5): Comparison between the start and the end of the study according to laboratory data in group I and II

Group I				
Lab	**The start**	**The end**	**Test of**	**p**

	(n = 37)	(n = 37)	Sig.	
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		
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= 0.338	0.737
Mean ± SD.	89.24 ± 22.34	90.62 ± 19.48		
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= 0.204	0.838
Mean ± SD.	6.56 ± 2.54	6.74 ± 2.87		
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= 1.924	0.054
Mean ± SD.	1137.84 ± 256.42	1264.9 ± 311.1		
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= 1.500	0.142
Mean ± SD.	128.59 ± 5.18	127.0 ± 5.25		

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= 0.423	0.675
Mean ± SD.	4.11 ± 0.57	4.05 ± 0.67		
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= 1.936	0.053
Mean ± SD.	25.61 ± 17.69	31.73 ± 22.90		
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= 0.704	0.486
Mean ± SD.	10.06 ± 1.31	9.95 ± 1.32		
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= 0.928	0.359
Mean ± SD.	130.27 ± 97.41	122.0 ± 89.73		
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= 1.117	0.264
Mean ± SD.	7.12 ± 3.79	6.49 ± 2.44		
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= 4.643*	<0.001*
Mean ± SD.	1227.03 ± 350.91	1527.0 ± 384.2		
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= 0.040	0.968
Mean ± SD.	126.99 ± 5.88	127.0 ± 5.72		
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= 1.574	0.124
Mean ± SD.	4.13 ± 0.76	4.31 ± 0.68		
Median (IQR)	3.90 (3.50 – 4.50)	4.40(3.7 – 4.9)		
Urinary Na				
Min. – Max.	10.50 – 315.0	16.0 – 360.0	Z= 4.156*	<0.001*
Mean ± SD.	42.97 ± 55.21	82.70 ± 68.12		
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= 0.729	0.466
Mean ± SD.	3.42 ± 3.59	2.82 ± 2.17		
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= 1.127	0.260
Mean ± SD.	1.14 ± 0.29	1.20 ± 0.40		
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= 1.260	0.208
Mean ± SD.	61.16 ± 30.01	1.20 ± 0.40		
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= 0.507	0.612
Mean ± SD.	2.58 ± 0.37	2.63 ± 0.33		
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= 0.771	0.441
Mean ± SD.	36.65 ± 23.57	34.68 ± 17.77		
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= 0.632	0.528
Mean ± SD.	56.16 ± 30.30	54.11 ± 28.52		
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= 0.519	0.607
Mean ± SD.	1.59 ± 0.25	1.61 ± 0.26		
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 between **Start** and **End** *: Statistically significant at $p \leq 0.05$

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