THE EFFECTS OF MIDODRINE ON PATIENTS WITH LIVER CIRRHOSIS AND REFRACTORY ASCITES: A RANDOMIZED CONTROLLED TRIAL.

**Abstract**

**Background:** splanchnic vasodilatation is a major contributor to development of ascites in cirrhotic patients. so midodrine which is, alpha 1 agonist, may improve circulatory abnormality in cirrhotic patients via its vaso-constrictive action thus ameliorating 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:** 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) (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 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). additionally, both systolic and diastolic blood pressure were higher in midodrine patients at the end of the study(P<0.001)

**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 increase 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 as well as distal tubular sodium reabsorption rather than to a decrease of filtered sodium load .The mediators of the enhanced proximal tubular reabsorption of sodium have not been elucidated completely, while the increased reabsorption of sodium along the distal tubule is mostly related to hyperaldosteronism secondary to Portal hypertension and splanchnic vasodilatation [4]

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). A more severe reduction in dietary sodium content is considered unnecessary on the contrary, 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 difficult to comply with [5] .

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) . All patients initiating diuretics should be monitored for adverse events, such as renal failure, hepatic encephalopathy, electrolyte disorders, gynecomastia, and muscle cramps. Almost half with adverse events require diuretic discontinuation or dose reduction [6]

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 [7]

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 aim of studyto assess the efficacy and the safety of midodrine (alpha adrenergic agonist) on 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 from 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 of the trial team influencing the allocation of participants

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

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 with non-refractory ascites (6) Patient unwilling to participate in the study.

The primary outcome of the study is to assess the effect of midodrine on body weight, abdominal girth, 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:

Complete medical history taking including Personal data like age, residence, sex, special 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), 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 examination for evaluation of the patient for hepatic encephalopathy, pallor, jaundice, pleural effusion, lower limb oedema. Abdominal examination for any abdominal distension, tenderness, rigidity, or palpable mass or organomegaly, degree of ascites.

Laboratory tests, such as a full 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.

The physical examination 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 safety of the drug were assessed by follow up visits and measurement of blood pressure 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, as well as 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 that were used included: (1)Chi-square In order 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 on the basis of quantitative variables that have an irregular distribution, Method 5: The McNamar 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.

**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 to the follow up and 1 patient who died due to hepatorenal syndrome. While in group II, there was 1 patient stopped the drug after development of epistaxis, another did not complete 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 regards the etiology of cirrhosis, we found that the main 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 regard furosemide intake. While there was significant difference between the two groups as regard spironolactone intake at baseline with 38 patients in group I and 34 patients in group II which was attributed to randomization of the patients

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 at the end of the study (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 significantly apparent in midodrine patients than in control patients **(Table 3)**

As regard 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 (**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 pathophysiology of cirrhotic ascites is that vasodilatation and hyperdynamic circulatory dysfunction induce the nonosmotic release of antidiuretic hormone, reflex activation of neurohormonal systems, and activation of the renin-angiot tensin-aldosterone system (RAAS) with sodium and water retention. Large-volume paracentesis (LVP) is used in patients with cirrhosis and tense ascites. Lead to decrease in effective arterial blood volume and systemic vasodilatation and it is associated with impaired renal function and increased activity of the RAAS in approximately 80% of cases [4]. Previous studies demonestrsted that use of a vasocontrictor may be effective in preventing 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]

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, Angeli et al., 1998[13] but it studied the acute effects of oral midodrine on hemodynamics of cirrhotic patients. Another study, Tandon et al., 2009[10] showed the same results but it used different doses of Midodrine.

Regarding body weight, it significantly decreased in 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 the body weight was not statistically significant but the study was only for 7 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] 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.

In our study, regarding serum sodium and potassium, there was no discernible difference between the two groups at the end of the study. This is in agreement 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 normal 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 where it found that oral midodrine improve serum hyponatremia in cirrhotic patients, but this study was for only 72 hours along with albumin infusion.

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.

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

Also, Singh et al., 2012[14] 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 the same results appeared in Tandon et al., 2009[10] 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[19] 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.

The natriuretic effects of midodrine may be attributed to the suppression of 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, 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.

Urine output during the course of 24 hours showed that it was higher in the midodrine group compared to the placebo group. Furthermore, it increased in the midodrine group from baseline to endpoint, but it remained stable in the control group throughout the study.

These results disagree with those of Ali et al., 2014[15] 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[21], Obiedallah et al., 2017[16] and Rai et al., 2017[12] and agreed with our results as regard 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 beginning to the end of the study. 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 1 month of therapy with midodrine, octreotide-LAR, and albumin, but then recovered to baseline following 1 month of discontinuation of medication.

Kalil et al., 2018[23] 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, there was no statistically significant difference between the 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 by Kalambokis et al., 2007[11], Oda et al., 2011[24], Singh et al., 2013[21] and Ali et al., 2014[15].

To the contrary, Tandon et al., 2009[10] 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 statistically, we identified no distinguishing features 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[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 effective circulating volume. On the other hand, Krag et al., 2007[26] 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[24] which looked at the effects of midodrine on blood flow in cirrhotic patients with and without ascites and found that the drug improved renal hemodynamics in non-ascetic patients but had no effect on patients with refractory ascites; it did, however, find a significant rebound in plasma renin activity after treatment with midodrine was discontinued. That's what an increase in renal vascular resistance, a decrease in renal blood flow, and a modest drop-in glomerular filtration rate explain this. The sympathetic nervous system and the renin-angiotensin-aldosterone system are both heavily activated during this period.

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[14]. 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[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 for compliance of many patients.

* **In conclusion**: The addition of midodrine to SMT is linked to more effective therapeutic management of ascites (reduction of body weight, abdominal girth) 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.

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**Table (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 girth (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 (mmHg)** |  |  |
| 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 (mmHg)** |  |  |
| 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**  **(13.8-17.2 gm/dl) in males**  **(12.1-15.1 gm/dl) in females** |  |  |
| 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/mm3)** |  |  |
| 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**  **(4-11\*109/L)** |  |  |
| 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 (800-2000ml/day))** |  |  |
| 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**  **(135-145mmol/L).** |  |  |
| 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**  **(3.5-5.5mEq/L).** |  |  |
| 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**  **( 40-220mEq/day)** |  |  |
| 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**  **(0.1-1.2mg/dL)** |  |  |
| 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**  **(0.7-1.3mg/dL)** |  |  |
| 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**  **(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) |
| **Alanine transaminase (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) |
| **Aspartate transaminase**  **(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) |
| **International normalized ratio**  **(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) |

**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)** | | **χ2** | **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) | |
| **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 | χ2= 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**

χ2: **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= 6.274\* | | | <0.001\* |
| Mean ± SD. | 119.57 ± 16.40 | | 117.0 ± 15.94 | | | | |
| 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 ≤ 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 (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 |
| 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 ≤ 0.05

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