Clinical Study on the Therapeutic Role of Midodrine in Non azotemic Cirrhotic Patients with Tense Ascites: A Double-Blind, Placebo-Controlled, Randomized Trial

Ahmed Ali¹, Samar Farid², Mona Amin³, Mohamed Kassem⁴ and Nouman Al-Garem³

¹Department of Pharmaceutics, Egyptian Russian University, ²Department of Clinical Pharmacy, Cairo University, ³Department of Internal Medicine, Cairo University ⁴Department of Pharmaceutics, Cairo University.

Background: Midodrine is an α-agonist prodrug of desglymidodrine used for the management of hypotension. Midodrine has demonstrated usefulness in hepatorenal syndrome. Objective: The objective of the present work was to study the role of midodrine in patients with non-azotemic cirrhosis with tense ascites. Methods: This prospective randomized double blind placebo-controlled study was conducted on 67 non azotemic inpatients with liver cirrhosis and tense ascites (52 men and 15 women; age range, 45-72). One patient declined to participate in the study, 33 patients were randomly assigned to take midodrine hydrochloride, and 33 patients were randomly assigned to take placebo. Out of 67 enrolled patients, 60 patients (30: in midodrine group; 30: in placebo group) completed the study and 6 patients lost to follow up. Patients were assessed for patients’ characteristics, history of tapping their ascitic fluid, laboratory values, and Doppler parameters before and after the study. Average 24-h urine volume was assessed before and after the start of the study. Results: significant reduction in body weight and abdominal girth was observed after 2 weeks of midodrine therapy. Conclusion: Midodrine appeared to be effective in lowering body weights and abdominal girths of non azotemic cirrhotic patients with tense ascites.

INTRODUCTION

Cirrhosis is a chronic liver disease that causes damage to liver tissue, scarring of the liver (fibrosis - nodular regeneration), progressive decrease in liver function, excessive fluid in the abdomen (ascites), bleeding disorders (coagulopathy), increased pressure in the blood vessels (portal hypertension), and brain function disorders (hepatic encephalopathy). Excessive alcohol use is the leading cause of cirrhosis(1).

It is a leading cause of death worldwide. The rising global burden of cirrhosis and its complications is the focus of much attention in Europe, the US and elsewhere (2, 3). In the US it is the eighth leading cause of death affecting approximately 5.5 million patients at an annual cost of >$1.5 billion(4), which is expected to rise further in the next 10 years due to aging hepatitis C populations (5).

Ambulatory patients with an episode of cirrhotic ascites have a 3-year mortality rate of 50%. The development of refractory ascites carries a poor prognosis, with a 1-year survival rate of less than 50%(6)

Ascites is the most common cause of hospital admissions in cirrhotic patients and the development of ascites predicts a mortality of approximately 15% and 44% at 1 and 5 years, respectively(7).

The majority (75%) of patients who present with ascites have underlying cirrhosis, with the remainder being due to malignancy (10%), heart failure (3%), tuberculosis (2%), pancreatitis (1%), and other rare causes(8).

Since splanchnic arterial vasodilatation is a constant feature of cirrhosis, arterial vasoconstrictors could be of value in cirrhotic patients. Administration of alpha adrenergic agonist (midodrine) significantly improves systemic haemodynamics, renal function and sodium excretion in non azotemic cirrhotic patients with tense ascites(9).

Midodrine hydrochloride forms an active metabolite, 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(10, 11).

Desglymidodrine does not stimulate cardiac beta-adrenergic receptors. Desglymidodrine diffuses poorly across the blood-brain barrier, and is therefore not associated with effects on the central nervous system(12).

Midodrine has been prescribed for various aetiologies of symptomatic hypotension. These comprise neurocardiogenic syncope(13, 14), including vasovagal syncope(15, 16), orthostatic hypotension in the elderly(17, 18), autonomic nervous system dysfunction, haemodi-
alyssis-induced hypotension,(19), spinal cord injury(20, 21), and infiltrative protein deposition disorders (e.g. amyloidosis)(22).

We conducted a randomised double blind placebo-controlled study to assess the effect of midodrine in patients with non-azotemic cirrhosis with tense ascites and identifying if there was significant improvement in ascites (assessed by abdominal girth, body weight, average urine volume, and Doppler parameters) after 2 weeks of treatment with midodrine as compared to placebo. We also compared AST, ALT, serum creatinine, sodium, potassium, and albumin between midodrine group and placebo group at baseline, and 2 weeks after taking midodrine and placebo respectively.

METHODOLOGY
Study design and setting
Suitable patients were recruited by physicians, under supervision of supervisor physician (MA), at the internal medicine unit at Kasr-Elaini Hospital, Cairo University, Cairo, Egypt. This double blind, placebo-controlled, randomized trial was conducted at the inpatient internal medicine wards of the hospital on 67 patients (1 July 2012-30December 2012). Eligible patients were randomized to receive either midodrine or placebo capsules for 14 days. The study drugs (midodrine 2.5mg or placebo) were administered orally 3 times daily. The compliance of patients to study medication was assessed based on the patient diary at each study visit, 2 visits weekly, for inpatients and contact by the telephone, every 3 days, for patients discharged before the 14 days duration of the study.

Ethics
This study was approved by the Research Ethics Committee of Faculty of Pharmacy, Cairo University, Cairo, Egypt. All patients were given an oral explanation about the nature of the study and about study drug by the investigator. An information sheet was provided in a language understood by the patient, in simple Arabic language, and then written informed consent was obtained from each participant.

Selection of participants
Patients (with cirrhosis secondary to any etiology and tense ascites) of either sex, aged 18-75 years, diagnosed of cirrhosis and tense ascites as per Doppler, complete physical examinations, past history of liver cirrhosis, and laboratory values, willing to sign informed consent and ready for regular follow-up were enrolled in the study.

Patients with a history of chronic renal failure were excluded from the study. acute renal failure, hypertension, coronary artery disease, or congestive heart failure, hepatocellular carcinoma (HCC) or portal vein thrombosis, gastrointestinal bleeding, hepatic encephalopathy, or infection within one month preceding the study or during the study were excluded from the study.

Randomization
Randomisation procedures were automated, using centrally-allocated computer-generated random numbers. Participants were randomized to either the intervention (midodrine) or the placebo group. Thus there was no possibility of any of the trial team influencing the allocation of participants and concealment of allocation was complete.

Blinding
The randomization list was prepared by the data coordinating center of the hospital where empty capsules, from faculty of pharmacy Cairo University along with lactose powder, were filled either with midodrine tablet 2.5mg (one tablet per each capsule) or with small amount of lactose powder to form the placebo capsules. Then in a plastic containers 42capsule contained midodrine were packaged in the container and take a certain number, based on the randomization process. By the same way every 42capsule contained lactose powder were packaged in another plastic container with the same appearance as the previous one, stand for placebo given another number. No one of the investigators was allowed to know which one was the drug or the placebo until after the statistical analysis was done.

Interventions
At initial visit, patients were assigned either to midodrine group (n=33) or placebo group (n=33) using the randomization chart. Body weight, history of tapping of ascitic fluid, history of diuretic use, abdominal girth were recorded at baseline and at the end of 2 weeks therapy for all patients enrolled in the study.

Abdominal girth was measured by clinical pharmacist and based on International Diabetes Federation (IDF) guidelines as follow:

After location of the top of the hip bone (iliac crest) and taking the measurement just above this bony landmark, just where one finger can fit between the iliac crest and the lowest rib, the tape measure was positioned horizontally, parallel to the floor. Measurement was done at a level just above the iliac crest, and positioning the tape horizontally, irrespective of whether the umbilicus is above or below the tape. The patient was standing erect and has relaxed the abdominal muscles. Measurement was taken at the end of normal expiration without compressions in the skin with the tape measure. This method was done 3 times within 15 minutes and average was taken as the value(23). Average 24-h urine volume was also obtained. Patients were asked to evacuate their bladder at 9 AM. and discard the urine, not to be added to the container. The patients were told then to collect their urine in graduated containers over 3 days where the last bladder evacuation, which was added to the containers, was at 9 am. Three days later from the first day and 1 day before the study. The three days collected urine volume, in milliliters, was divided by 3 to account for the average 24-h urine volume, and by the same method we calculated the average 24-h urine volume over 3 days after starting the study, this was done by nurses under supervision of clinical pharmacist, AA.

Blood samples were obtained at baseline and at the end of 2 weeks therapy to perform hematology and biochemistry tests including serum electrolytes (Na+, K+), albumin, creatinine, AST, and ALT. Doppler parameters were also tested in all patients, including portal vein diameter, portal vein velocity, and portal vein resistivity index, at baseline and at the end of 2 weeks of therapy.

Percent of patients performed tapping of ascitic fluid on a weekly basis to relieve respiratory distress or abdominal pain was recorded for one month before and during the two weeks period of the study for the 2 studied groups

Midodrine tablets were filled into empty capsules
for patients in the midodrine group to ensure the blind-
ing of the trial and the same type of the empty capsules
were filled with lactose to make the placebo capsules
for patients in placebo group. Neither the investigator
nor the patients were allowed to know whether the cap-
sules contained midodrine or placebo.

Statistical method

The primary objective was to show if midodrine
therapy is superior to placebo with respect to mean fall
in body weight, abdominal girth, average urine output,
and/or other some Doppler parameters at the end of
therapy from baseline. The sample size calculation re-
quired approximately 66 patients to be randomized and
60 evaluable patients (30 patients per treatment group)
to complete the study to detect a treatment difference
with a power of 80% at 5% level of significance.
The data was coded and entered using the statisti-
cal package SPSS version 15 (IBM, New York, United
States). The data was summarized using descriptive
statistics: mean, standard deviation, minimal and max-
imum values for quantitative variables and number and
percentage for qualitative variables. Statistical differ-
ences between groups were tested using Chi Square test for
qualitative variables, independent sample t test quan-
titative normally distributed variables while Wilcoxon
Signed Ranks Test was used for quantitative variables,
which aren’t normally distributed. Testing the effect of intervention, baseline vs. 2-weeks post-treat-
ment, was done using paired sample t test for quanti-
tative normally distributed variables while Nonpara-
metric Mann Whitney test was used for quantitative
variables, which aren’t normally distributed. Testing the
effect of intervention, baseline vs. 2-weeks post-treat-
ment, was done using paired sample t test for quanti-
tative normally distributed variables while Wilcoxon
Signed Ranks Test was used for quantitative variables,
which aren’t normally distributed. P-values less than
0.05 were considered statistically significant (24).

RESULTS

Figure 1 shows the flow diagram of the progress
through the phases of a parallel randomised trial of
midodrine and placebo groups. One patient declined
to start the study before signing the informed consent
form and 6 patients couldn’t complete the study due
to loss to follow up and the large distance between the
hospital and their houses, Kasr-Elaini Hospital provides
products and services for free so patients come from
different Governorates of Egypt, and we expected some
loss to follow up so we started with larger numbers of
patients, started with 67 patients and ended with 60.

Patient distribution

A total of 67 eligible patients satisfying inclusion/
xclusion criteria were enrolled on the study. All the
patients recruited in the study were suffering from cir-
rhosis secondary to hepatitis C virus (HCV). One patient
decided to participate and 6 patients were lost to fol-
low-up. A total of 60 patients completed the study (mid-
odrine therapy: 30; placebo therapy: 30). The two treat-
ment groups were similar with respect to demographics
and baseline disease characteristics (Table 1).

There were no statistically significant differences be-
tween the 2 groups as regards the age (p = 0.96), body
weight (p = 0.27, average urine volume (p = 0.38) and ab-
dominal girth (p = 0.3). There were no statistically
significant differences between the two groups as regards
the serum ALT (p = 0.29), serum AST (p = 0.88), serum
albumin (p = 0.62), serum sodium level (p = 0.88), se-
rum creatinine (p = 0.72), and serum potassium (p = 0.2).

The two treatment groups were subjected to Doppler
ultrasound evaluations for the abdomen at baseline (Ta-
ble 2). There were no statistically significant differences
found in portal vein diameter (p = 0.65), portal vein flow
velocity (p = 0.99), and hepatic artery resistivity index
(p = 0.12) between both groups.

Efficacy after 2 weeks of therapy

At the end of 2 weeks of therapy with placebo and mi-
odrine there was no statistically significant differences
in abdominal girth (p = 0.25) in placebo group (Table 3),
while in midodrine group there was statistically signifi-
cant differences in abdominal girth (p < 0.001) (Figure
3), (Table 4). In placebo group there was no statistically
significant differences in body weight (p = 0.75), but sta-
tistically significant differences was recorded in mido-
дрine group as regards body weight (p < 0.001) (Figure
2), (Table 4). There were no statistically significant dif-
fences in 24-h average urine volume in both placebo
and midodrine groups (p = 0.96) (Table 3), and (p = 0.27)
(Table 4).

The laboratory tests were done at baseline and at the
end of therapy. Mean changes from baseline for various
laboratory parameters were evaluated at the end of 2
weeks for placebo and midodrine groups. There were
no statistically significant differences in serum ALT
(p = 0.34, serum AST (p = 0.14), serum albumin (p = 0.44),
serum Na (p = 0.19), serum K (p = 0.77), serum creatinine
(p = 0.93) in placebo group (Table 3), and also there were
no statistically significant differences in serum ALT
(p = 0.1), serum AST (p = 0.14), serum albumin (p = 0.24),
serum Na (p = 0.78), serum K (p = 0.37), serum creatinine
(p = 0.93) in midodrine group (Table 4).

The Doppler parameters evaluations were done at
baseline and at the end of therapy. Mean changes from
baseline for various Doppler parameters were evaluated
at the end of 2 weeks for placebo and midodrine groups.
There were no statistically significant differences
in portal vein diameter (p = 0.274), portal vein flow
velocity (p = 0.97), hepatic artery resistive index (RI)
(which is the commonest Doppler parameter used for
hepatic arterial evaluation) (p = 0.31) in placebo group
(Table 3). As in placebo group, there were no statistical-
ly significant differences in midodrine group regarding
to the same previously mentioned parameters which are
portal vein diameter (p = 0.4), portal vein flow veloc-
ity (p = 0.56), and hepatic artery RI (p = 0.56) (Table 4).

Percent of patients performed tapping of ascetic fluid
in all patients was recorded and it was 90% at baseline
for midodrine group and this percent dropped after two
weeks of midodrine treatment to 80% (Figure 4). In the
Placebo treated group it was 90% at base line and unlike
midodrine treated group there was no change in this
percent after two weeks of placebo treatment (Figure 4).

There were no statistically significant differences
in all values at the end of 2 weeks between midodrine
group and placebo one, except for the trend toward dif-
ference in abdominal girth.

As regards patients characteristics; body weight
(p = 0.2), average urine output (p = 0.1), laboratory
tests; ALT (p = 0.27), AST (p = 0.19), albumin (p = 0.5), Na
(p = 0.15), K (p = 0.3), serum creatinine (p = 0.9), and
Doppler parameters evaluations; portal vein diameter
(p = 0.5), portal vein flow velocity (p = 0.4), and hepatic
artery resistivity index (p = 0.9) (Table 5).
DISCUSSION

Our results showed that there were no statistically significant differences in age, body weight and average 24-h urine volume among midodrine group and placebo group at baseline.

In midodrine group there was significant reduction in body weight after taking the drug for 2 weeks, in agreement with previous findings of decreased body weight by midodrine in some of patients(25). We suggested that this reduction in body weight was due to reduction in fluid accumulation by midodrine because midodrine causes inactivation of the renin-angiotensin-aldosterone system (RAAS) with subsequent reduction in renal retention of sodium and water as detected by a previous study in which the authors observed a significant reduction in plasma renin and aldosterone concentration and a trend toward a reduction in the volume of ascitic fluid removed by paracentesis without an effect on renal function1(25). The reduction in abdominal girths detected in midodrine group after 2 weeks of midodrine therapy also may be explained by the reduction in fluid accumulation and the volume of ascitic fluid as recognized by Another study of 2 patients. One patient had been on hemodialysis for human immunodeficiency virus (HIV)-related nephropathy and the other patient had hepatorenal syndrome (HRS) requiring hemodialysis. In both cases, midodrine was apparently initiated to treat hypotension. In these 2 patients, the addition of midodrine was found to be beneficial, causing a decrease in both the frequency of large volume paracentesis (LVP) and the volume of ascitic fluid drained(26).

Monitoring body weight and abdominal girth of cirrhotic patients with tense ascites are routinely performed in both the inpatient and outpatient settings. Monitoring fluid intake and urine output are performed primarily for inpatients, owing to practical constraints in the outpatient setting. Electrolytes and renal function tests of Patients with tense ascites should be monitored daily while hospitalized and once or twice weekly early after hospital discharge to as infrequently as every 3 months for the very stable patient. Laboratory Tests like serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, AST:ALT ratio, prothrombin time (PT), and platelet count can be used in the diagnosis and monitoring of hepatic injury(27).

Abdominal ultrasound is a useful imaging modality, which can provide clinically important information when applied to patients with suspected chronic liver disease (28).

Weight and abdominal girth reduction are from the target goals and monitoring parameters in observing patients with ascites(29). In our results midodrine decreased body weight and abdominal girth despite all patients in the 2 groups were on diuretics, either single diuretic or in combination.

In midodrine group, 18 patients were taking furosemide plus spironolactone, 7 patients were taking furosemide alone, and the remainder 5 patients were taking spironolactone alone. In placebo group the figure was not great different as 16 patients were taking furosemide plus spironolactone, 6 patients were taking furosemide alone, and the remainder 8 patients were taking spironolactone alone.

Our study reconfirmed the previously observed non-significant differences in natriuretic response of IV furosemide to midodrine in non-azotemic cirrhotics with ascites(30). This Previous double-blind, placebo-controlled, cross-over study which was done to test the hypothesis that midodrine significantly increases natriuretic response of IV furosemide in non-azotemic cirrhotics with ascites found that oral midodrine did not increase the natriuretic response to furosemide in non-azotemic cirrhotic patients with ascites and in our patients who received midodrine for 2 weeks there were no statistically significant difference in average 24-h urine volume before and during treatment.

Midodrine, by improving the circulatory dysfunction in patients with diuretic-resistant ascites, significantly reduces ascites production which can improve the management of ascites(9).

History of tapping was recorded for each patient on a weekly basis for one month before the study and then during the study period. We didn’t calculate the volume of ascites removed but we were concerned with the frequency of tapping only.

Ninety% of patients, either in midodrine or in placebo group were tapping their ascitic fluid once weekly for 1 month, at least, prior to the study. Twenty seven patients in midodrine group and 27 patients in placebo group. Three patients in midodrine group stopped performing tapping during the 2 weeks of the study duration while the remainder 24 patients continued to do tapping once weekly. The twenty seven patients in placebo group continued to perform tapping their ascites once weekly, as before conducting the study, during the 2 weeks of study period. Percent of patients performed tapping of ascitic fluid, on a weekly basis to relieve respiratory distress or abdominal pain, in midodrine treated group at base line was 90% which dropped to 80% after 2 weeks of receiving midodrine. One study documented that there was a trend towards a reduction in the volume of ascites removed by paracentesis(20). This study and ours go with previous study on the effect of oral midodrine monotherapy in 8 patients with type 2 HRS which observed that there was evidence that a reduction in fluid accumulation may occur with use of vasoconstrictors such as midodrine in patients with end-stage liver disease without a significant renal function improvement(31).

The results of our study disagreed with a study that found midodrine treatment was associated with a significant improvement of systemic hemodynamic leading to significant increase in diuresis in patients with ascites and administration of alpha adrenergic agonist (midodrine) significantly improves systemic haemodynamics, renal function and sodium excretion in non azotemic cirrhotic patients with tense ascites(32), as our results didn’t notice any statistically significant differences in average 24-h urine volume in both groups. The midodrine dose might be the issue as the authors in the previous study used large doses of midodrine, 10mg three times daily while in our study we only used 2.5mg three times daily.

CONCLUSION

In conclusion, this study has shown that midodrine is a promising drug that may decrease body weight, abdominal girth, and frequency of tapping in patients with non azotemic liver cirrhosis with tense ascites. Wight and abdominal girth reduction are very important parameters in improving and observing patients with
ascites, but larger studies need to be done on a larger number of patients before midodrine can be recommended for use in this patient population. We suggest larger doses of midodrine for this trend.

ACKNOWLEDGMENTS
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REFERENCES


Midodrine in Non-azotemic Cirrhotic Patients

**Enrollment**
- Assessed for eligibility (n=67)

  - Excluded (n=1)
    - Declined to participate (n=1)

  Randomized (n=66)

**Allocation**
- Allocated to midodrine group (n=33)
  - Received allocated intervention (n=33)
  - Did not receive allocated intervention (n=0)

- Allocated to placebo group (n=33)
  - Received allocated intervention (n=33)
  - Did not receive allocated intervention (n=0)

**Follow-Up**
- Lost to follow-up (n=5)
  - Due to large distance between the hospital and their houses

  - Analyzed (n=30)

- Lost to follow-up (n=5)
  - Due to large distance between the hospital and their houses

  - Analyzed (n=30)

**Analysis**

Bar chart showing body weight before and after treatment with placebo and midodrine.
TABLE 1. Baseline characteristics of patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo Group (n=30)</th>
<th>Midodrine Group (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>mean</td>
<td>mean</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.4</td>
<td>57.2</td>
<td>0.93</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75.2</td>
<td>7.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Abdominal girth (cm)</td>
<td>100.1</td>
<td>10.4</td>
<td>101.33</td>
</tr>
<tr>
<td>Average urine output (mL/24h)</td>
<td>1470</td>
<td>85</td>
<td>1420</td>
</tr>
<tr>
<td>ALT (mg/dL)</td>
<td>31.1</td>
<td>10.68</td>
<td>33.8</td>
</tr>
<tr>
<td>AST (mg/dL)</td>
<td>31.47</td>
<td>38.73</td>
<td>38.73</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.05</td>
<td>3.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Na(mEq/L)</td>
<td>129.7</td>
<td>126.2</td>
<td>126.2</td>
</tr>
<tr>
<td>K(mEq/L)</td>
<td>4.2</td>
<td>4.31</td>
<td>0.84</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.93</td>
<td>0.95</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Abbreviations: y, year; mL, milliliter; h, hour; kg, kilogram, n, number; SD, standard deviation, mEq, millequivalent; dL, deciliter; L, liter; cm, centimeter; mg, milligram; K, potassium; Na, sodium; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

TABLE 2. Baseline sonographic and doppler parameters of patients.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo Group (n=30)</th>
<th>Midodrine Group (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>mean</td>
<td>mean</td>
<td></td>
</tr>
<tr>
<td>portal vein diameter (cm)</td>
<td>14.06</td>
<td>14.053</td>
<td>0.2013</td>
</tr>
<tr>
<td>Portal vein flow velocity (cm/s)</td>
<td>12.37</td>
<td>12.36</td>
<td>2.74</td>
</tr>
<tr>
<td>Hepatic artery resistivity index</td>
<td>0.66</td>
<td>0.67</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abbreviations: cm, centimeter; s, second.

TABLE 3. Changes in baseline characteristics for the placebo treated group at the end of 2 weeks of therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Base line</th>
<th>2 weeks later</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>mean</td>
<td>mean</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75.2</td>
<td>7.4</td>
<td>0.93</td>
</tr>
<tr>
<td>Abdominal girth (cm)</td>
<td>100.1</td>
<td>101.33</td>
<td>15.61</td>
</tr>
<tr>
<td>Average urine output (mL/24h)</td>
<td>1470</td>
<td>1420</td>
<td>154</td>
</tr>
<tr>
<td>ALT (mg/dL)</td>
<td>31.1</td>
<td>33.8</td>
<td>8.44</td>
</tr>
<tr>
<td>AST (mg/dL)</td>
<td>31.47</td>
<td>38.73</td>
<td>28.6</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.05</td>
<td>3.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Na(mEq/L)</td>
<td>129.7</td>
<td>126.2</td>
<td>12.46</td>
</tr>
<tr>
<td>K(mEq/L)</td>
<td>4.2</td>
<td>4.31</td>
<td>0.84</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.93</td>
<td>0.95</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Abbreviations: g, gram.
### TABLE 4. Changes in baseline characteristics for the midodrine treated group at the end of 2 weeks of therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Base line</th>
<th></th>
<th>2 weeks later</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.33</td>
<td>9.9</td>
<td>72.57</td>
<td>9.97</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Abdominal girth (cm)</td>
<td>101.33</td>
<td>15.6</td>
<td>99.37</td>
<td>15.15</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Average urine output</td>
<td>1420</td>
<td>155</td>
<td>1450</td>
<td>193</td>
<td>0.27</td>
</tr>
<tr>
<td>(mL/24h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (mg/dL)</td>
<td>33.8</td>
<td>8.4</td>
<td>34.17</td>
<td>8.69</td>
<td>0.1</td>
</tr>
<tr>
<td>AST (mg/dL)</td>
<td>38.73</td>
<td>28.6</td>
<td>38.97</td>
<td>28.66</td>
<td>0.14</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.1</td>
<td>0.5</td>
<td>3.08</td>
<td>0.47</td>
<td>0.24</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>126.2</td>
<td>12.4</td>
<td>126.27</td>
<td>12.43</td>
<td>0.78</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.31</td>
<td>0.84</td>
<td>4.33</td>
<td>0.81</td>
<td>0.37</td>
</tr>
<tr>
<td>Serum creatinine (mg/</td>
<td>0.95</td>
<td>0.23</td>
<td>0.93</td>
<td>0.26</td>
<td>0.93</td>
</tr>
<tr>
<td>dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>portal vein diameter</td>
<td>14.05</td>
<td>0.2</td>
<td>14.02</td>
<td>0.27</td>
<td>0.4</td>
</tr>
<tr>
<td>(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal vein flow velocity(cm/s)</td>
<td>12.36</td>
<td>2.74</td>
<td>12.24</td>
<td>2.72</td>
<td>0.56</td>
</tr>
<tr>
<td>Hepatic artery resistivity index</td>
<td>0.67</td>
<td>0.01</td>
<td>0.67</td>
<td>0.02</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*P-value < 0.05 statistically significant

### TABLE 5. Comparison between midodrine group and placebo group at the end of two weeks of treatment.

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th></th>
<th>Midodrine</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75.27</td>
<td>7.11</td>
<td>72.57</td>
<td>9.97</td>
<td>0.2</td>
</tr>
<tr>
<td>Abdominal girth (cm)</td>
<td>100.47</td>
<td>9.8</td>
<td>99.37</td>
<td>15.15</td>
<td>0.09*</td>
</tr>
<tr>
<td>Average urine output</td>
<td>1475</td>
<td>87</td>
<td>1450</td>
<td>193</td>
<td>0.1</td>
</tr>
<tr>
<td>(mL/24h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (mg/dL)</td>
<td>31.73</td>
<td>8.51</td>
<td>34.17</td>
<td>8.69</td>
<td>0.27</td>
</tr>
<tr>
<td>AST (mg/dL)</td>
<td>31.53</td>
<td>11.02</td>
<td>38.97</td>
<td>28.66</td>
<td>0.19</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.05</td>
<td>0.31</td>
<td>3.08</td>
<td>0.47</td>
<td>0.5</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>130.8</td>
<td>12.1</td>
<td>126.27</td>
<td>12.43</td>
<td>0.15</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.22</td>
<td>0.58</td>
<td>4.33</td>
<td>0.81</td>
<td>0.3</td>
</tr>
<tr>
<td>Serum creatinine (mg/</td>
<td>0.93</td>
<td>0.3</td>
<td>0.93</td>
<td>0.26</td>
<td>0.9</td>
</tr>
<tr>
<td>dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>portal vein diameter</td>
<td>14.043</td>
<td>0.27</td>
<td>14.02</td>
<td>0.27</td>
<td>0.5</td>
</tr>
<tr>
<td>(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal vein flow velocity(cm/s)</td>
<td>12.38</td>
<td>2.71</td>
<td>12.24</td>
<td>2.72</td>
<td>0.4</td>
</tr>
<tr>
<td>Hepatic artery resistivity index</td>
<td>0.67</td>
<td>0.02</td>
<td>0.67</td>
<td>0.02</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*There is a trend toward difference between the two groups as regards the abdominal girth.