Comparison of the effect of midodrine versus octreotide on hemodynamic status in cirrhotic patients with ascites

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Abstract

BACKGROUND: In cirrhotic patients peripheral vasodilatation may decrease renal blood flow and subsequently raises plasma renin activity. Octreotide with several mechanisms causes peripheral arterial vasoconstriction. Midodrine is an alpha agonist and acts as a peripheral vasoconstrictor; therefore it may reduce plasma renin activity and improve renal function. In this study the effects of these two agents were compared on cirrhotic patients to determine their ability to reduce plasma renin activity and increase GFR.

METHODS: This study was a randomized clinical trial and was performed in Al-Zahra hospital in 2008-2009; 34 patients with CHILD C cirrhosis enrolled in this study. They were randomly divided into two groups. First group were treated by 3 days of subcutaneous octreotide 50 µg tid (n = 17). For the second group oral midodrine 7.5 mg tid was administered for 3 days. Plasma renin activity, blood pressure, glomerular filtration rate, and body weight were measured and compared before and after therapy in both groups.

RESULTS: In both groups, plasma rennin activity decreased significantly after treatment. The present study showed that both midodrine and octreotide can reduce plasma renin activity but midodrine can reduce PRA and increase GFR more potently than octreotide.

CONCLUSIONS: Midodrine has a favorable hemodynamic effect in nonazotemic cirrhotic patients by decreasing plasma renin activity and increasing GFR.

KEYWORDS: Liver Cirrhosis, Plasma, Renin, Midodrine, Octreotide.
in renal vascular bed and vasodilators are high in the splanchnic arterial bed.\textsuperscript{11}

Some studies showed that metaraminol and angiotensin II increased urine Na in nonazo-
temic cirrhotic patients with ascites\textsuperscript{12,13} whereas norepinephrine had not any outcome in them.\textsuperscript{14,15} Assessing vasoconstrictor agents in patients with cirrhosis and ascites and patients with hepatorenal syndrome have shows differ-
ent results.\textsuperscript{16-18} Ornipressin, an arterial vaso-
constrictor, improve splanchnic circulation and does not have any effect on renal ciculation. So, using vasoconstrictors is not recommended in renal sodium retention in patients with cirrho-
sis and ascites with or without hepatorenal syndrome (HRS).

There is no efficient oral arterial vasocon-
strictor for this omission. Of course, midodrine hydrochloride is oral alpha-mimetic and act directly on the peripheral alpha-receptors.\textsuperscript{19-21} But its effect on plasma renin activity and the treatment of arterial vasodilation in patients with cirrhosis is not studied before. This study aimed to assess the acute effects of oral ad-
ministration of midodrine on plasma renin activity and hemodynamic parameters in cir-
rhotic patients with ascites.

\textbf{Methods}

\textbf{Case Selection and Randomization}

As a prospective randomized clinical trial, cir-
rhotic patients with ascites who were referred to Al-Zahra Hospital were included in this study from January 2007 to January 2009. Their ages ranged from 15 to 75 years old. All pa-
tients were of group C based on Child-Pugh scoring system. In all patients, cirrhosis and ascites were confirmed by abdominal ultra-
sound, clinical and laboratory findings.

The study was approved by the local ethic committee and written informed consent was acquired from all patients. Inclusion criteria were being a CHILD-C cirrhosis patient who: (I) age more than 15 years old; (II) do not had GI bleeding during last 7 days and/or had an unstable hemodynamics; (III) do not have hep-
atic encephalopathy; (IV) have no infection (sepsis, spontaneous bacterial peritonitis) with-
in the last 30 days; (V) do not have diabetes mellitus; (VI) do not have cardiovascular dis-
eases and hypertension; (VII) have no proven hepatocellular carcinoma; (VIII) do not have hepatorenal syndrome; and (IX) have no known allergy to drugs.

Exclusion criteria were having hepatic en-
cephalopathy, hepatorenal syndrome, hemo-
dynamic instability, infection or gastrointesti-
nal bleeding during the course of admission.

All patients were managed by a single gas-
troenterologist. Based on the calculation the fair needed number for performing this study was 17 per group. All candidates were ran-
domly allocated based on envelope method into either midodrine group (group A, n = 17) or octreotide group (group B, n = 17).

\textbf{Treatment Strategy}

Group A patients were treated by 7.5 mg oral midodrine three times daily for 3 days. Treatment in group B was performed by 50 mg sub-
cutaneous octreotide three times daily for 3 days. The dose of diuretics like furosemide or spironolactone was not changed during the past 2 or 4 days before initiation of therapy. In addition, no diuretics were started or discon-
tinued during the last 4 days prior to the treatment and during treatment.

Serum creatinine level was checked before therapy and at the forth day of treatment by Jaffe method (Biosystem® kits). Fasting weight and blood pressure (seated) were also meas-
ured before and after treatment.

Plasma renin activity was checked before initiation of treatment and at the 4\textsuperscript{th} day based on the following method. Five ml of venous blood sample was drawn at seating position, 2 hours after waking up. Blood samples were mixed by EDTA and plasma was isolated from the whole blood. The samples were sent to the hospital laboratory in ice bag. PRA was meas-
ured by Radioimmunoassay method using Immunotech® kits. All patients were in the su-
pine position for at least 8 hours before blood samples were taken.

The data included age, sex, etiology of cir-
rhosis, cause of admission, type of therapy (mi-
dodrine or octreotide), systolic and diastolic blood pressure, serum creatinine, and PRA.

**Statistical Analysis**
Chi square test was used to compare genders between two groups and the independent sample t-test, and paired t-test was used to compare other data between the two groups. Less than 0.05 p values were considered significant. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software.

**Results**
Thirty four patients were included in this study. There was no statistically significant difference in mean, age, PRA, GFR, MAP, body weight and sex between the two groups at the beginning of the study (Table 1).

The etiology of cirrhosis in group A included: 6 out of 17 (35%) had hepatitis B virus (HBV) infection, 2 (12%) had hepatitis C virus (HCV) infection, 1 (6%) had Wilson’s disease, and 8 (47%) had cryptogenic. The etiology of cirrhosis in group B included: HBV infection in 3 out of 17 (18%) patients, HCV in 4 (23%), cryptogenic in 6 (35%), autoimmune hepatitis in 2 (12%) and primary biliary cirrhosis (PBC) in 2 (12%).

The reason of admission in group A was ascites with edema for 5 out of 17 (29%) patients, ascites for 3 (18%) patients, edema for 4 (23%) patients, and band ligation for 5 (29%) patients. In group B, 6 out of 17 (35%) patients were hospitalized due to ascites with edema, 3 (18%) had ascites, 3 (18%) had edema, and 5 (29%) were referred for band ligation of esophageal varices. Neither the etiology of cirrhosis, nor the causes of hospitalization showed any significant difference between two groups (p = 0.22 and p = 0.07, respectively).

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<th>Table 1. Patients’ baseline characteristics</th>
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<td>Mean age ± SD (Years)</td>
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<td>PRA before therapy ± SD (ng/ml/h)</td>
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<td>MAP before therapy ± SD (mmHg)</td>
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<td>Weight before therapy ± SD (Kg)</td>
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<th>Table 2. The values of PRA, GFR, MAP, body weight, after treatment</th>
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<td><strong>Midodrine (A)</strong></td>
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<td>PRA after therapy ± SD (ng/ml/h)</td>
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<td>Mean weight after therapy ± SD (Kg)</td>
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Table 2 shows the comparison of mean of plasma renin activity (PRA), glomerular filtration rate (GFR), mean arterial pressure (MAP) and body weight after treatment in 2 groups, as well as the difference of these variables with the baseline. As it’s shown in table 2, although both midodrine and octreotide decreased PRA, the mean of PRA after treatment was significantly lower in group A. The difference of PRA after treatment was significantly higher in group A. The mean of GFR after treatment was also significantly higher in group A and the difference of GFR, after and before therapy was higher in this group. There was no significant difference in the mean of arterial pressure or body weight after treatment, between the 2 groups (Table 2).

Discussion

This randomized clinical trial was performed to find a simple and safe treatment method as an ideal treatment for cirrhotic patients with ascites. This study showed that both midodrine and octreotide can reduce plasma renin activity but midodrine can reduce PRA and increase GFR more potently than octreotide.

In recent years, the use of vasoactive drugs to combat splanchnic vasodilatation in cirrhotic patients with ascites has been promising. The pathophysiology of responding to octreotide or midodrine seems to be based on "peripheral arterial vasodilatation hypothesis."20 It says that severe renal vasoconstriction due to systemic arterial vasodilatation among arterial underfilling and activation of different vasoconstrictor systems tend to renal dysfunction in cirrhosis. So, reducing the amount of arterial vasodilatation and increasing intravascular volume may decrease renal function and improve natriuresis.

Using vasoconstrictor drugs in cirrhotic patients with hepatorenal syndrome (HRS) is related with improvement of systemic hemodynamics and natriuresis;20-22 but there are some evidences that vasoconstrictor therapy could be useful in patients with cirrhosis without HRS. Some intravenous vasoconstrictors such as terlipressin,23,24 metaraminol,24 angiotensin II, and norepinephrine could improve systemic hemodynamics in these patients in acute administration23,24 without any effect on renal function and natriuresis.25 There are no studies on chronic administration of these vasoconstrictor.

Midodrine hydrochloride is an alpha-mimetic drug with direct effect on the peripheral alpha-receptors of the sympathetic nervous system. It is usually used in orthostatic hypotension and secondary hypotensive disorders.25,26 There is no evidences of using it for treatment of renal disorders in patients with cirrhosis. In the current study, oral midodrine improved systemic hemodynamics in patients with cirrhotic without HRS. Animal studies have shown that midodrinn had a more effect on increasing splanchnic arterial resistance compared to renal arterial resistance.27

The combination of oral midodrine, subcutaneous octreotide, and albumin in patients with HRS and ascites could be considered as promising treatment.21,28 In recent studies, a 10-day treatment with subcutaneous octreotide induced renal dysfunction in nonazotemic patients with ascites, which was improved by adding midodrine,29 an evidence of relation between midodrine with albumin and improvement of renal function in patients with ascites and HRS. Accordingly, the present data showed significant improvement of GFR after midodrine therapy. In the same study octreotide administration caused significant increase in cardiac output and cardiac index while MAP, heart rate and systemic vascular resistance were not significantly modified. Also they did not found any significant modification on serum creatinine.29 Another study reported results of octreotide and placebo administration on renal function and hormonal parameters, which showed that serum creatinine, creatinine clearance, and 24-hour urinary sodium excretion were not modified during either period of treatment.30 These finding are in the line with the presented data.

In another study, a 7-day treatment with midodrine in cirrhotic patients without ascites
was associated with a significant improvement of systemic hemodynamics; and there were no significant changes on renal blood flow, and calculated renal vascular resistance after 7 days treatment with midodrine in cirrhotic patients with ascites. More specifically, an increase in MAP was noted in line with a fall in cardiac output and heart rate and a consequent marked increase in calculated systemic vascular resistance.\textsuperscript{31}

Another study showed that administration of octreotide after the discontinuation of diuretic treatment caused a significant increase in cardiac output and cardiac index, without modification of MAP, heart rate, and systemic vascular resistance.\textsuperscript{32}

Angeli et al revealed that the acute oral administration of midodrine significantly improve systemic hemodynamics in nonazotemic cirrhotic patients with ascites. Renal perfusion and urinary sodium excretion improved in these patients, too. By contrast they showed that midodrine only improves systemic hemodynamics in patients with type 2 hepatorenal syndrome, with no effect on renal function.\textsuperscript{19}

Interestingly, a previous study showed that midodrine also significantly reduce serum metabolites of nitric oxide, thought to be one of the most important factors in the pathogenesis of arterial vasodilation in cirrhosis.\textsuperscript{19} As there are no reasons for a direct effect of midodrine on nitric oxide release, the authors concluded that the mentioned reduction may be secondary to reduction of the endothelial shear stress caused by the improved systemic hemodynamics.\textsuperscript{19}

The present results showed no significant improvement in blood pressure, but it is obvious that marked suppression of PRA (which is considered to be the most sensible index of arterial underfilling) is due to improvement in systemic hemodynamics. In this study neither midodrine nor octreotide could increase MAP significantly, but midodrine could decrease PRA and increase GFR. This is hard to explain, but may be due to stronger vasoconstrictor effect of midodrine on splanchnic rather than peripheral arterial system. Although previous studies have used different doses of octreotide and some of them prescribed it by continuous intravenous infusion, we decided to administer the drug subcutaneously, with the lowest possible dose. Since octreotide is an expensive drug and 3 subcutaneous injections per day are cheaper and more comfortable for the patients, we used this method. Perhaps using higher subcutaneous doses or intravenous infusions lead to more significant hemodynamic effects.

**Limitations**

Unfortunately we could not measure some variables such as renal blood flow, cardiac output systemic vascular resistance and urinary sodium excretion. Other limitations of this study were small size of the groups and short duration of treatment. It is believed that a larger study which measures all of these variables can be useful for better understanding of the effect of vasoconstrictors on hemodynamic parameters in cirrhosis.

**Conclusions**

In conclusion, the results of the current study show that the oral administration of midodrine is associated with a significant suppression of plasma renin activity and increase in GFR and probable subsequent improvement of systemic hemodynamics in nonazotemic cirrhotic patients with ascites.

**Conflict of Interests**

Authors have no conflict of interests.

**Authors’ Contributions**

MM designed the study, gathered the data, did the data analysis, and helped in writing the manuscript. LF gathered the data and helped in writing the manuscript. MR did the data analysis and
helped writing in the manuscript. AS designed the study, gathered the data and helped in writing the manuscript. All authors have read and approved the content of the manuscript.

References


