Received: 14.5.2010 **Accepted: 22.6.2010**

Original Article

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

Mohammad Minakari[a], Leila Faiiaz[b], Mehdi Rowshandel[c], Ahmad Shavakhi[d]*

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 administrated 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.

JRMS 2011; 16(1): 87-93

Cirrhosis is a global health problem and in 2001, is has been the 10th top cause of death for men and the 12th for women in the United States, killing about 27,000 patiens each year.[1]

It is assumed that the main reson of peripheral arterial vasodilation is the functional renal abnormalities in patients with cirrhosis.[2-4] It seemed that arterial vasodilation is associated with increasing local or systemic vasodilators like bile acids, prostacyclin, nitric oxide, vasoactive intestinal peptide, substance P, and glucagon.[4-8] The site of arterial vasodilation and its relation with renal sodium retention is also questionable. According to previuos studies, reduing arterial vascular resistance mainly is seen in the spleen in patients with ascites due to cirrhosis.[9,10] Then the intrinsic systems such as renin-angiotensin-aldosterone system, nonosmotic release of antidiuretic hormone (ADH), and sympathetic nervous system would be activated by the splanchnic arterial vasodilation and tend to renal vasoconstriction and sodium retention. So, the ascites occurs in with cirrhosis because of imbalance between endogenous vasoactive systems; as vasoconstrictors are made

[a] Assistant Professor of Gastroenterology and Hepatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
[b] Resident of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
[c] Researcher, Poursina Hakim Research Center, Isfahan, Iran.
[d] Associate Professor of Gastroenterology and Hepatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
* Corresponding Author
E-mail: shavakhi@med.mui.ac.ir

in renal vascular bed and vasodilators are high in the splanchnic arterial bed.[11]

Some studies showed that metaraminol and angiotensin II increased urine Na in nonazotemic cirrhotic patients with ascites[12,13] whereas norepinephrine had not any outcome in them.[14,15] Assessing vasoconstrictor agents in patients with cirrhosis and ascites and patients with hepatorenal syndrome have shows different results.[16-18] Ornipressin, an arterial vasoconstrictor, 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 cirrhosis and ascites with or without hepatorenal syndrome (HRS).

There is no efficient oral arterial vasoconstrictor for this omission. Of course, midodrine hydrochloride is oral alpha-mimetic and act directly on the peripheral alpha-receptors.[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 administration of midodrine on plasma renin activity and hemodynamic parameters in cirrhotic patients with ascites.

Methods

Case Selection and Randomization

As a prospective randomized clinical trial, cirrhotic 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 patients were of group C based on Child-Pugh scoring system. In all patients, cirrhosis and ascites were confirmed by abdominal ultrasound, 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 hepatic encephalopathy; (IV) have no infection (sepsis, spontaneous bacterial peritonitis) within the last 30 days; (V) do not have diabetes mellitus; (VI) do not have cardiovascular diseases 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 encephalopathy, hepatorenal syndrome, hemodynamic instability, infection or gastrointestinal bleeding during the course of admission.

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

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 subcutaneous 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 discontinued 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 measured before and after treatment.

Plasma renin activity was checked before initiation of treatment and at the 4th 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 measured by Radioimmunoassay method using Immunotech® kits. All patients were in the supine position for at least 8 hours before blood samples were taken.

The data included age, sex, etiology of cirrhosis, 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).

Table 1. Patients' baseline characteristics

		Midodrine (A)	Octreotide (B)	P value
Number of patients		17	17	-
Gender	Male	12 (70.6%)	14 (82.4%)	0.69
	Female	5 (29.4%)	3 (17.6%)	
Mean age ± SD (Years)		59.47 ± 14.08	49.59 ± 18.03	0.08
PRA before therapy ± SD (ng/ml/h)		30.99 ± 10.93	28.32 ± 8.65	0.43
GFR before therapy ± SD		73.98 ± 29.72	86.64 ± 32.73	0.25
MAP before therapy ± SD (mmHg)		73.84 ± 10	78.43 ± 8.13	0.15
weight before therapy ± SD (Kg)		67.47 ± 11.16	76.58 ± 17.73	0.08

Table 2. The values of PRA, GFR, MAP, body weight, after treatment

	Midodrine (A)	Octreotide (B)	P value
PRA after therapy ± SD (ng/ml/h)	12.94 ± 7.62	20.64 ± 8.23	0.008
Delta PRA ± SD (ng/ml/h)	18.06 ± 4.7	7.67 ± 6.77	0.001
GFR after therapy ± SD	108.64 ± 24.38	92.11 ± 13.5	0.03
Delta GFR ± SD	21.99 ± 16.84	5.12 ±12.36	0.01
MAP after therapy ± SD (mmHg)	81.57 ± 11.25	85.19 ± 7.9	0.29
Delta MAP ± SD (mmHg)	7.7 ± 13.1	6.8 ± 6.8	0.8
Mean weight after therapy ± SD (Kg)	63.82 ± 11.95	73.34 ± 16.64	0.4
Delta mean weight ± SD (Kg)	3.65 ± 2.71	2.23 ± 3.58	0.3

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 edidences 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 administration[23,24] 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 midodrin 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.[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.[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.[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.[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.[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

1. Roguin A. Rene Theophile Hyacinthe Laënnec (1781-1826): the man behind the stethoscope. Clin Med Res 2006;4(3):230-5.
2. Epstein M. Renal sodium handling in liver disease. In: Epstein M, editor. The kidney in liver diseases. 4th ed. Philadelphia: Hanley and Belfus; 1996. p. 1-31.
3. Arroyo V, Ginès P, Jiménez W, Rodés J. Ascites, renal failure, and electrolyte disorders in cirrhosis. Pathogenesis, diagnosis, and treatment. In: McIntyre N, editor. Oxford textbook of clinical hepatology, Volume 1. Oxford: Oxford Medical Publications; 1991. p. 429-70.
4. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8(5):1151-7.
5. Bosch J, Ginés P, Arroyo V, Navasa M, Rodés J. Hepatic and systemic hemodynamics and the neurohumoral system in cirrhosis. In: Epstein M, editor. The kidney in liver disease. 3rd ed. Baltimore: Williams and Wilkins; 1988. p. 286-305.
6. Guarner C, Soriano G, Tomas A, Bulbena O, Novella MT, Balanzo J, et al. Increased serum nitrite and nitrate levels in patients with cirrhosis: relationship to endotoxemia. Hepatology 1993;18(5):1139-43.
7. Lee FY, Colombato LA, Albillos A, Groszmann RJ. N omega-nitro-L-arginine administration corrects peripheral and systemic capillary hypotension and ameliorates plasma volume expansion and sodium retention in portal hypertensive rats. Hepatology 1993;17(1):84-90.
8. Morales-Ruiz M, Jiménez W, Pérez-Sala D, Ros J, Levias A, Lamas S, et al. Increased nitric oxide synthase expression in arterial vessels of cirrhotic rats with ascites. Hepatology 1996;24(6):1481-6.
9. Fernandez-Seara J, Prieto J, Quiroga J, Zozaya JM, Cobos MA, Rodrigues-Eire JL, et al. Systemic and regional hemodynamics in patients with liver cirrhosis and ascites with and without functional renal failure. Gastroenterology 1989;97(5):1304-12.
10. Maroto A, Ginés P, Arroyo V, Ginés A, Saló J, Clária J, et al. Brachial and femoral artery blood flow in cirrhosis: relationship to kidney dysfunction. Hepatology 1993;17(5):788-93.
11. Laragh JH, Cannon PJ, Bentzel CJ, Sicinski AM, Meltzer JI. Angiotensin II, norepinephrine, and renal transport of electrolytes and water in normal man and in cirrhosis with ascites. J Clin Invest 1963;42(7):1179-92.
12. Lancestremere RG, Klinger EL Jr, Frisch E, Papper S. Simultaneous determination of cardiac output and renal function in patients with Laennec's cirrhosis during the administration of the pressor amine, metaraminol. J Lab Clin Med 1963;61:820-5.
13. Gutman RA, Forrey AW, Fleet WP, Cutler RE. Vasopressor-induced natriuresis and altered intrarenal haemodynamics in cirrhotic man. Clin Sci 1973:45(1):19-34.
14. Shapiro MD, Nicholls KM, Groves BM, Kluge R, Chung HM, Bichet DG, et al. Interrelationship between cardiac output and vascular resistance as determinants of effective arterial blood volume in cirrhotic patients. Kidney Int 1985;28(2):206-11.
15. Badalamenti S, Borroni G, Lorenzano E, Incerti P, Salerno F. Renal effects in cirrhotic patients with avid sodium retention of atrial natriuretic factor injection during norepinephrine infusion. Hepatology 1992;15(5):824-9.
16. Cohn JN, Tristani FE, Khatri IM. Systemic vasoconstrictor and renal vasodilator effects of PLV-2 (octapressin) in man. Circulation 1968;38(1):151-7.
17. Lenz K, Hörtnagl H, Druml W, Reither H, Schmid R, Schneeweiss B, et al. Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis. Effects on renal haemodynamics and atrial natriuretic factor. Gastroenterology 1991:101(4):1060-7.
18. Saló J, Ginés A, Quer JC, Fernádez-Esparrach G, Guevara M, Ginés P, et al. Renal and neurohormonal changes following simultaneous administration of systemic vasoconstrictors and dopamine or prostacyclin in cirrhotic patients with hepatorenal syndrome. J Hepatol 1996:25(6):916-23.
19. Angeli P, Volpin R, Piovan D, Bortoluzzi A, Craighero R, Bottaro S, et al. Acute effects of the oral administration of midodrine ,an alpha-adrenergic agonist, on renal hemodynamics and renal function in cirrhotic patients with ascites. Hepatology 1998;28(4):937-43.
20. Mulkay JP, Louis H, Donckier V, Bourgeois N, Adler M, Deviere J, et al. Long-term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome: a pilot study. Acta Gastroenterol Belg 2001;64(1):15-9.
21. Duvoux C, Zanditenas D, Hézode C, Chauvat A, Monin JL, Roudot-Thoraval F, et al. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. Hepatology 2002;36(2):374-80.

22. Angeli P, Volpin R, Gerunda G, Craighero R, Roner P, Merenda R, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29(6):1690-7.
23. Therapondos G, Stanley AJ, Hayes PC. Systemic, portal and renal effects of terlipressin in patients with cirrhotic ascites: a pilot study. J Gastroenterol Hepatol 2004;19(1):73-7.
24. Kalambokis G, Economou M, Paraskevi K, Konstantinos P, Pappas C, Katsaraki A, et al. Effects of somatostatin, terlipressin and somatostatin plus terlipressin on portal and systemic hemodynamics and renal sodium excretion in patients with cirrhosis. J Gastroenterol Hepatol 2005;20(7):1075-81.
25. McTavish D, Goa KL. Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. Drugs 1989;38(5):757-77.
26. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA 1997;277(13):1046-51.
27. Tsuchida K, Yamazaki R, Kaneko K, Aihara H. Effects of midodrine on blood flow in dog vascular beds. Arzneimittelforschung 1986;36(12):1745-8.
28. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004;40(1):55-64.
29. Kalambokis G, Economou M, Fotopoulos A, Al Bokharhii J, Pappas C, Katsaraki A, et al. The effects of chronic treatment with octreotide versus octreotide plus midodrine on systemic hemodynamics and renal hemodynamics and function in nonazotemic cirrhotic patients with ascites. Am J Gastroenterol 2005;100(4):879-85.
30. Pomier-Layrargues G, Paquin SC, Hassoun Z, Lafortune M, Tran A. Octreotide in Hepatorenal syndrome: a randomized, double-blind, placebo-controlled, crossover study. Hepatology 2003;38(1):238-43.
31. Kalambokis G, Fotopoulos A, Economou M, Pappas K, Tsianos EV. Effects of a 7-day treatment with midodrine in non-azotemic cirrhotic patients with and without ascites. J Hepatol 2007;46(2):213-21.
32. Kalambokis G, Economou M, Fotopoulos A, Bokharhii JA, Katsaraki A, Tsianos EV. Renal effect of treatment with diuretics, octreotide or both, in non-azotemic cirrhotic patients with ascites. Nephrol Dial Transplant 2005;20(8):1623-9.