The Effect of Midodrine Hydrochloride on Chronic Hypotension in Patients with Diabetes Mellitus Undergoing Hemodialysis Therapy

Hemodiyaliz Tedavisi Alan Diabetes Mellitus'lu Hastalarda Midodrin Hidrokloridinin Kronik Hipotansiyona Etkisi

A. Metin SARIKAYA, MD,[a]
Funda SARI, MD,[a]
Ayşe Jini GÜNEŞ, MD,[a]
Mustafa EREN, MD,[a]
A. Edip KORKMAZ, MD,[a]
Mehmet KÜÇÜKSU, MD,[a]
Ramazan ÇETİNKAYA, MD[a]

[a]Clinic of Nephrology,
Antalya Training and Research Hospital,
Antalya

Geliş Tarihi/*Received:* 05.04.2011
Kabul Tarihi/*Accepted:* 21.09.2011

This study was presented as a verbal announcement at 27th National Congress of Nephrology, Hypertension, Dialysis and Transplantation, 22-26 September 2010, Antalya, Turkey

Yazışma Adresi/*Correspondence:*
A. Metin SARIKAYA, MD
Antalya Training and Research Hospital,
Clinic of Nephrology, Antalya,
TÜRKİYE/TURKEY
dr.metinsarikaya@gmail.com

ABSTRACT Objective: Chronic hypotension is a common complication of hemodialysis in patients with diabetes mellitus. Midodrine hydrochloride is an alpha-1 agonist that effectively corrects intradialytic hypotensive attacks. However, the effect of midodrine on chronic hypotension is still unknown in hemodialysis patients. In the present study, we aimed to evaluate the effects of midodrine treatment on chronic hypotension in patients with diabetes mellitus undergoing hemodialysis. **Material and Methods**: A total of 21 diabetic patients undergoing hemodialysis and had chronic hypotension (systolic blood pressure <100 mmHg before dialysis) were included in the study. Midodrine was given 5 mg p.o. twice a day and 5 mg before every dialysis session to all patients. Blood pressures (pre-hemodialysis systolic, diastolic and mean arterial pressure) were measured. Intra-dialytic hypotension attacks, orthostasis, dizziness, fatigue, blurred vision, dullness, and headache were recorded. Data obtained before midodrine therapy were compared to those collected at the 3rd month of hemodialysis when the patients were under midodrine therapy. **Results:** Pre-dialysis systolic, diastolic and mean arterial blood pressures, vertigo and syncope attacks were significantly ($p< 0.05$) improved by midodrine therapy. No significant difference was seen in mean ultra-filtration volume per hemodialysis session and number of intra-dialytic hypotensive attacks according to baseline values over the course of study ($p>0.05$). **Conclusion:** Midodrine appears to be an effective and safe treatment option in diabetic hemodialysis patients with symptomatic chronic hypotension, but it has no effect on intra-dialytic hypotensive attacks.

Key Words: Diabetes mellitus; hypotension; renal dialysis; Midodrine

ÖZET Amaç: Kronik hipotansiyon diyabetli hastalarda hemodiyalizin sık görülen bir komplikasyonudur. Midodrin hidroklorid diyaliz sırasındaki hipotansif atakları etkili şekilde düzelten alfa-1 agonist bir ilaçtır. Fakat hemodiyaliz hastalarında midodrinin kronik hipotansiyondaki etkisi halen bilinmemektedir. Bu çalışmada midodrin tedavisinin hemodiyaliz tedavisi alan diyabet hastalarında kronik hipotansiyona etkilerini değerlendirmeyi amaçladık. **Gereç ve Yöntemler**: Kronik hipotansiyonu olup (diyalizden önce sistolik kan basıncı <100 mmHg) hemodiyaliz tedavisi alan toplam 21 diyabetik hasta çalışmaya alındı. Tüm hastalara günde iki kez 5 mg ve her diyaliz seansından önce 5 mg oral midodrin tedavisi verildi. Kan basınçları (hemodiyalizden önce sistolik, diastolik ve ortalama arter basıncı) ölçüldü. Diyaliz sırasındaki hipotansiyon atakları, ortostaz, baş dönmesi, halsizlik, bulanık görme, sersemlik, sıkıntı ve baş ağrısı varsa kaydedildi. Midodrin tedavisinden önce elde edilen veriler midodrin tedavisi sırasında hemodiyaliz seanslarının üçüncü ayında toplanan verilerle karşılaştırıldı. **Bulgular:** Diyaliz öncesi sistolik, diastolik ve ortalama arter basınçları, vertigo ve senkop atakları midodrin tedavisi ile belirgin olarak düzeldi ($p< 0.05$). Çalışma boyunca her hemodiyaliz seansında ortalama ultra-filtrasyon hacminde ve diyaliz sırasındaki hipotansif ataklarda başlangıç değerlerine göre önemli fark saptanmadı ($p>0.05$). **Sonuç:** Çalışmamızın sonuçlarına göre midodrin tedavisi semptomatik kronik hipotansiyonu olan diyabetik hemodiyaliz hastalarında etkili ve güvenli bir tedavi seçeneği olarak görünmekte, fakat diyaliz sırasındaki hipotansif atakların tedavisinde etkili görünmemektedir.

Anahtar Kelimeler: Diabetes mellitus; hipotansiyon; böbrek diyalizi; Midodrin

doi:10.5336/medsci.2011-24144

Turkiye Klinikleri J Med Sci 2011;31(6):1527-31

Chronic hypotension (CH), defined by a systolic blood pressure < 100 mmHg in the inter-dialytic period, affects 5-10% of all hemodialysis patients.[1] Elderly patients and those with diabetes, as well as those with autonomic nervous system dysfunction, are particularly affected.[2] Hemodynamically, chronic hypotension is characterized by preserved cardiac index, heart rate or stroke volume, but reduced total peripheral vascular resistance.[3] Although its pathophysiology is not well defined, a reduced cardiovascular response to vasopressor agents (such as norepinephrine and angiotensin II) related to down-regulation of their receptors, as well as an increased production of vasodilators (such as nitric oxide or adrenomedullin) are possibly involved.[4] Various signs and symptoms associated to HD hypotension are numbness of the extremities, dizziness, general fatigue, epigastric discomfort, fainting, sweating, yawning, vomiting, incontinence and even occlusion of the arteriovenous fistula.[5]

There are two common types of HD-associated hypotension.[6]One typically occurs during the later stages of HD; the other is a chronic, persistent form of hypotension. The latter has been estimated to affect approximately 5-10% of the dialysis patients and becomes even more prevalent in long-term HD patients especially in those with diabetes.[7] More recently, midodrine, an oral selective alpha-1 adrenergic agonist, has been successfully used in the treatment of dialysis hypotension, especially in combination with cooling dialysate.[8] However, there is limited experience with the use of midodrine in HD patients with chronic hypotension, even no experience with diabetic subset of HD patients.[1,5,9] For this reason, we tried to demonstrate the effect of midodrine treatment on diabetic HD patients with chronic hypotension.

MATERIAL AND METHODS

Study subjects were 21 diabetic patients who underwent maintenance hemodialysis treatment and had systolic blood pressures less than 100 mmHg at pre-dialytic and inter-dialytic periods for at least 6 months and further declining blood pressures during hemodialysis. None had evidence of cardiac disease as documented by normal echocardiography, electrocardiogram, chest X-ray and adequate cardiac output established by ejection fraction. There were 7 males and 14 females with a mean age of 63.0 ± 15.8 (range: 47-82) years. Mean duration of HD treatment was 76.8 ± 28.7 (range: 36-126) months. Dialysate flow was 500 mL/min during HD, whereas blood flow was 300 mL/min and dialysate temperature was continuously maintained at 36.5°C. HD was performed using the same dialyzer (Synthetic low flux FX membrane, Fresenius). The dialysate contained 140 mmol/L sodium, 1.25 mmol/L calcium and the duration of each HD session was 4 hours.

These patients, after obtaining their written informed consent and ethical committee approval, were given 5.0 mg midodrine twice a day for three months to treat chronic hypotension. On HD day, 5 mg midodrine was given 30 minutes before HD. Data obtained before midodrine therapy were compared to those collected at the 3rd month of HD sessions under midodrine therapy. Objective evaluation, including systolic and diastolic blood pressure, hypotensive episodes during HD (a drop in systolic blood pressure> 20 mmHg during HD) and pulse rate was performed before every hemodialysis session. Mean arterial pressure was calculated as the sum of diastolic pressure and one third of pulse pressure. Blood biochemistry, hemoglobin, clearance of dialysis (Kt/V), weight of patient and amount of dialytic fluid ultra-filtration volume were analyzed, and values before and after medication were compared. Subjective symptoms, including orthostasis, dizziness, fatigue, blurred vision, dullness and headache were evaluated prior to and every other day following midodrine hydrochloride administration during hemodialysis. The severity of symptoms was classified into four categories; severe (3 score), moderate (2 score), mild (1 score), and no (0 score) symptoms. Patients completed a symptom questionnaire at each hemodialysis day, and the symptoms were scored accordingly by the severity of subjective symptoms. Patients recorded any side effects during midodrine treatment.

STATISTICAL ANALYSIS

Statistical analyses were performed by SPSS statistical software (10.0 versions, SPSS, Cary, NC, USA). All results are expressed as mean ± SD (standard deviation). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Parametric tests were used in our study, because the distribution of the variables was normal. Comparison of parameters before and after midodrine treatment was performed by using paired t-tests. Categorical variables were evaluated by using McNemar test. Differences were considered as statistically significant if p values were less than 0.05.

RESULTS

During the three months of midodrine therapy, weights of the patients and the amount of dialytic fluid removal remained unchanged (p> 0.05). Predialysis systolic (p= 0.011), diastolic (p= 0.008) and mean arterial blood pressures (p= 0.014) increased; vertigo (p= 0.04) and syncope attacks (p= 0.035) were significantly improved by midodrine therapy (Table 1). During HD, number of hypotensive attacks before and after midodrine therapy were 62 and 59, respectively (p= 0.06). No change was seen in the amount of saline infusion needed in hypotensive attacks after midodrine treatment (p= 0.29) (Table 1). The improvements of subjective symptoms are shown in (Table 2). No significant change was found in weight of patients, amount of dialytic fluid removal, blood biochemistry, Kt/V or hemoglobin before and after midodrine treatment (Table 1) Side effects after midodrine such as scalp tingling, headache and weakness were mild and well-tolerated by patients.

DISCUSSION

Approximately 5-10% of patients undergoing hemodialysis have difficulty of maintaining a normal blood pressure, and they are chronically hypotensive between dialysis sessions. In a national sample consisting of 4500 dialysis patients, it was found that the presence of a low predialysis systolic blood pressure (less than 100 mmHg) was significantly related to increased mortality rate (relative risk of 1.86).[10] When compared to younger HD patients, particularly in the presence of diabetes mellitus, left ventricle hypertrophy and severe

TABLE 1: Comparison of demographic, clinical and laboratory parameters before and after midodrine treatment.

	Before	After	P value
Systolic blood pressure (mmHg)	94.3 ± 6.6	104.0 ± 19.6	0.011
Diastolic blood pressure (mmHg)	61.2 ± 4.2	65.9 ± 10.1	0.008
Mean arterial blood pressure (mmHg)	68.3 ± 6.5	76.0 ±7.4	0.014
Pulse rate (bpm)	76 ± 6	78 ± 5	0.19
Body weight (kg)	69 ± 3	68 ± 3	0.38
Fluid removal (mL)	2800 ± 120	2900 ±100	0.30
Fluid infused (mL)	300 ± 50	320 ± 40	0.29
Kt//V	1.40 ± 0.1	1.38 ± 0.1	0.45
rHuEPO (IU/session)	2020 ± 250	1980 ± 220	0.42
Heparin dose (IU/session)	2600 ±160	2580 ± 200	0.24
Hemoglobin (g/dL)	10.7 ± 0.8	10.9 ± 0.7	0.26
Creatinine (mg/dL)	9.4 ± 1.1	9.6 ± 1.2	0.31
Albumin (g/dL)	3.9 ± 0.2	4.0 ± 0.1	0.26
Total calcium (mg/dL)	9.8 ± 0.1	9.9 ± 0.1	0.49
Inorganic phosphate (mg/dL)	5.4 ± 0.4	5.3 ± 0.3	0.30
I-PTH (pg/mL)	228 ± 28	216 ± 36	0.25
Hypotensive attacks (number)	62	59	0.06
Necessity of saline infusion (number)	6	5	0.29

rHuEPO, recombinant human erythropoietin; Kt/V, dialyser clearance x time/volume; I-PTH, intact parathyroid hormone.

TABLE 2: Total subjective symptom scores after midodrine treatment.

	Before (N)	After (N)	Improvement (%)	p
Orthostasis	18	12	71	0.025
Dizziness	16	11	68	0.03
Fatigue	16	10	63	0.035
Blurred vision	18	10	55	0.045
Dullness sensation	17	9	52	0.04
Headache	12	9	75	0.02

congestive heart failure, the elderly have impaired cardiopulmonary/pressor receptor reflex function.[11-13] Furthermore, chronically hypotensive individuals undergoing HD therapy exhibited a significant down-regulation in alpha and beta adrenergic receptors, suggesting an inability to produce an adequate sympathetic response.[14] In addition, diabetic hemodialysis patients may also have autonomic dysfunction in which hypotension may result from a combination of central and peripheral cardiovascular sympathetic denervation. This reflects vasoconstriction failure in splanchnic and peripheral vascular beds.[15] Therefore, due to these multiple risk factors, diabetic hemodialysis patients are susceptible to chronic hypotension more than other hemodialysis patients.

Although it has been shown that midodrine, an oral selective alpha-1 adrenergic agonist, effectively prevents hypotension during HD in some recent studies,[2,3,8,16-18] only two studies have been reported which describe its effects on HD patients with chronic hypotension.[5,9] This disagreement may be related to characteristics of the patient population, study design and the dose of midodrine given. Fang and Huang reported their experience with midodrine in the treatment of chronic hypotension in patients on maintenance HD.[5] Patients were given 5 mg midodrine (twice daily) on HD days and 2.5 mg (twice daily) on non-dialysis days. There was a significant increase in both pre-and post-HD blood pressures. In the second study, Lin and Wang confirmed that in HD patients with chronic hypotension had moderate to severe autonomic dysfunction, midodrine significantly improved autonomic function, especially sympathetic function.[5] In addition to improvement in autonomic dysfunction, midodrine also caused an increase in systolic, diastolic and mean arterial blood pressures during HD and inter-dialysis period.[9]

It was seen that there was no subset of diabetic patients in these studies.[5,9] The main purpose of the present study was to evaluate the effects of midodrine treatment in patients with diabetes mellitus and chronic hypotension undergoing haemodialysis therapy. Accordingly, this is the first study on the effectiveness of midodrine in diabetic patients with chronic hypotension. Our study showed that midodrine significantly increased systolic, diastolic and mean arterial blood pressures before hemodialysis. Our results are consistent with aforementioned studies. [5,9] In addition to objective parameters (systolic, diastolic and mean arterial pressure, etc.), the subjective symptoms (orthostasis, dizziness, fatigue, blurred vision, dullness sensation and headache) were improved by midodrine treatment. With these subjective improvements, the patients felt better by improvement of their quality of life.

On contrary to previous studies, however, in our study it was seen that midodrine was weakly effective in reducing the number of intra-dialytic hypotensive attacks in diabetic patients ($p= 0.06$). Despite insufficient data in the literature, one should speculate that adequate response could not be achieved because of increased hypotension incidence due to diabetic neuropathy in patients with diabetes.[15,19] Combination of midodrine with cold dialysate, using dialysate with high calcium and sodium profile were found effective in the previous studies.[18-22] Combining alternative methods used in the treatment of hypotensive attacks with midodrine may be more effective than using midodrine alone. Further studies are needed to es-

tablish efficiency of this approach in this subset of patients with diabetes.

Presumably, removal of fluid during dialysis creates an additional hypotensive effect; thereby, reduces efficiency of midodrine.[23-25] Major factors including temperature, sodium and calcium level of dialysate, which could affect hypotension were kept constant in our study. The weight of patients and amount of dialytic fluid removal remained unchanged; hemoglobin and blood biochemistry, including albumin, calcium and potassium, were not affected during midodrine therapy. This suggests that these factors had no contribution to the blood pressure.

When side effects of midodrine were considered, there were only minor side effects after midodrine such as scalp tingling, headache, and weakness. These were well-tolerated in the course of midodrine treatment. There were no changes in biochemical and hematologic parameters after midodrine therapy. These safety results are consistent with the previous studies[23-26] and suggest the safety of midodrine administration in diabetic hemodialysis patients.

In conclusion, autonomic impairment and reduced peripheral resistance can contribute to chronic hypotension in HD patients and to frequent hypotensive episodes during HD. Chronic hypotension can be ameliorated, at least in part, by administration of midodrine, which modulates autonomic function and has direct effects on peripheral vessels. Midodrine may be a therapeutic option for diabetic HD patients with chronic hypotension and hypotensive symptoms.

REFERENCES

1. Cases A, Coll E. Chronic hypotension in the dialysis patient. J Nephrol 2002;15(4):331-5.
2. Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA. Midodrine is effective and safe therapy for intradialytic hypotension over 8 months of follow-up. Clin Nephrol 1998;50(2): 101-7.
3. Hoeben H, Abu-Alfa AK, Mahnensmith R, Perazella MA. Hemodynamics in patients with intradialytic hypotension treated with cool dialysate or midodrine. Am J Kidney Dis 2002; 39(1):102-7.
4. Sułowicz W, Radziszewski A. Dialysis induced hypotension--a serious clinical problem in renal replacement therapy. Med Pregl 2007; 60(Suppl 2):14-20.
5. Lin YF, Wang JY, Denq JC, Lin SH. Midodrine improves chronic hypotension in hemodialysis patients. Am J Med Sci 2003;325(5):256-61.
6. Perazella MA. Approach to patients with intradialytic hypotension: a focus on therapeutic options. Semin Dial 1999;12:175-81.
7. Jassal SV, Douglas JF, Stout RW. Prevalence of central autonomic neuropathy in elderly dialysis patients. Nephrol Dial Transplant 1998;13(7): 1702-8.
8. Prakash S, Garg AX, Heidenheim AP, House AA. Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. Nephrol Dial Transplant 2004;19(10):2553-8.
9. Fang JT, Huang CC. Midodrine hydrochloride in patients on hemodialysis with chronic hypotension. Ren Fail 1996;18(2):253-60.
10. Port FK, Hulbert-Shearon TE, Wolfe RA, Bloembergen WE, Golper TA, Agodoa LY, et al. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. Am J Kidney Dis 1999; 33(3):507-11.
11. Cléroux J, Giannattasio C, Grassi G, Seravalle G, Sampieri L, Cuspidi C, et al. Effects of ageing on the cardiopulmonary receptor reflex in normotensive humans. J Hypertens Suppl 1988;6(4):S141-4.
12. Sucu M, Akçay M, Davutoglu A. [Current perspective to postural orthostatic tachycardia syndrome: review]. Turkiye Klinikleri J Cardiovasc Sci 2009:21(2):267-74.
13. Şahin S, Akçiçek F. [Management of syncope in the elderly]. Turk Geriatri Derg 2010; 13(3):208-18.
14. Esforzado Armengol N, Cases Amenós A, Bono Illa M, Gaya Bertrán J, Calls Ginesta J, Rivera Fillat F. Autonomic nervous system and adrenergic receptors in chronic hypotensivehaemodialysis patients. Nephrol Dial Transplant 1997;12(5):939-44.
15. Stevens MJ, Edmonds ME, Mathias CJ, Watkins PJ. Disabling postural hypotension complicating diabetic autonomic neuropathy. Diabet Med 1991;8(9):870-4.
16. Blowey DL, Balfe JW, Gupta I, Gajaria MM, Koren G. Midodrine efficiacy and pharmacokinetics in a patient with recurrent intradialytic hypotension. Am J Kidney Dis 1996; 28(1): 132-6.
17. Montagnac R, Clavel P, Delhotal-Landes B, Flouvat B, Poulain S, Schllinger F. Use of midodrine (Gutron) to treat permanent hypotension in a chronic hemodialysis patient. Clin Nephrol 2001(56):162-8.
18. Alappan R, Cruz D, Abu-Alfa AK, Mahnensmith R, Perazella MA. Treatment of severe intradialytic hypotension with the addition of high dialysate calcium concentration to midodrine and/or cool dialysate. Am J Kidney Dis 2001;37(2):294-9.
19. Hornung RS, Mahler RF, Raftery EB. Ambulatory blood pressure and heart rate in diabetic patients: an assessment of autonomic function. Diabet Med 1989;6(7):579-85.
20. Sang GL, Kovithavongs C, Ulan R, Kjellstrand CM. Sodium ramping in hemodialysis: a study of beneficial and adverse effects. Am J Kidney Dis 1997;29(5):669-77.
21. Alappan R, Cruz D, Abu-Alfa AK, Mahnensmith R, Perazella MA. Treatment of severe intradialytic hypotension with the addition of high dialysate calcium concentration to midodrine and/or cool dialysate. Am J Kidney Dis 2001;37(2):294-9.
22. Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA. Midodrine and cool dialysate are effective therapies for symptomatic intradialytic hypotension. Am J Kidney Dis 1999;33(5):920-6.
23. Kaufmann H, Brannan T, Krakoff L, Yahr MD, Mandeli J. Treatment of orthostatic hypotension due to autonomic failure with a peripheral alpha-adrenergic agonist (midodrine). Neurology 1988;38(6):951-6.
24. Kouw PM, Kooman JP, Cheriex EC, Olthof CG, de Vries PM, Leunissen KM. Assessment of post-dialysis dry weight: a comparison of techniques. J Am Soc Nephrol 1993;4(1):98-104.
25. Bégin V, Déziel C, Madore F. Biofeedback regulation of ultrafiltration and dialysate conductivity for the prevention of hypotension during hemodialysis. ASAIO J 2001;48(3):312-5.
26. Jankovic J, Gilden JL, Hiner BC, Kaufmann H, Brown DC, Coghlan CH, et al. Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. Am J Med 1993; 95(1):38-48.