A Randomized Crossover Clinical Trial of Sertraline for Intradialytic Hypotension

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Introduction. Intradialytic hypotension (IDH) has been reported in 15% to 50% of hemodialysis patients and increases patients morbidity and mortality. Some small noncontrolled studies evaluated the effect of sertraline on IDH with conflicting results. This study is a randomized crossover controlled trial on the effectiveness of sertraline to reduce IDH.

Materials and Methods. Patients on hemodialysis who suffered IDH in at least 50% of their dialysis sessions were enrolled. Each patient received either sertraline or placebo for 4 weeks and after a 4-week washout period, was switched to the other arm of the trial. All patients started sertraline at a daily dose of 50 mg that increased to 100 mg after 1 week.

Results. Twelve patients completed all phases of the study. Sertraline therapy increased nadir intradialysis diastolic and systolic blood pressure by 3.8 mm Hg and 4.9 mm Hg at the end of the intervention, respectively. Sertraline therapy also significantly increased postdialysis diastolic and systolic blood pressure by 6.0 mm Hg and 8.7 mm Hg. Sertraline therapy significantly reduced the risk of hypotension episodes by 43%. The improvement of intradialysis and postdialysis diastolic and systolic blood pressure were only significant in nondiabetic patients.

Conclusions. Sertraline therapy significantly increases intradialysis and postdialysis blood pressure. These effects of sertraline can result in significant decrease in hypotension episodes during dialysis treatment and the number of interventions required to manage IDH. However, not all patients may benefit from sertraline depending on comorbidities such as diabetes mellitus.

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INTRODUCTION

Intradialytic hypotension (IDH) has been reported in 15% to 50% of patients on maintenance hemodialysis.[1] Intradialytic hypotension increases patients' morbidity and mortality by increasing the risk of cardiac and cerebral ischemia, suboptimal dialysis adequacy and ultrafiltration, and left ventricular hyperthrophy.[2-4] Some modalities have been applied to manage IDH, including Trendenlenburg position, bolus administration of normal saline or hypertonic solution, holding antihypertensive agents before scheduled dialysis, avoiding eating just before and during dialysis sessions, cool dialysate, dialysate sodium modeling, and pharmacotherapy including midodrine, carnitine, and sertraline.[1-3,5-13] Regular intradialytic

exercise has also been proposed to improve cardiac systolic and diastolic function in these patients.[14]

Selective serotonin reuptake inhibitors (SSRIs) have been shown to improve patients' symptoms with idiopathic orthostatic hypotension and neurocardiogenic syncope.[15,16] These disorders have similar pathogenic mechanism to IDH that is a paradoxical withdrawal of sympathetic outflow and subsequent sudden decline in blood pressure.[17,18] Volume removal during ultrafiltration is suspected to induce reflex sympathetic activation and vasoconstriction to preserve normal blood pressure; however, paradoxical sympathetic withdrawal may occur due to sudden surge of serotonin in central nervous system that causes hypotension and vasodepressive syncope.[16,19,20] Selective serotonin reuptake inhibitors decrease postsynaptic serotonin receptor density due to chronic increased intrasynaptic concentration of serotonin,[21] they and may ameliorate the response to sudden serotonin surge following sympathetic withdrawal.[19-21]

Some small noncontrolled studies evaluated the effect of sertraline, an SSRI, on IDH with conflicting results.[10-13] This study is a randomized double-blinded placebo-controlled trial on the effectiveness of sertraline against IDH.

MATERIALS AND METHODS

Settings and Patients

This randomized controlled trial was conducted at 2 academic dialysis centers in Iran from the end of December 2011 to the end of August 2013. Inclusion criteria consisted of patients on maintenance hemodialysis for at least 3 months who suffered IDH in at least 50% of their dialysis sessions during the past 3 months. Hypotension was defined as any of the following: prehemodialysis systolic blood pressure (SBP) of 100 mm Hg and less, at least 40 mm Hg decline in SBP during dialysis, any SBP of 90 mm Hg and less, any diastolic blood pressure (DBP) of 40 mm Hg and less, or any decrease in blood pressure causing symptoms such as nausea, vomiting, muscle cramps, dizziness, or lightheadedness during hemodialysis.[10] All patients received hemodialysis for 4 hours 3 times per week using low-flux polysulphone dialysis membrane and bicarbonate buffer at a concentration of 35 mEq/L; sodium, 140 mEq/L; calcium, 2.5 mEq/L; potassium, 2 mEq/L; and magnesium, 1 mEq/L. Dialysate and blood flow rates were 500 mL/min to 600 mL/min and 250 mL/min to 300 mL/min, respectively. Ultrafiltration volumes were removed constantly during dialysis sessions. All patients received their antihypertensive drugs on nondialysis days.

Each patient went through 4-week periods of the study including washout and sertraline and placebo periods. Washout periods were defined as the 4 weeks immediately before sertraline or placebo initiation. Patients were randomly allocated by a computer-generated randomization list in a 1:1 ratio to start the study by sertraline or placebo. All patients started sertraline or placebo period after an initial 4-week washout. Sertraline was administered at a daily dose of 50 mg that was increased to 100 mg after 1 week. Since the full therapeutic effect of sertraline manifests 4 weeks after its initiation, sertraline and placebo administrations were continued for 4 weeks (week 4 to week 8). The 4-week washout period was considered to ensure complete plasma clearance of sertraline.[13]

Measured Outcomes

During each 4-week period of the study, the patients underwent 12 dialysis treatment sessions. Blood pressure was assessed before dialysis, every 20 minute during dialysis, and after dialysis during 6 of these 12 dialysis sessions at each periods of the study. Mean arterial pressure (MAP) was calculated. The lowest SBP and DBP during dialysis treatment were considered as nadir SBP and nadir DBP, respectively. Data of midperiod dry weight, hematocrit, and serum albumin were collected for all periods of the study. The ultrafiltration volumes and any therapeutic interventions to treat hypotension episodes including sodium modeling, administration of normal saline or hypertonic dextrose solution, cool dialysate, or dialysis cessation were recorded for each dialysis session. Any changes in antihypertensive drugs during all phases of the study were recorded. The number of left medications and their blisters were checked at each visit to ensure that the patient had used their allocated drugs. Patients were considered compliant if at least 80% of all doses were taken. Patients were asked about any possible drug side effect at each visit.

Ethics Approval

The study protocol was approved by the local ethics committee of Tehran University of Medical Sciences and registered in the Iranian Registry of Clinical Trials (IRCT201112033043N3). All patients signed informed consent forms.

Data Analysis

Data were analyzed using the Stata (version 11.0, StataCorp LP, College Station, TX, USA). The normality of distributions of continuous variables was tested by the quantile normal plot, the normal probability plot, and the Kolmogorov-Smirnov test. The paired *t* test and the Wilcoxon matched-pairs signed-rank test were used to compare predialysis, nadir, and postdialysis SBP, DBP, MAP, ultrfiltration volumes, hypotensive episodes, number of interventions needed to manage IDH, midperiod hematocrit, dry weight, and serum albumin before and after sertraline and placebo periods. The same tests were used to compare abovementioned parameters between sertraline and placebo periods at the initiation and at the end of these study periods. We used a random effect model to test for carryover effect with adding sequence of receiving treatment and placebo for each patient to the model. After ruling out the carryover effect, treatment effect was estimated with a fixed effect linear regression model or fixed effect Poisson model for continuous and count variables, respectively, with period and baseline values in the model to adjust for period effect and baseline variations in the patients. We also estimated the interaction of diabetes mellitus (DM) as the cause of end-stage renal disease with intervention by entering the interaction term in the above models in separate analyses.

Average values of blood pressure measured from week 4 to weak 8 after allocation of treatment or placebo were used as outcome. For hypotension episodes and therapeutic interventions, the total number of episodes in the same period was considered as outcome. After ruling out the carryover effect, treatment effect was estimated with a fixed effect model with period and baseline values in the model to adjust for period effect and baseline variations in the patients. To estimate the time trend changes in intervention effect, we also fitted a population-averaged panel-data model with autoregressive one correlation structure to account for within-group correlation structure of individuals. The results were presented as point estimate, 95% confidence interval, and *P* value. *P* values less than .05 were considered significant.

RESULTS

Twelve patients (2 men and 10 women) with a mean age of 62.2 ± 8.8 years old, a mean dry weight of 74.6 ± 13.7 kg, and a mean dialysis treatment duration of 5.7 ± 2.6 years completed all four phases of the study and included in the analysis. Primary causes of kidney failure were DM in 5 patients, hypertension in 4, nephritic syndrome in 1, and unknown reason in 2. Antihypertensive medications of all of the patients remained constant during all periods of the study.

Table 1 shows all outcomes assessed in this study including predialysis SBP, DBP, and MAP; nadir SBP, DBP, and MAP during dialysis; and postdialysis SBP, DBP, and MAP as well as the total number of hypotension episodes, total number of the required interventions to manage IDH, and midperiod hematocrit, serum albumin concentration, and dry weight. There were no differences in the measured outcomes between the periods before initiation of placebo and initiation of sertraline, except for serum albumin concentration that was before starting sertraline. Although decreasing trends in nadir SBP, DBP, and MAP and also postdialysis SBP and MAP were observed both after sertraline and after placebo administrations, adjusting for period effect and patients baseline values, nadir SBP, DBP, and MAP and also postdialysis SBP, DBP, and MAP were significantly higher after sertraline as compared with the values after placebo. The total number of hypotension episodes and total number of required interventions to manage IDH episodes were significantly lower during the sertraline period compared to the placebo period (Table 1).

Carryover effects were ruled out for all measured outcomes using random effect model (the results are not shown). Table 2 shows the tests for intervention effect adjusted for period effect and patients' baseline values on patients' blood pressure measurements before, during, and after dialysis treatment sessions and on the total number of hypotension episodes and total number of required managements. Time trend effects of placebo and sertraline interventions on measured

Table 1. Before-After Comparisons Within Sertraline and Placebo Groups and Between-group Comparisons before and After Intervention

Parameter	Sertraline			Placebo			Between-group *P*	
	Before	After	*P*	Before	After	*P*	Before	After
Blood Pressure, mm Hg								
Predialysis systolic	135.1 ± 28.3	129.9 ± 23.1	.08	125.3 ± 26.4	132.7 ± 25.3	.01	.09	.52
Predialysis diastolic	77.8 ± 13.6	74.3 ± 11.6	.07	73.9 ± 14.1	78.7 ± 16.4	.03	.18	.13
Predialysis mean arterial	96.9 ± 17.9	92.8 ± 14.5	.049	91.0 ± 17.0	96.7 ± 18.8	.006	.11	.21
Nadir systolic	97.3 ± 21.7	91.8 ± 11.8	.29	86.7 ± 12.9	83.1 ± 8.8	.35	.10	.007
Nadir diastolic	59.8 ± 13.1	57.8 ± 10.3	.35	54.8 ± 10.4	52.4 ± 7.4	.22	.07	.02
Nadir mean arterial	72.3 ± 15.3	69.1 ± 10.4	.31	65.4 ± 10.8	62.7 ± 7.5	.27	.08	.01
Post-dialysis systolic	119.7 ± 25.2	114.9 ± 16.9	.32	111.7 ± 18.6	105.4 ± 16.1	.06	.22	.02
Post-dialysis diastolic	70.3 ± 14.6	70.5 ± 13.2	.92	69.3 ± 14.4	65.1 ± 9.6	.10	.78	.048
Post-dialysis mean arterial	86.8 ± 17.1	85.3 ± 13.2	.61	83.4 ± 14.8	78.6 ± 11.3	.06	.45	.03
Total number of hypotension episodes	14.7 ± 13.2	11.2 ± 14.5	.20	16.5 ± 14.3	19.5 ± 13.0	.35	.56	.02
Total number of hypotension treatments	1.2 ± 1.1	1.0 ± 0.9	.70	2.2 ± 2.2	1.8 ± 1.3	.50	.20	.04
Ultrafiltration volume per session, L	3.3 ± 0.8	3.1 ± 0.7	.01	3.2 ± 0.8	3.1 ± 0.8	.22	.29	.95
Dry weight, kg	74.8 ± 13.8	74.6 ± 13.8	.35	74.7 ± 14.3	74.8 ± 13.9	.70	.70	.59
Midpoint hematocrit, %	34.3 ± 4.9	35.7 ± 4.7	.08	36.2 ± 4.5	34.1 ± 4.2	.07	.08	.21
Midpoint albumin, g/dL	3.7 ± 0.2	4.0 ± 0.3	.009	3.9 ± 0.2	3.9 ± 0.2	.88	.006	.28

Table 2. The effect of Sertraline Therapy on Measured Outcomes Adjusted for Period Effect and Patients' Baseline Values

Parameter	Intervention Effect			Period Effect		
	Coefficient/ Relative Risk*	95% Confidence Interval	*P*	Coefficient/ Relative Risk*	95% Confidence Interval	*P*
Blood Pressure, mm Hg						
Predialysis systolic	-6.041	-14.211 to 2.128	.13	6.290	-1.108 to 13.688	.09
Predialysis diastolic	-4.189	-9.921 to 1.543	.13	5.161	-0.220 to 10.542	.06
Predialysis mean arterial	-4.801	-10.385 to 0.783	.08	5.539	0.430 to 10.648	.04
Nadir systolic	6.858	0.096 to 13.620	.047	-2.585	-10.367 to 5.197	.47
Nadir diastolic	3.756	-1.758 to 9.269	.16	-2.244	-8.892 to 4.405	.46
Nadir mean arterial	5.191	-0.265 to 10.647	.06	-2.882	-9.307 to 3.543	.34
Post-dialysis systolic	7.155	-0.718 to 15.028	.07	-2.089	-11.397 to 7.219	.62
Post-dialysis diastolic	6.012	2.071 to 9.953	.003	-1.467	-0.801 to 0.040	.08
Post-dialysis mean arterial	5.216	-0.726 to 11.159	.08	-2.997	-10.417 to 4.423	.39
Total number of hypotension episodes	0.511	0.393 to 0.665	< .001	1.009	0.779 to 1.308	.95
Total number of hypotension treatments	0.829	0.290 to 2.368	.73	0.835	0.315 to 2.212	.72

*Values are relative risks for the total number of hypotension episodes and total number of interventions.

outcomes are shown on Table 3. As seen in these two tables, sertraline therapy increased nadir DBP, SBP, MAP by 3.8 mm Hg, 4.9 mm Hg, and 4.1 mm Hg at the end of week 8 of the sertraline administration, respectively. These changes reached statistical significance only for nadir DBP ($P = .047$). Sertraline therapy also significantly increased postdialysis SBP, DBP, and MAP by 8.7 mm Hg, 6 mm Hg, and 7.2 mm Hg, respectively ($P = .01$, $P = .003$, and $P = .002$, respectively) at the end of week 8 of the intervention. Compared with placebo, sertraline therapy significantly reduced the risk of hypotension episodes by 43% (relative risk, 0.57; $P < .001$). Although not significant, the total number of interventions required to treat IDH during the study period decreased by 29% with sertraline therapy. Paradoxically, at the end of 8-week sertraline treatment, predialysis SBP, DBP, and MAP significantly decreased by 12.1 mm Hg, 6.9 mm Hg, and 8.6 mm Hg, respectively ($P = .001$, $P = .003$, and $P = .001$, respectively).

When we assessed the interaction of DM on sertraline effects, the results showed that while not different during the placebo period, nadir DBP

Table 3. Time Trend Effect of Sertraline Therapy on Intradialytic Hypotension

Parameter	Intervention Effect at the End of Intervention Time			Intervention Effect per Each Unit of Time		
	Coefficient/ Relative Risk*	95% Confidence Interval	*P*	Coefficient/ Relative Risk*	95% Confidence Interval	*P*
Blood Pressure, mm Hg						
Predialysis systolic	-12.084	-19.482 to -4.686	.001	-1.504	-2.586 to -0.423	.007
Predialysis diastolic	-6.890	-11.414 to -2.365	.003	-0.767	-1.437 to -0.097	.025
Predialysis mean arterial	-8.635	-13.565 to -3.705	.001	-1.013	-1.736 to -0.290	.006
Nadir systolic	4.855	-1.622 to 11.332	.141	0.127	-0.831 to 1.086	.794
Nadir diastolic	3.808	0.052 to 7.565	.047	0.327	-0.220 to 0.875	.241
Nadir mean arterial	4.121	-0.339 to 8.581	.070	0.265	-0.392 to 0.921	.428
Post-dialysis systolic	8.655	2.12 to 15.195	.010	0.669	-0.314 to 1.651	.181
Post-dialysis diastolic	6.012	2.071 to 9.953	.003	0.678	0.083 to 1.272	.026
Post-dialysis mean arterial	7.164	2.713 to 11.616	.002	0.675	.001 to 1.348	.050
Total number of hypotension episodes	0.569	0.427 to 0.760	<.001	0.948	0.910 to 0.987	.013
Total number of hypotension treatments	0.708	0.253 to 1.988	.513	1.016	0.886 to 1.166	.821

*Values are relative risks for the total number of hypotension episodes and total number of interventions.

and MAP and postdialysis SBP were significantly lower at the end of the sertaline period by 13.4 mm Hg, 13.8 mm Hg, and 15.3 mm Hg, respectively, among diabetics compared with nondiabetic patients ($P = .008$, $P = .019$, and $P = .04$, respectively).

Sertraline at a daily dose of 100 mg was well tolerated by all of the patients. Only 1 of 11 patients that entered the first stage of the study showed sertraline-induced nausea that resulted in withdrawal from the study.

DISCUSSION

The results of the present study, as the first randomized double-blinded crossover placebo-controlled trial, showed that sertraline therapy significantly increases intradialysis and postdialysis SBP and DBP. These effects of sertraline resulted in 43% decrease in the total number of hypotension episodes during dialysis treatment and 29% decline in the total number of interventions required to manage IDH. It is noteworthy that the beneficial effects of sertraline in managing IDH were only seen in hemodialysis patients without DM.

Sertraline is considered a first-line treatment for depressive disorders due to its efficacy, tolerability, and low pharmacokinetic interactions.[22,23] It does not require dosage adjustment in patients with renal impairment and can be administered as a single daily dose of 50 mg to 200 mg.[24,25] Based on its favorable pharmacokinetic and pharmacodynamic profiles, we also selected it among other members of the SSRI family in this study. The use of SSRIs for treatment of hypotension in hemodialysis patient started with a case report on the effect of fluoxetine on postural hypotension during hemodialysis in a diabetic patient.[26] Thereafter, Dheenan and colleagues retrospectively collected the data of 9 middle-aged hemodialysis patients (6 with DM) who were receiving sertraline for neuropsychiatric reasons. They compared data before and 6 weeks after sertraline therapy and found that nadir MAP during the dialysis session was significantly higher in the sertraline period than that before sertraline therapy. The number of hypotension episodes per dialysis session, defined as in our study, and the number of required therapeutic interventions for hypotension were significantly lower during the sertraline period.[10]

Yalcin and colleagues[11] performed a prospective before-after non–placebo-controlled study on 9 middle-aged patients with IDH (22% with DM). They measured outcomes before and after a 4-week of sertraline administration. The results showed that postdialysis values of weight, ultrafiltration volumes, albumin, and hematocrit were similar between before and after sertraline administration. Predialysis SBP and DBP did not differ either. The nadir SBP and DBP during dialysis sessions and postdialysis SBP were significantly higher during sertraline period compared with the preceding washout period. The number of interventions to manage IDH decreased significantly during the sertraline period. In conclusion, their data showed that sertraline increased intradialysis and postdialysis blood pressure.[11] In their second study on 10 nondiabetic hemodialysis patients who

suffered from IDH, Yalcin and colleagues showed that urea reduction ratio, ultrafiltration volumes, number of interventions to treat IDH per dialysis sessions, and predialysis MAP did not differ before and after sertraline, but nadir MAP during dialysis and postdialysis MAP were significantly higher during sertraline period.[12] The question that has not been answered for us is that in the previous study of Yalcin and colleagues,[11] 7 nondiabetic patients were included that may be the 7 of 10 patients in this study and not all 10 subjects in this study were new patients.[12] Since in previous Yalcin and colleagues' study, some patients suffered side effects due to sertraline administration at a daily dose of 100 mg, sertraline was administered at a dosage of 50 mg/d in their second study. They saw the same therapeutic effect on IDH with 50 mg/d of sertraline administration. In this study, they supported the hypothesis of paradoxical withdrawal of sympathetic tone in the pathophysiology of IDH.[12]

In spite of encouraging results of sertraline effects against IDH by the abovementioned authors,[10-12] Brewster and coworkers failed to show any effect of sertraline, 50 mg/d, on IDH. They defined IDH as at least 3 episodes of a decrease in SBP (at least 20 mm Hg to a level less than 100 mm Hg) that caused symptoms in more than 50% of hemodialysis sessions over a period of 1 month. Some of these patients had resistant IDH and were under treatment with sodium modeling, cool dialysate, and midodrine. This discrepancy may also be due to a lower dose of sertraline in this study (50 mg versus 100 mg). Additionally, some patients in Brewster and coworkers' study were on midodrine, a potent alpha-1 agonist medication for the management of IDH that might mask any impact of sertraline. Although Brewster and coworkers presented their study as a prospective crossover trial, this study was not double-blinded randomized placebo-controlled clinical trial as our study with crossing from sertraline to placebo or vice versa. Another limitation of their study was that they assessed patients during sertraline period after a 4-week successive drug administration for 2 consecutive midweek dialysis treatment sessions; however, in this study, we assessed patients for a longer period of sertraline treatment during 6 dialysis sessions.[13] As seen in our results, time exert significant impact on the magnitude of sertraline effect against IDH.

All previous studies showed no changes in predialysis blood pressure before and after sertraline.[10-13] Yalcin and colleagues reported that sertraline did not increase the predialysis blood pressure since it was not a vasoactive agent and supported the mechanism of modulating paradoxical sympathetic withdrawal within and after dialysis by this drug.[11] Sertraline did not show any effect on peripheral vascular resistance in Brewster and coworkers' study either.[13] However, we conversely saw significant decreases in predialysis SBP and DBP in the sertraline period.

Although some patients in studies of Dheenan and colleagues[10] and first study of Yalcin and colleagues[11] suffered from DM (66.7% and 22%, respectively), their studies showed the positive ameliorating effect of sertraline against IDH. During their second study, Yalcin and colleagues excluded patients with DM, amyloidosis, and structural heart disease in order to exclude the effect of these diseases on cardiac autonomic function and considered uremia as an independent risk factor for autonomic dysfunction in their research.[12] Sertraline improved IDH in this study as well.[12] Brewster and colleagues reported no effect of sertraline on intradialysis and postdialysis blood pressure. About 40% of patients in Brewster and colleagues' study were diabetic. They postulated that lack of sertraline effect may be due to the presence of DM-associated autonomic dysfunction. They concluded that sertraline effect on central sympathetic discharge may be absent in patients with autonomic dysfunction.[13] Although low sample size in our study limited us for exact conclusion, by further analysis on the data of diabetic and nondiabetic patients, we also found that in contrast to nondiabetic patients, sertraline did not improve IDH among diabetic patients. As seen in our results, diabetic patients may show undesirable effects on intradialysis hypotension by sertraline administration. The National Kidney Foundation Kidney Disease Outcome Quality Initiative guideline[2] has introduced sertraline as a treatment option for IDH management based on the available noncontrolled studies.[10-13] Since DM is a leading cause to end-stage renal disease and hemodialysis therapy, we recommend larger clinical trials to clarify the impact of sertraline on IDH in diabetic patients for possible need for modification of this guideline on administration

of sertraline to manage IDH only in hemodialysis patients who do not suffer from DM.

The main limitation of this research was the small sample size. Although we assessed the patients of 2 hemodialysis center, due to limited number of patients with the inclusion criteria and refusal of some patients to participate in the study, we finished the study with 12 patients.

CONCLUSION

Sertraline therapy significantly increases intradialysis and postdialysis SBP and DBP. These effects of sertraline resulted in significant decrease in hypotension episodes during dialysis treatment and a decline in the total number of interventions required to manage IDH. Although low sample size limited the exact conclusion, the beneficial effects of sertraline in managing IDH were only seen in hemodialysis patients without DM.

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CONFLICT OF INTEREST

None declared.

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