



Effect of sertraline on intradialytic hypotension: a randomized controlled trial

Farahnaz Ghahremanfard¹ , Gholam Ali Mahdavi¹ , Majid Mirmohammadkhani² , Maliheh Yarmohammadi^{1*}

¹Department of Internal Medicine, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

²Social Determinants of Health Research Center, Semnan University of Medical Sciences, Semnan, Iran

ARTICLE INFO

Article Type:
Original

Article History:
Received: 9 March 2022
Accepted: 31 May 2022
Published online: 19 June 2022

Keywords:
Hypotension
Sertraline
Hemodialysis

ABSTRACT

Introduction: Intradialytic hypotension is an important and common complication of hemodialysis. However, it seems that selective serotonin reuptake inhibitors (SSRIs) can manage patients' blood pressure during hemodialysis.

Objectives: The present study aimed to investigate the effect of sertraline on intradialytic hypotension of the patients under hemodialysis.

Patients and Methods: The present randomized controlled trial included 18 patients under hemodialysis for end-stage renal disease (ESRD). The patients were randomly divided into the intervention and control groups. The intervention group received sertraline solely for intradialytic hypotension management, while the control group did not receive such intervention. The blood pressure assessments were conducted before, during, and after hemodialysis in both groups, then the data were analyzed.

Results: According to our results, the participants' mean age was 63.72 ± 9.91 years. The mean systolic and diastolic blood pressures were higher in the intervention group than in the control group before the hemodialysis. However, this difference was not significant for systolic blood pressure ($P=0.279$), while it was significant for diastolic blood pressure ($P=0.02$). Additionally, no significant intergroup difference in systolic and diastolic blood pressure during and after hemodialysis was detected ($P>0.05$).

Conclusion: Sertraline had no significant effect on systolic and diastolic blood pressure during and after hemodialysis. However, it increased the mean systolic and diastolic blood pressure before hemodialysis which could prevent pre-dialytic hypotension without significant side effects. Therefore, it can be effective in preventing hypotension in patients under hemodialysis.

Trial Registration: The trial protocol has been approved by the Iranian Registry of Clinical Trial (identifier: IRCT2017080625732N23; <https://en.irct.ir/trial/21499>, ethical approval code: IR.SEMUMS.REC.1395.156).

Implication for health policy/practice/research/medical education:

Intradialytic hypotension is one of the most important and common complications of hemodialysis. In the present study, sertraline did not cause a significant change in the intradialytic and postdialytic blood pressure of the patients; however, it increased the mean systolic and diastolic blood pressure of the intervention group without any notable adverse effects. Therefore, sertraline can be used to prevent hypotension in patients under hemodialysis.

Please cite this paper as: Ghahremanfard F, Mahdavi GA, Mirmohammadkhani M, Yarmohammadi M. Effect of Sertraline on Intradialytic Hypotension: A Randomized Controlled Trial. J Nephropharmacol. 2022;11(2):e10492. DOI: 10.34172/npj.2021.10492

Introduction

Intradialytic hypotension (IDH) is one of the most common and important complications of hemodialysis, occurring in 15%-70% of the patients under long-term hemodialysis (1). According to the evidence, hemodialysis can reduce the venous return to the heart during ultrafiltration-induced hypovolemia, decreasing ventricular filling and cardiac output. However, these imbalances cannot be

repaired by the related compensatory mechanisms, such as increased heart rate and peripheral vascular resistance, which results in IDH (2). This disorder can lead to several complications, such as cerebral and cardiac ischemia and left ventricular hypertrophy. Subsequently, it limits the fluid intake during hemodialysis, increasing the chance of end-stage renal disease (ESRD)- and hemodialysis-related complications and mortality in the patients under

hemodialysis (3-6).

Several studies have investigated the potential strategies for preventing and managing IDH and its complications. The suggested strategies include the Trendelenburg positioning during hemodialysis, administration of normal saline and hypertonic fluids, antihypertensive agent cessation shortly before the hemodialysis, avoiding oral intake immediately before and during hemodialysis, and finally, administration of pharmacological treatments, such as midodrine and carnitine (7-13). Moreover, it has been shown that regular activity during hemodialysis can prevent IDH by improving the cardiac systolic and diastolic function (14).

Previous studies have reported that selective serotonin reuptake inhibitors (SSRIs) can improve the symptoms of the patients with idiopathic orthostatic hypotension and neurocardiogenic syncope (15,16). Since the underlying mechanisms in the mentioned problems and IDH are almost similar, there is a possibility that SSRIs, especially sertraline, can prevent IDH (17,18). In fact, the volume removal during ultrafiltration stimulates the sympathetic reflex, which causes vasoconstriction to maintain the blood pressure at its normal levels. However, sudden sympathetic stimulation can prevent the sudden serotonin release from the central nervous system, which is the cause of hypotension and syncope (19,20). Therefore, SSRIs, especially sertraline, may increase the serotonin levels in the ganglia by downregulating the serotonin receptors located next to the nervous ganglia (21), which can prevent the reduction of serotonin levels in the ganglia during hypotension (19-21). These processes can reduce the risk of a sudden blood pressure decline, especially during hemodialysis (12,13).

Objectives

As a common complication of hemodialysis, a large number of patients under hemodialysis are predisposed to IDH. Therefore, given the considerable prevalence and importance of this problem, the present study aimed to investigate the effect of sertraline on IDH in patients with hemodialysis. If sertraline is found to be effective, it can be administered to the related patients as a prophylactic medication to prevent the additional costs imposed on the healthcare systems and patients for the treatment of hemodialysis-related complications, especially IDH.

Patients and Methods

Study design

The present randomized controlled clinical trial was a single-blinded study. Therefore, the statistical consultant was not aware of the type of treatment used. Moreover, they were fully explained about the side effects of sertraline while filling the related questionnaires. Afterward, the participants (n=18) were randomly divided into two groups: the intervention and control groups. Each group included nine patients.

The study duration was 8 weeks. It included a 4-week washout period, during which both groups received no intervention, followed by a 4-week intervention period, during which the intervention group received 50 mg of sertraline daily (Hayyan Daroo Corporation, Iran). At the same time, the control group did receive any intervention. We used a 4-week intervention period because the related studies had reported 4 weeks for sertraline to fully exert its effects (13).

During the intervention period, all the study participants continued their scheduled hemodialysis at least three times a week at the Dialysis Department of the Kowsar hospital. Moreover, all the participants underwent blood pressure assessments before each hemodialysis session, every 20 minutes during the hemodialysis, and after each session.

The date of dry weight achievement, hematocrit level, serum albumin levels, ultrafiltration volume, potential dose changes of antihypertensive agents, and any potential measure for hypotension management during dialysis (e.g., use of intravenous drugs and cold dialysis) were recorded for each patient. The medication boxes of the patients were controlled at each hemodialysis session to ensure their adherence. In addition, the patients were questioned about the potential side effects experienced throughout the intervention period. If any complication developed, necessary measures were taken immediately to resolve the problem and improve the patient's condition. Moreover, the incident was recorded in the patients' questionnaires.

Data analysis

Data were analyzed using the IBM SPSS software version 20.0. The data normality was confirmed using the Kolmogorov-Smirnov test. Moreover, quantitative data were described using the range, mean, standard deviation, and median, and the significance level was set at 0.05. Moreover, the *t* test was used for intergroup comparisons of quantitative variables with normal distribution, the post hoc test (Turkey's test) was conducted for paired comparisons, and the Mann-Whitney U test was used for intergroup comparisons of quantitative variables without normal distribution.

Results

The present study included 18 patients (9 patients in each group) with ESRD who underwent hemodialysis at the dialysis department of Kowsar hospital, Semnan, Iran (Figure 1). The study participants were 44-80 years old, with a mean age of 63.72 ± 9.91 years. Moreover, 12 patients were women, while six were men.

According to our results presented in Table 1, there was no intergroup difference in systolic blood pressure assessed before ($P=0.279$), during ($P=0.308$), and after hemodialysis ($P=0.747$). However, the mean systolic and diastolic blood pressure of the intervention group was

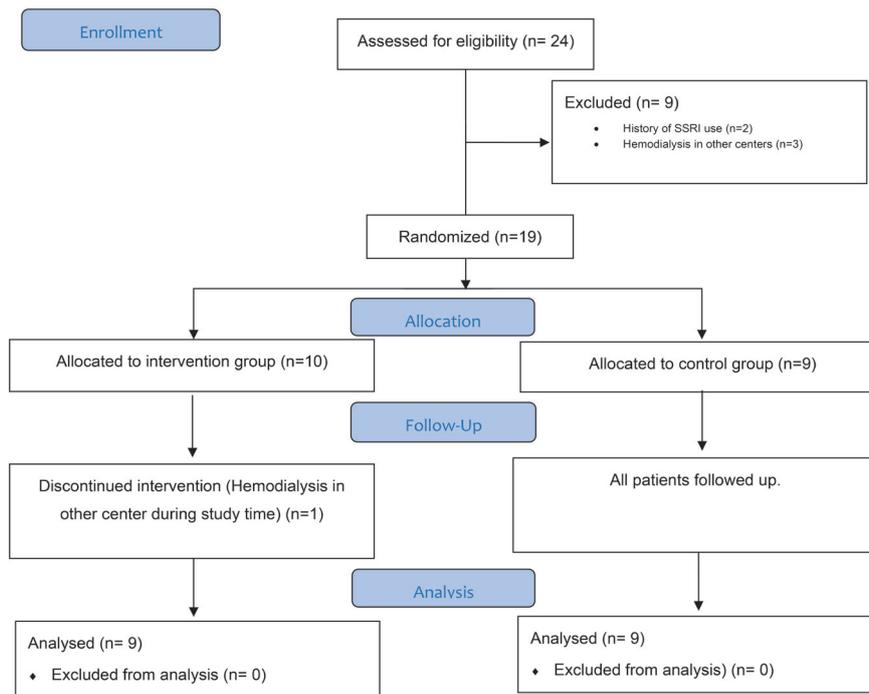


Figure 1. Flowchart of enrollment and random assignment of study participants.

higher than those of the control group.

Moreover, according to the results presented in Table 2, the diastolic blood pressure assessed before the hemodialysis was significantly higher in the intervention group compared to the control group ($P=0.02$), while such difference was not significant in the diastolic blood pressure assessed during and after the hemodialysis ($P=0.357$). In general, the intervention group had a higher mean blood pressure compared to the control group.

Discussion

According to our results, the diastolic blood pressure of the intervention group was significantly higher than the control group ($P=0.02$). Therefore, sertraline could

increase the blood pressure in patients under hemodialysis and can be recommended as a medical therapy for improving the diastolic blood pressure before the dialysis. Our findings were compatible with a study by Yalcin et al that included 10 patients with IDH who received 50 mg of sertraline for 4 weeks, showing the effectiveness of sertraline in blood pressure increase (22). However, the present study was not compatible with another study by Yalcin et al on the patients with IDH, which reported that 100 mg of sertraline daily could significantly increase the blood pressure of the patients compared to the control group, showing the effectiveness of sertraline in improving the patients' blood pressure (23).

According to our results, the systolic blood pressure

Table 1. Effect of sertraline on systolic blood pressure before, during and after dialysis

Groups	No	Mean of systolic blood pressure		
		Before dialysis	During dialysis	After dialysis
Control	9	10.82 ± 1.16	10.0 ± 1.24	9.94 ± 1.30
Intervention	9	11.51 ± 1.42	10.56 ± 0.97	10.12 ± 0.94
Total	18	11.16 ± 1.31	10.28 ± 1.11	10.02 ± 1.10

Table 2. Effect of sertraline on diastolic blood pressure before, during and after dialysis

Groups	No	Mean of systolic blood pressure		
		Before dialysis	During dialysis	After dialysis
Control	9	6.58 ± 0.64	6.24 ± 0.69	6.24 ± 0.62
Intervention	9	7.41 ± 0.72	6.86 ± 0.72	6.50 ± 0.58
Total	18	6.99 ± 0.78	6.55 ± 0.75	6.37 ± 0.60

assessed before and after the hemodialysis and the diastolic blood pressure assessed before, during, and after the hemodialysis were higher in the intervention group compared to the control group. However, the differences were not significant. It is worth noting that there is a possibility that a larger sample size or more extended intervention period could increase these differences to become significant. On the other hand, the diastolic blood pressure assessed in the intervention group was the mean of all the measurements during the four weeks before and after the intervention, while the diastolic blood pressure used for control group was the mean of patients' diastolic blood pressure measurements during and after the hemodialysis. Therefore, sertraline could reduce the blood pressure of the patients. Moreover, some other factors, including nutrition and psychological factors (such as stress), could have affected the patients' blood pressure. However, we did not consider these factors.

Our findings showed no significant intergroup difference in systolic blood pressure assessed before the hemodialysis. However, this variable was higher in the intervention group compared to the control group insignificantly. Moreover, the systolic blood pressure assessed during the hemodialysis was not significantly different between the study groups ($P=0.308$). These findings were compatible with the studies by Brewster et al (24) and Yalcin et al (23). However, the mentioned studies were placebo-controlled. Moreover, we used a 4-week washout period in the present study and performed the assessments in both washout and intervention periods. Furthermore, our findings were incompatible with a study by Yalcin et al (22) on 10 patients divided into three groups of IDH, non-IDH, and control groups, showing the effectiveness of sertraline in blood pressure increase of the patients. Such difference can be explained by the inclusion of patients without IDH in the present study.

Our results showed no significant intergroup difference in the systolic blood pressure assessed after the hemodialysis ($P=0.747$). However, this variable was slightly higher in the intervention group compared to the control group. These findings were compatible with the studies by Brewster et al (24) and Yalcin et al (23) and incompatible with another study by Yalcin et al (22). This can be explained by the fact that the blood pressure used in the present study was the mean of all measurements of blood pressures assessed before, during, and after hemodialysis. It means that all the measurements during the 4-week period were recorded, and their mean was compared. Moreover, the sertraline dose used in the study by Yalcin et al (22) was twice the present study. Accordingly, in the mentioned study, the intervention period was two weeks, and the rate of hypertension was only assessed in the intervention group. On the other hand, a study by Dheenan et al (12) on patients older than 54 reported that the systolic blood pressure assessed after the hemodialysis

was significantly higher compared to the systolic blood pressure assessed before the hemodialysis, which was not compatible with our findings. This can be explained by the fact that the mentioned study was placebo-controlled. Moreover, they used 100 mg of sertraline daily, and the intervention period was 6 weeks.

Finally, there was no significant intergroup difference in diastolic blood pressure assessed during and after the hemodialysis ($P>0.05$) in the present study, which was compatible with the studies by Yalcin et al (23) and Brewster et al (24). However, these findings were not compatible with the studies by Yalcin et al (22) and Dheenan et al (12) that showed the effect of sertraline on diastolic blood pressure (22). This can be explained by different sertraline doses and intervention periods.

Conclusion

According to our results, sertraline had no significant effect on the blood pressure of the patients under hemodialysis; however, it could slightly increase their blood pressure. Therefore, it can be potentially effective in preventing IDH in patients under hemodialysis. Moreover, it caused no significant side effects in the patients. Thus, we recommend performing more comprehensive studies with larger sample sizes and more extended intervention periods to evaluate the effect of sertraline on the blood pressure of the patients under hemodialysis.

Limitations of the study

The present study had some limitations as well. For example, the sample size was small, and it was possible that the intervention period (4 weeks) was not enough for sertraline to fully exert its effects. Moreover, we did not make an intergroup comparison based on the participants' gender. In addition, the diet, physical activity, hemodialysis profile, and use of other pharmacological measures, such as midodrine, to increase the patients' blood pressure were not investigated or controlled in the present study.

Authors' contribution

MY and FG were the principal investigators of the present study. MY, MM, and GM contributed to the development of the study concept and design. Moreover, MY, FG, MM, and GM revised and re-evaluated the manuscript. Further, all authors participated in writing the final manuscript, read it, approved it, and confirmed its accuracy and integrity.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical issues

The present study was conducted in accordance with the tenets of the Declaration of Helsinki, and all the study protocols were approved and accepted by the

Ethics Committee of the Semnan University of Medical Sciences (IR.SEMUMS.REC.1395.156). Accordingly, all the participants gave written informed consent before any intervention. Moreover, the present study was a part of the medical specialty thesis by Gholam-Ali Mahdavi, a resident of internal medicine at the Semnan University of Medical Sciences. Also, the trial protocol was approved by the Iranian Registry of Clinical Trial (identifier: IRCT2017080625732N23; <https://en.irct.ir/trial/21499>). It is worth noting that the potential ethical issues, including plagiarism, data fabrication, and double publication, were entirely observed by the authors.

Funding/Support

This work was supported by the Deputy of Research and Technology of the Semnan University of Medical Sciences (Grant #1144).

References

1. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol.* 2015;26:724-34. doi: 10.1681/ASN.2014020222.
2. Stefánsson BV, Brunelli SM, Cabrera C, Rosenbaum D, Anum E, Ramakrishnan K, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol.* 2014;9:2124-32. doi: 10.2215/CJN.02680314
3. Orotino L, Marcen R, Querada C. Epidemiology of symptomatic hypotension in hemodialysis: Is cool dialysate beneficial for all patients? *Am J Nephrol.* 1990;10:177-80.
4. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis.* 2005;45:S1-153.
5. 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;33:507-17. doi: 10.1016/s0272-6386(99)70188-5.
6. Yadla M, John JB, Mummadi M. A study of clinical assessment of frailty in patients on maintenance hemodialysis supported by cashless government scheme. *Saudi J Kidney Dis Transpl.* 2017;28:15-22. doi: 10.4103/1319-2442.198102.
7. Jost CM, Agarwal R, Khair-el-Din T, Grayburn PA, Victor RG, Henrich WL. Effects of cooler temperature dialysate on hemodynamic stability in "problem" dialysis patients. *Kidney Int.* 1993;44:606-12.
8. Maggiore Q, Dattolo P, Piacenti M, Morales MA, Pelosi G, Pizzarelli F, et al. Thermal balance and dialysis hypotension. *Int J Artif Organs.* 1995;18:518-25.
9. Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. *J Am Soc Nephrol.* 2001;12:151-156.
10. Cruz DN. Midodrine: a selective alpha-adrenergic agonist for orthostatic hypotension and dialysis hypotension. *Expert Opin Pharmacother.* 2000;1:835-40.
11. Bellinghieri G, Santoro D, Calvani M, Mallamace A, Savica V. Carnitine and hemodialysis. *Am J Kidney Dis.* 2003;41:S116-22.
12. Dheenana S, Venkatesan J, Grubb BP, Henrich WL. Effect of sertraline hydrochloride on dialysis hypotension. *Am J Kidney Dis.* 1998;31:624-30.
13. Brewster UC, Ciampi MA, Abu-Alfa AK, Parazella MA. Addition of sertraline to other therapies to reduce dialysis-associated hypotension. *Nephrol (Carlton).* 2003;8:296-301.
14. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol.* 1999;33:1227-30.
15. Grubb BP, Samoil D, Kosinski D, Kip K, Brewster P. Use of sertraline hydrochloride in the treatment of refractory neurocardiogenic syncope in children and adolescents. *J Am Coll Cardiol.* 1994;24:490-4.
16. Converse RL, Jacobsen TN, Jost CM. Paradoxical withdrawal of reflex vasoconstriction as a cause of hemodialysis-induced hypotension. *J Clin Invest.* 1992;90:1657-65.
17. Kosinski DJ, Grubb BP, Temesy-Armos PN. Pathophysiologic aspects of neurocardiogenic syncope. *Pacing Clin Electrophysiol.* 1995;18:716-24.
18. Helle CJ, McDonald CH, Phillips ET. Hypotensive effects of 5HT1A receptors activation: ventral medullary sites and mechanism of action in the patient. *J Auton Nerv Syst.* 1993;42:177-88.
19. Samoil D, Grubb BP. Vasovagal (neutrally mediated) syncope: pathophysiologic aspects. *Eur J Cardiac Pacing Electrophysiol.* 1992;2:234-41.
20. Rickels K, Schweizer E. Clinical overview of the serotonin reuptake inhibitors. *J Clin Psychiatry.* 1990;51:9-12.
21. McRae AL, Brady KT. Review of sertraline and its clinical applications in psychiatric disorders. *Expert Opin Pharmacother.* 2001;2:883-92.
22. Yalcin AU, Kudaiberdieva G, Sahin G, Gorenek B, Akcar N, Kuskus S, et al. Effect of sertraline hydrochloride on cardiac autonomic dysfunction in patients with hemodialysis-induced hypotension. *Nephron Physiol.* 2003;93:21-8. doi: 10.1159/000066655.
23. Yalcin AU, Sahin G, Erol M, Bal C. Sertraline hydrochloride treatment for patients with hemodialysis hypotension. *Blood Purification.* 2002;20:150-3.
24. Brewster UC, Ciampi MA, Abu-Alfa AK, Perazella MA. Addition of sertraline to other therapies to reduce dialysis-associated hypotension. *Nephrology (Carlton).* 2003;8:296-301. doi: 10.1111/j.1440-1797.2003.00216.x.

Copyright © 2022 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.