www.nephropathol.com DOI: 10.34172/jnp.2020.25 J Nephropathol. 2020;9(3):e25

Journal of Nephropathology

Comparison of the effects of pramipexole and gabapentin on the treatment of restless leg syndrome in end-stage chronic renal failure patients undergoing hemodialysis

Sepideh Hajian[1*], Mohammad Reza Rajabpoor Nikfam[2], Zahra Esmayeilzad[2]

[1]Department of Nephrology, Velayat Hospital, Qazvin University of Medical Sciences, Qazvin, Iran
[2]Velayat Hospital, Qazvin University of Medical Sciences, Qazvin, Iran

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 19 December 2019
Accepted: 5 February 2020
Published online: 12 February 2020

Keywords:
Restless legs syndrome (RLS)
Chronic kidney disease
Hemodialysis
Pramipexole
Gabapentin
End-stage kidney disease

ABSTRACT

Introduction: Despite the high prevalence of restless legs syndrome (RLS) in hemodialysis patients, few studies have investigated the effect of pramipexole and gabapentin on the severity of RLS in these patients.

Objectives: The study aimed to evaluate the effects of pramipexole and gabapentin on the treatment of RLS in end-stage chronic renal failure patients undergoing hemodialysis.

Patients and Methods: Using the diagnostic criteria the presence of RLS was investigated in all hemodialysis patients admitted to the dialysis ward of Bu Ali Sina and Velayat hospitals in Qazvin, Iran. Out of 162 patients, 96 patients had RLS and 60 patients with moderate to severe RLS were enrolled in the study. The selected patients were randomly divided into two groups including pramipexole (0.18 mg daily) and gabapentin (100 mg daily). The two groups were treated for 4 weeks.

Results: The prevalence of RLS was 59% (96 out of 162 patients). After the intervention, the severity of RLS was significantly decreased in all patients and also in each of the pramipexole and gabapentin groups ($P<0.001$). Moreover, after the intervention, the rate of improvement in RLS severity in the pramipexole group (16.8 ± 6.5) was significantly higher than that in the gabapentin group (13.0 ± 7.3; $P=0.036$).

Conclusion: The findings of the study showed that the severity of RLS in hemodialysis patients undergoing 4 weeks of treatment with pramipexole or gabapentin was significantly reduced; in addition, the rate of improvement in RLS severity was higher in pramipexole group.

Trial registration: Registration of trial study has been approved in the Iranian Registry of Clinical Trials (identifier: IRCT20191106045350N1; https://irct.ir/trial/43557, ethical code; IR.QUMS.REC.1396.167).

Implication for health policy/practice/research/medical education:
In a clinical trial to study the effects of pramipexole and gabapentin on the treatment of RLS in end-stage chronic renal failure patients undergoing hemodialysis, we found the severity of RLS in hemodialysis patients undergoing four weeks of treatment with pramipexole or gabapentin was significantly reduced. In addition, the rate of improvement in RLS severity was higher in the pramipexole group.

Please cite this paper as: Hajian S, Rajabpoor Nikfam MR, Esmayeilzad Z. Comparison of the effects of pramipexole and gabapentin on the treatment of restless leg syndrome in end-stage chronic renal failure patients undergoing hemodialysis. J Nephropathol. 2020;9(3):e25. DOI: 10.34172/jnp.2020.25.

Original Article

Introduction

Restless legs syndrome (RLS) is a neurological sensory motor disorder that involves and affects limbs. It is diagnosed based on the criteria developed by the international RLS study group (IRLSSG) (1). The prevalence of this disorder among the general population is 2%–15% (2-4), but it is higher in patients with chronic kidney disease and those undergoing dialysis (5).

RLS is divided into primary and secondary categories. Iron deficiency anemia, pregnancy, Lyme disease,

*Corresponding author: Sepideh Hajian,
Email: s.hajian@qums.ac.ir

monoclonal gammopathy, neurological disorders such as cerebrovascular accident, and chronic renal failure are among the important causes of secondary RLS (2). Concerning the pathophysiology of RLS, dopamine deficiency and dopaminergic system dysfunction are suggested as the items involved in the emergence of the problem and dopamine agonists have been shown to play an important role in alleviating symptoms in patients (6). RLS is an annoying disorder in end-stage kidney disease (ESKD) patients undergoing hemodialysis, because it leads to sleep disturbance and a decrease in the quality of life of patients (6). Under the same conditions like age, gender and duration of dialysis, the mortality rate of patients with chronic renal disease undergoing dialysis with concurrent RLS is higher than those without RLS (7). Numerous studies have been conducted to find appropriate ways for treating RLS, especially in hemodialysis patients. For instance, non-pharmacological methods such as exercise during dialysis, more frequent sessions of dialysis, treatment of iron deficiency anemia, and the administration of medications such as gabapentin or levodopa were suggested (8).

Pramipexole, an ergot-derived dopamine agonist, is suggested as an effective medication for the treatment of RLS in the general population, with few side effects (9-11). In spite of the high prevalence of RLS among hemodialysis patients, few studies focused on drugs that may treat this disorder, including pramipexole and gabapentin (12).

Objectives

The aim of the present study was to evaluate the effects of pramipexole and gabapentin on the treatment of RLS in end-stage chronic renal failure patients undergoing hemodialysis.

Patients and Methods

Study design

In this clinical trial, the presence of RLS was assessed using the IRLSSG diagnostic criteria (13), in all end-stage renal failure patients undergoing hemodialysis who were admitted to dialysis ward of the two hospitals of Bu Ali Sina and Velayat in Qazvin, Iran. Regarding inclusion criteria, the study was conducted on patients with end-stage chronic renal failure (at least 6 months), under permanent hemodialysis, and having moderate to severe RLS based on IRSLSS diagnostic criteria. Exclusion criteria were pregnancy, iron deficiency anemia, concomitant neurodegenerative diseases such as cerebrovascular accident and Parkinson's disease, Lyme disease, or presence of complications such as nausea, vomiting, and abdominal pain due to the medications. Of 162 patients, 96 were diagnosed with RLS; of whom 60 patients with moderate to severe disease were enrolled in the study after explaining the study design (Figure 1).

Initially, a checklist was used to collect the data on the patients including age, gender, cause of ESKD, duration of illness, proportion of dialysis hours per week, dialysis adequacy, and laboratory test results (hemoglobin, calcium,

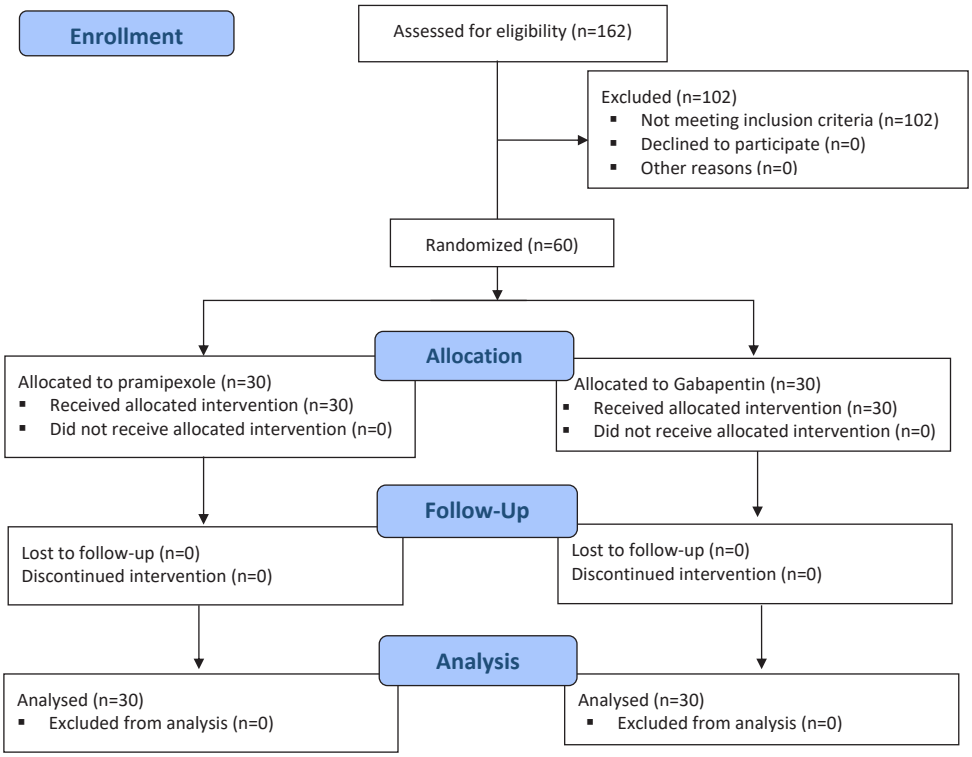

Figure 1. Flow diagram of the study.

phosphorus, vitamin D, parathyroid hormone [PTH], and creatinine). Patients were then randomly divided into two groups, one group was treated with pramipexole 0.18 mg daily and the other group was treated with gabapentin 100 mg daily and the treatment lasted for four weeks. RLS severity was measured before and after the intervention using the IRSLSS diagnostic criteria. Finally, the rate of change in the severity of RLS after the intervention was measured in all of the patients, in each group separately, since the severity of RLS before and after the treatment was compared between the two groups.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Qazvin University of Medical Sciences approved this study (IR.QUMS.REC.1396.167). All study protocols were approved by the institutional ethical committee at Qazvin University of Medical Sciences. Additionally, the study was registered as a clinical trial at Iranian Registry of Clinical Trials (IRCT20191106045350N1; https://irct.ir/trial/43557, Approval date; 2019-11-23). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from the M.D thesis of Mohammad Reza Rajabpoor Nikfam (Thesis#555) at this university.

Statistical analysis

SPSS software was used for data analysis. Qualitative variables were described using frequency and percentage and quantitative variables were presented using means and standard deviation. Chi-square test, independent *t* test and paired *t* test were used for data analysis and $P<0.05$ was set as the level of significance.

Results

Mean (SD) age of the patients was 64 ± 10 years, ranging from 31 to 87 years. Of all, 37 patients (62%) were female and 23 patients (38%) were male. Table 1 compares demographic data of the subjects and kidney disease characteristics between two groups. There was no significant difference between the two groups in terms of gender ($P=0.791$), but the age of patients in the gabapentin group was significantly lower than that in the pramipexole group ($P=0.042$). The most common cause of ESKD in all the patients was hypertension concurrent with diabetes. There was no significant difference between the groups in terms of the cause of ESKD. Mean (SD) duration of ESKD in all the patients was 3.8 ± 2.3 years, ranging from 1 to 11 years. The duration of dialysis per week in all the patients was 12 hours. Mean (SD) dialysis adequacy (Kt/V) in all the patients was 1.2 ± 0.2, ranging from 0.75-1.66. There was no significant difference between the two groups regarding the duration of ESKD and dialysis adequacy. Table 2 compares the results of laboratory tests between the two groups.

The prevalence of RLS among the studied dialysis patients was 59% (96 out of 162 patients). Table 3 shows the categorization of RLS severity based on the IRLSSG diagnostic criteria before and after the intervention in all the patients and in each group separately. Table 4 also compares RLS severity scores before and after the intervention in all of patients and in each group separately.

Table 1. Comparison of demographic and renal disease characteristics between the two groups of pramipexole and gabapentin

	Pramipexole group (n=30)	Gabapentin group (n=30)	*P* value
Age, year	67 ± 10	61±10	0.042*
Gender			
Male	12 (40%)	11 (37%)	0.791**
Female	18 (60%)	19 (63%)	
ESKD causes			
HTN & DM	10 (33%)	16 (53%)	0.384*
HTN	10 (33%)	6 (20%)	
DM	6 (20%)	6 (20%)	
Others	4 (14%)	2 (7%)	
ESKD duration, year	4.2±2.2	3.5±2.4	0.264*
Kt/V	1.25±0.2	1.19±0.22	0.300*

Abbreviations: HTN, hypertension, DM, diabetes mellitus; ESKD, end-stage kidney disease.
*Independent sample *t* test, **Chi-square test.

Table 2. Comparison of plasma laboratory tests results between the two groups of pramipexole and gabapentin

	All patients (n=60)	Pramipexole group (n=30)	Gabapentin group (n=30)	*P* value*
Hemoglobin, g/dL	12.0 ± 1.4	11.7 ± 1.1	12.2 ± 1.6	0.184
Calcium, mg/dL	8.6 ± 0.8	8.6 ± 0.7	8.5 ± 0.8	0.722
Phosphorus, mg/dL	5.7 ± 1.6	5.8 ± 1.8	5.6 ± 1.4	0.610
Vitamin D, ng/mL	22.1 ± 10.2	25.5 ± 12.4	18.5 ± 5.4	0.008
PTH, pg/mL	257.5 ± 195.6	224.5 ± 131.0	290.4 ± 241.8	0.195
Creatinine, mg/dL	8.6 ± 2.9	8.4 ± 3.1	8.7 ± 2.8	0.728

*Independent sample *t* test.

Table 3. Prevalence of RLS severity before and after study in all patients and pramipexole and gabapentin groups

RLS severity	All patients (n=60)		Pramipexole group (n=30)		Gabapentin group (n=30)	
	Before	After	Before	After	Before	After
Mild	0 (0%)	45 (75%)	0 (0%)	23 (77%)	0 (0%)	22 (74%)
Moderate	34 (57%)	12 (20%)	10 (33%)	5 (17%)	24 (80%)	7 (23%)
Severe	19 (32%)	2 (3%)	16 (54%)	2 (6%)	3 (10%)	0 (0%)
Very severe	7 (11%)	1 (2%)	4 (13%)	0 (0%)	3 (10%)	1 (3%)

As presented, after the intervention, the severity of RLS decreased significantly in all of patients as well as in each of pramipexole and gabapentin groups ($P<0.001$). However, comparison between groups showed that, after the intervention, the rate of improvement in the severity of RLS was significantly higher in the pramipexole group (16.8 ± 6.5) than in the gabapentin group (13.0 ± 7.3; $P=0.036$).

Discussion

The findings of our study showed that more than half of hemodialysis patients were suffering from RLS. The severity of RLS after the intervention was significantly decreased in each of pramipexole and gabapentin groups, while the level of improvement in RLS severity was higher in the pramipexole group than in the gabapentin group. Thus, pramipexole and gabapentin seem to be effective in the treatment of RLS in dialysis patients.

Our study showed that both pramipexole and gabapentin decreased the severity of RLS after four weeks of administration; however, the reduction in the RLS severity was greater in the pramipexole group than in the gabapentin group. Several studies have investigated the effects of these two drugs on RLS in general population, however few studies have been conducted on hemodialysis patients (10,11). Study regarding the effect of pramipexole on RLS in hemodialysis, limited to the study by Miranda et al. They used pramipexole for 10 months in ten patients with severe RLS that interfered with dialysis. The drug was started at a dose of 0.125 mg two hours before bedtime and increased to 0.75 mg depending on patient's tolerance. The results revealed that 9 patients showed improvement of RLS within the first week. Additionally, pramipexole was well tolerated during the follow-up for an average period of 8 months since the severity of RLS was significantly reduced after the treatment. Finally, they concluded that, pramipexole was a useful treatment for RLS in uremic patients undergoing dialysis, although they highlighted the need for further clinical trials (12). Our study, which was conducted on a larger sample size, also showed that pramipexole was able to significantly reduce the severity of RLS after 4 weeks of treatment.

Table 4. Comparison of RLS severity score before and after the study in all patients and pramipexole and gabapentin groups

	Before the study	After the study	*P* value*
All patients	22.3 + 7.5	7.4 + 6.4	<0.001
Pramipexole group	24.2 + 6.6	7.4 + 5.4	<0.001
Gabapentin group	20.3 + 7.9	7.3 + 7.3	<0.001

* Paired *t* test.

Several studies have evaluated the effect of gabapentin on RLS in hemodialysis patients. However, these studies are few and have been conducted on a small sample size. Thorp et al examined the effect of gabapentin versus placebo on the treatment of 16 hemodialysis patients for six weeks. Their study was cross-over, with 13 patients eventually completing the study. The results indicated that 11 patients showed a positive response to gabapentin (14). Likewise, Micozkadıoglu et al compared the efficacy of gabapentin in the treatment of RLS in 15 hemodialysis patients with levodopa and found that the effect of gabapentin was significantly more than the effect of levodopa in reducing the severity of RLS symptoms. They also showed that gabapentin improved some aspects of patient quality of life and sleep (8).

Our study is one of the few studies that have compared the efficacy of pramipexole and gabapentin in the treatment of RLS in hemodialysis patients. As noted, both drugs were effective in reducing the severity of RLS symptoms, however, the efficacy was significantly higher in the pramipexole group. Therefore, it is recommended to apply appropriate pharmacological and non-pharmacological therapies, including gabapentin or pramipexole, for the treatment of RLS in patients undergoing dialysis, especially in cases suffering from severe disease because their condition may interfere with the dialysis process. However, the use of medications in dialysis patients still requires extensive studies, with a larger sample size, multicenter designs, with longer periods to evaluate the side effects suggests.

Conclusion

The findings of the present study showed that more than half of the studied hemodialysis patients had RLS. The severity of RLS after the intervention was significantly decreased in both pramipexole and gabapentin groups. In addition, the rate of improvement in RLS severity was

higher in the pramipexole group than in the gabapentin group. Thus, pramipexole and gabapentin seem to be effective in the treatment of RLS in dialysis patients, as in other cases with RLS.

Limitations of the study

Some of our study limitations were small sample size, single-center study, and short treatment period. The use of medications in dialysis patients still requires extensive studies, with a larger sample size, multicenter designs, and longer periods to evaluate the side effects of the drug too.

Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. SH and ZE designed the protocol of study. MRRN developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by SH, MRRN, and ZE. Analysis of data was performed by MRRN. All authors read and approved the final paper.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by Qazvin University of Medical Sciences.

References

1. Montplaisir J, Allen RP, Arthur W, Ferini-Strambi L. Restless legs syndrome and periodic limb movements during sleep. Principles and Practice of Sleep Medicine. 5th ed. Elsevier Inc; 2010. p. 1026-37.
2. Thorpy M, Ehrenberg B, Hening W, Mahowald M, Malow B, Phillips B, et al. Restless legs syndrome: detection and management in primary care. Am Fam Physician. 2000;62:108-14.
3. Kumar V, Bhatia M, Tripathi M, Srivastava A, Jain S. Restless legs syndrome: diagnosis and treatment. The Journal of the Association of Physicians of India. 2003;51:782-783.
4. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med. 2000;160:2137-41. doi: 10.1001/archinte.160.14.2137.
5. Higuchi T, Abe M, Mizuno M, Yamazaki T, Suzuki H, Moriuchi M, et al. Association of restless legs syndrome with oxidative stress and inflammation in patients undergoing hemodialysis. Sleep Med. 2015;16:941-8. doi: 10.1016/j.sleep.2015.03.025.
6. Mucsi I, Molnar MZ, Ambrus C, Szeifert L, Kovacs AZ, Zoller R, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. Nephrol Dial Transplant. 2005;20:571-7. doi: 10.1093/ndt/gfh654.
7. Earley CJ, Allen RP, Beard JL, Connor JR. Insight into the pathophysiology of restless legs syndrome. J Neurosci Res. 2000;62:623-8. doi: 10.1002/1097-4547(20001201)62:5<623::AID-JNR1>3.0.CO;2-H.
8. Micozkadıoglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: an open-label study. Ren Fail. 2004;26:393-7. doi: 10.1081/jdi-120039823.
9. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, Pantzaris MC, Stefanidis I, Sakkas GK. Epidemiology, impact, and treatment options of restless legs syndrome in end-stage renal disease patients: an evidence-based review. Kidney Int. 2014;85:1275-82. doi: 10.1038/ki.2013.394.
10. Rye DB, Trotti LM. Restless legs syndrome and periodic leg movements of sleep. Neurol Clin. 2012;30:1137-66. doi: 10.1016/j.ncl.2012.08.004.
11. Manconi M, Ferri R, Zucconi M, Oldani A, Giarolli L, Bottasini V, et al. Pramipexole versus ropinirole: polysomnographic acute effects in restless legs syndrome. Mov Disord. 2011;26:892-5. doi: 10.1002/mds.23543.
12. Miranda M, Kagi M, Fabres L, Aguilera L, Alvo M, Elgueta L, et al. Pramipexole for the treatment of uremic restless legs in patients undergoing hemodialysis. Neurology. 2004;62:831-2. doi: 10.1212/01.wnl.0000113752.14744.15.
13. Davison SN. The prevalence and management of chronic pain in end-stage renal disease. J Palliat Med. 2007;10:1277-87. doi: 10.1089/jpm.2007.0142.
14. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. Am J Kidney Dis. 2001;38:104-8. doi: 10.1053/ajkd.2001.25202.