ORIGINAL ARTICLE

COMPARISON OF LACOSAMIDE VERSUS LEVODOPA IN THE TREATMENT OF RESTLESS LEGS SYNDROME IN HEMODIALYSIS PATIENTS

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ABSTRACT

Background: Restless legs syndrome (RLS) is a prevalent issue that affects 20–30% of uremic patients and increases morbidity and mortality in those receiving hemodialysis (HD). Lacosamide act on voltage-gated sodium channels but there is not enough work done till now on its effectiveness on RLS.

Objectives: To compare Lacosamide and Levodopa for treating restless-legs-syndrome in hemodialysis patients in terms of mean change of International Restless Leg Syndrome (IRLS) score.

Methods: It was a Randomize control trail done at Department of Medicine & Nephrology Department of Mayo hospital, Lahore from April 2019 to March 2020. After taking approval from institutional-Review-board (IRB) of the King Edward Medical University (KEMU), sixty patients coming to hemodialysis unit of Mayo Hospital, Lahore and fulfilling the inclusion criteria were enrolled for study. We used lottery method and randomly divided them in to two groups that is Group-A: Lacosamide (50 mg) given at bedtime. (30 cases) and Group-B: Levodopa (110 mg) given daily 2 hours before bedtime (30 cases). Treatment was continued for 4 weeks. We calculated IRLS score at start of study and four weeks after treatment and any Change from baseline was calculated for every patient. That difference of –IRLS score documented on the attached Performa along with demographic details about patient.

Results: This study showed that after 4 weeks of treatment there was not much difference seen in International Restless Leg Syndrome score in each treatment groups. i.e. [Pre-Treatment (Lacosamide: 20.80±4.78 vs. Levodopa: 22.60±4.66), Post Treatment (Lacosamide: 14.20±2.89 vs. Levodopa: 15.73±3.58), Mean change of score (Lacosamide: 7.10±4.99 vs. Levodopa: 6.86±6.63. p - Value = 0.878)

Conclusion: This trial concludes that Levodopa and Lacosamide were equally good in treating Restless-Legs-Syndrome among patients who are on Hemodialysis.

Key words: Restless legs syndrome, Hemodialysis, Lacosamide, Levodopa.

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INTRODUCTION

Restless-Legs-Syndrome (RLS) patient got persistent desire for the leg's movement more often at night times so patient sleep is disturbed. Patient quality of life become compromise.[1] Restless Leg Syndrome is a sensorimotor disorder. Its prevalence in general population varies from 5%–15%.[2] Prevalence got higher as age increase. In this disease predominance for female is seen and ratio is 2:1.[3-5] The four main diagnostic points of Restless-leg-syndrome include a desire for limb movement along with uncomfortable feelings , rest makes symptoms to start or make them worse, physical activity gives some relief to patient

from uncomfortable feeling and these symptoms got worse especially during rest time of evening and night.[1, 4] This disease can occur as idiopathic form of restless-leg-syndrome mostly before 30 years of age and familial predisposition is seen.[5] While secondary Restless Leg Syndrome occurs with condition like but not limited to pregnancy, neuro-pathies, iron deficiency, kidney disease, rheumatoid arthritis, Parkinson's disease and diabetic patient etc. Secondary restless leg syndrome occurs late in life, and mostly have more rapid course than idiopathic Restless Leg Syndrome[3-6] Pathogenesis of Restless Leg Syndrome in hemodialysis patients is not well understood.[7] RLS affects between 3 and 9% of the general population, depending on age and gender. However, End stage renal disease (ESRD), which is defined as a persistent loss of renal function necessitating renal replacement treatment or dialysis, has a 6.6-70% prevalence of RLS, which is significantly greater than in the general population.[8]

The current treatment option for secondary restless leg syndrome is levodopa (a dopamine agonist). But there are few issues like the rebound of symptoms in morning and augmentation of restless leg syndrome symptom during evening. In augmentation patient symptoms got worse during evening time. Restless Leg Syndrome patient got day time symptoms so that patient need to take medicine during day hours. There are reports by many patient of involvement of other unaffected body parts like arms and trunk.[1, 6, 8] Lacosamide is a relatively new anticonvulsant and neuropathic pain drug that modulates voltage-gated sodium channels. When other medications are ineffective in treating RLS, Lacosamide appears to be a viable alternative. It can also be used as supplementary therapy when there has been just a partial response.[9,10] Lacosamide 50-250mg given once daily at night seen to improve RLS symptoms with 4-36 weeks of treatment.[9] Lacosamide can be used safely in patients of chronic kidney disease.[10]

There is limited work done on it, only few studies are available internationally and there is no such local published material. Therefore, local data is lacking on this topic. This study will help to decide about better treatment option among these two medicines. This study will also help to add up in the limited evidence on restless leg syndrome treatment. as well as in better management of hemodialysis patients with restless leg syndrome in future practice.

METHODS

It was a randomize control trial conducted at Department of Medicine & Nephrology Department of Mayo hospital, Lahore from April 2019 to March 2020. Sample size of 60 (30 in each group) was calculated with 90% Power of Test & 095 % Confidence interval when making Expected Mean Change in International Restless Leg Syndrome score to be 21±11.01 with Lacosamide and 13.4±3.2 with Levodopa in hemodialysis patients with restless legs syndrome. Simple-random-sampling technique was used.

Inclusion criteria include patients on hemodialysis, of either gender and Age in the range of 30 to 70 year with Restless Leg Syndrome SCORE=10 or >10.

Patients with Cerebral Vascular Accident (focal deficit on clinical examination, CT evidence of infarct or hemorrhage), pregnant women and RLS due to **o**ther causes like Rheumatoid arthritis, Cirrhosis and Parkinson were excluded.

Approval was taken from institutional review Board (IRB) King Edward Medical University (KEMU). Sixty patients which are presented to dialysis unit Mayo hospital, Lahore & satisfied inclusion criteria were included. They were explained about details of the trial. After written & informed Consent detailed History was taken from every included patient. Baseline International Restless Leg Syndrome score was assessed and noted. They were then randomly divided to following 02 GROUP by Lottery Method. GROUP A (Lacosamide 50 mg was given at bedtime. To 30 Cases) and GROUP B (Levodopa/carbidopa 100/25 mg was given daily 2 hours before bedtime to 30 Cases).

Management continued for 04 weeks. At the end of 04 Week of treatment International Restless Leg Syndrome score was reassessed and change in score from baseline was calculated for each patient. Change in International Restless Leg Syndrome score was recorded into the attached Performa along with demographic details of the patient. All the interviews were done by same researcher to exclude bias and confounding variables.

The collected data was entered and analyzed through SPSS Version 26. The quantitative-variables for example age were presented as mean ±SD and Qualitative-Variables for example gender was presented as frequency and percentage. Comparison between two groups, Lacosamide versus levodopa, was made and chi square was applied to see the statistical significance. P-value ≤ 0.05 was taken as significant.

RESULTS

Mean age in GROUP - A and GROUP - B of patients with Rest-Less-Syndrome was 44.46±13.30 and 43.40±13.81 years respectively. In Group-A 17(56.7%) Male and 13(43.4%) female patients were included while in Group-B 22 (073.3 %) Male and 08 (26.7%) Female patients were included. Mean duration for hemodialysis in GROUP - A & - GROUP - B patients were 4.01±2.61 and 3.66±2.82 months respectively. Mean urea level in GROUP - A & GROUP - B patients were 128.53±47.48 & 115.26±39.92 respectively. Mean creatinine level for GROUP - A & GROUP – B was 7.33±2.08 & 7.59±2.95 respectively. Mean Hemoglobin

level in GROUP - A & in GROUP - B was 12.01±14.14 and 9.46±2.50 respectively. Mean calcium level in Group-A patient was 7.77±1.07 and in Group-B it was 7.66±0.86 respectively. Mean phosphorous level in GROUP - A & GROUP - B was 05.11±01.55 & 4.95±1.66 respectively. Mean sodium level in GROUP A & GROUP B was 133.73±23.28 and 136.63±3.32 respectively. Mean Potassium level GROUP A & GROUP B patients 4.75±01.04 & 4.79±0.87 respectively. Mean Bicarbonate level GROUP A & GROUP B patients 17.70±2. 53 & 16.73±2.71 respectively. Mean chloride level GROUP A & GROUP B patients 103.23±6. 53 and 99.63±7.63 respectively.

Only 05 (016.7 %) patient in GROUP A and 01(3. 3 %) patient in GROUP B were positive for Hepatitis-B virus. In Group A 010 (33.3 %) Patient and in GROUP B 6(20%) patients were positive for Hepatitis C virus.

Mean International Restless Leg Syndrome score at baseline for GROUP A & GROUP B Patient 20.80±4.78 and 22.60±4.66 respectively. No significant difference was seen between International Restless Leg Syndrome Score in between two GROUPS that is. P – Value = 0.146. (Table 1)

After 4 weeks of treatment IRLS score was reassessed. Mean IRLS score in between GROUP A and GROUP B was 14.20±2.89 and 15.73±3.58 respectively. After 4 weeks there was no gross difference seen in IRLS-score among two GROUPS that is p – Value was 0.073. (Table 2)

Mean change in International Restless Leg Syndrome score did not show any significant difference among two Treatment Group. That is GROUP A: 7.10±4.99 vs. Group B: 6.86±6.63, p – value = 0.878. (Table 3)

Table - 1: Descriptive statistics for International Restless Leg Syndrome Score at Baseline

	GROUP – A (Lacosamide)	GROUP – B (Levodopa)
N	030	030
MEAN	20.80	22.60
SD	4.78	4.66
Minimum	13	15
Maximum	30	32
p-value	0.146	

Table-2: Descriptive statistics for International Restless Leg Syndrome Score at Follow up (4 week)

	GROUP – A (Lacosamide)	GROUP – B (Levodopa)
N	30	30
MEAN	14.20	15.73
S. D	2.89	3.58
Minimum	10	11
Maximum	21	24
p- value	0 .073	

Table-3: Descriptive statistics for Change in International Restless Leg Syndrome score

	GROUP – A (Lacosamide)	GROUP – B (Levodopa)
N	030	030
MEAN	7.10	6.86
SD	4.99	6.63
Minimum	0	0
Maximum	17	19
p- value	0 .878	

DISCUSSION

The medical data and available guideline have shown that non-Ergot derived Dopamine agonist is found to be first line drug in Idiopathic Restless Leg Syndrome management. On the other hand, second line alternative option included are antiepileptic drugs, opioids and benzodiazepines.[5]

First dopaminergic agonist used in treatment of RLS was the Levodopa. It was also found that levodopa cause quality of sleep to improve as well as periodic limb movement got better. Although, effectiveness of Levodopa keeps on decreasing with passage of time as well as there are more chance for complications to occur with Levodopa in contrast with other Dopaminergic drugs.[11] While usage of some Dopaminergic drugs for example Pergolide & Cabergoline is stopped as they got serious adverse effect like fibrosis and valvulopathy.[11,12]

Cristiane Fiquene Conti did a systematic review and reported that data is lacking to support the management by Antiepileptic drugs in Restless-Leg-Syndrome patient.[13]

Anticonvulsants are generally considering as structural analogues of g-amino butyric acid (GABA) although till now exact receptor and biochemistry is not understood. What is suggested is that Novel receptor attachment site as well as accumulating GABA in brains different region may be the reason for their effectiveness in Restless Leg Syndrome.[14]

Antiepileptic drugs like Gabapentin and Pregabalin have shown effectiveness in restless leg syndrome as well as for Neuropathic pain management. There is restricted success in management of restless leg syndrome due to limited effectiveness of available medicines, fluctuating symptoms and drugs side-effect.[11,12]

Lacosamide is recently introduced anticonvulsant and neurological pain management drug. Lacosamide act by modulating voltage-gated sodium channels. There is not enough data available about its effects on restless-leg-syndrome. Lacosamide can be used safely in patients of chronic kidney disease.[9,10] In current study Lacosamide is compared with Levodopa in management of Restless-Legs-Syndrome patient who

are on hemodialysis in terms of mean change of international-restless-leg -syndrome score. Results of our study showed that after 4 weeks of treatment no significant difference was seen in International Restless Leg Syndrome score between two treatment groups. i.e. [Pre-Treatment (Lacosamide:20.80±4.78 vs. Levodopa: 22.60±4.66), Post Treatment (Lacosamide: 14.20±2.89 vs. Levodopa: 15.73±3.58), Mean change of score (Lacosamide:7.10±4.99 vs. Levodopa: 6.86±6.63. p-value=0.878).

There is no study available in literature to compared these two medications for treating restless legs syndrome on hemodialysis patients. Although there were few studies comparing levodopa with other drugs which were used to treat restless legs syndrome.

F. Prieto et al[9] who belongs to Spain in his trial on eight patient of restless legs syndrome used Lacosamide as treatment. The sample size used in this study was very small and results showed that IRLS score improved significantly by Lacosamide. Pre-treatment score was 36±3.03 and its post-treatment score was 5.16±4.35. Thus, mean change in score was 30.83 ± 5.56. Our study has also shown the beneficial effects of Lacosamide in RLS patients.

Pellecchia & Co-workers[15] did a study on Hemodialysis patients suffering with restless leg syndrome. They used Ropinirole (0.25 to 02 milligram daily) and Levodopa (025 – 200 milligram daily) fourteen week each. They concluded that Ropinirole was found to be extra effective as compare to Levodopa in management for patient on hemodialysis with restless leg syndrome, improving IRLS scores by 73.5%. In our study Lacosamide was found non inferior to Levodopa in managing IRLS patients on hemodialysis.

Nazanin Razazian[7] in his randomized controlled trail compared the Gabapentin with Levodopa/Carbidopa to determine their effectiveness in decreasing Restless-Leg-Syndrome Symptom as well as sleeping issues among Hemodialysis patient suffering from restless leg syndrome. They found both were good in management for this disorder. Gabapentin showed more significant improvement in term of International Restless Leg Syndrome Total-score (change from baseline to post-treatment -17) as comparing to Levodopa-Carbidopa (change from baseline to post-treatment -13 (p-value= 0.016).[7]

Ali Met al[16] showed the similar results in their research. They concluded that both levodopa and gabapentin effectively relieve symptoms of restless leg syndrome and improve the quality of sleep and life in end stage renal disease (ESRD) patients undergoing hemodialysis. We achieved the similar results when we compared the Lacosamide with Levodopa in our study.

Research is being done to develop novel drugs and therapy methods that will treat RLS more effectively, either singly or in combination. [5,17-19] Results of above-mentioned studies clearly showed the beneficial effects of antiepileptic drugs in RLS patients on hemodialysis. Lacosamide can be used safely in patients of chronic kidney disease on hemodialysis. We can not only benefit the patients of RLS by relieving their symptoms but also improving their quality of life.[10,20]

This study has certain limitations. It is not a multicenter trial and the sample size was somehow, limited depending upon the study design and prerequisites. To support the findings of the current study, more multicentric interventional research is needed.

We suggest more trials of Lacosamide, either alone or with combination of other antiepileptic drugs like gabapentin, pregabalin, ropinirole etc., to enhance our treatment options and providing better management to RLS patients.

CONCLUSION

Results of this study showed that both medications i.e. Levodpoa and Lacosamide are equally effective in treating Restless Legs Syndrome among patient on hemodialysis. Further studies are needed to address its efficacy so that it can be used and recommended in clinical practice for treating restless leg syndrome in patient on hemodialysis.

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REFRENCES

1. Trenkwalder C, Paulus W. Restless legs syndrome: pathophysiology, clinical presentation and management. Nat Rev Neurol. 2010;6(6):337-346.
2. Ekbom K, Ulfberg J. Restless legs syndrome. J Intern Med. 2009;266(5):419-431
3. Vlasie A, Trifu SC, Lupuleac C, Kohn B, Cristea MB. Restless legs syndrome: An overview of pathophysiology, comorbidities and therapeutic approaches. Exp Ther Med. 2022;23(2):185.
4. Brzuszek A, Hazara AM, Bhandari S. The prevalence and potential aetiological factors associated with restless legs syndrome in patients with chronic kidney disease: a cross-sectional study. Int Urol Nephrol. 2022;54(10):2599-2607.

5. Gossard TR, Trotti LM, Videnovic A, St Louis EK. Restless legs syndrome: contemporary diagnosis and treatment. Neurotherapeutics. 2021;18(1):140-155.
6. Liu Z, Guan R, Pan L. Exploration of restless legs syndrome under the new concept: A review. Medicine. 2022;101(50): e32324.
7. Razazian N, Azimi H, Heidarnejadian J, Afshari D, Ghadami MR. Gabapentin versus levodopa-c for the treatment of restless legs syndrome in hemodialysis patients: a randomized clinical trial. Saudi J Kidney Dis Transpl. 2015;26(2):271-278.
8. Lin XW, Zhang JF, Qiu MY, Ni LY, Yu HL, Kuo SH, et al. Restless legs syndrome in end stage renal disease patients undergoing hemodialysis. BMC Neurol. 2019;19(1):47.
9. Prieto F, Saus-Cantos R, Puertas F. Treatment of restless legs syndrome with lacosamide. Report of eight cases. Sleep Med. 2013;14: e236.
10. Cawello W, Fuhr U, Hering U, Maatouk H, Halabi A. Impact of impaired renal function on the pharmacokinetics of the antiepileptic drug lacosamide. Clin Pharmacokinet. 2013;52(10):897-906.
11. Lv Q, Wang X, Asakawa T, Wang XP. Pharmacologic treatment of restless legs syndrome. Curr Neuropharmacol. 2021;19(3):372-382.
12. Trenkwalder C, Allen R, Högl B, Clemens S, Patton S, Schormair B, Winkelmann J. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol. 2018;17(11):994-1005.
13. Conti CF, Oliveira MMd, Valbuza JS, Prado LBF, Carvalho LBCd, Prado GFd. Anticonvulsants to treat idiopathic restless legs syndrome: systematic review. Arq Neuropsiquiatr. 2008;66(2B):431-435.
14. Garcia-Borreguero D, Silber MH, Winkelman JW, Högl B, Bainbridge J, Buchfuhrer M, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis–Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016; 21:1-11.
15. Pellecchia MT, Vitale C, Sabatini M, Longo K, Amboni M, Bonavita V, et al. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. Clin Neuropharmacol. 2004;27(4):178-181.
16. Ali M, Iram H, Nasim F, Solangi SA, Junejo AM, Nisa NU, Solangi SA. Comparison of the efficacy of gabapentin versus levodopa-C for the treatment of restless legs syndrome in end-stage renal disease on hemodialysis patients. Cureus. 2020;12(12).
17. Sun Y, van Valkenhoef G, Morel T. A mixed treatment comparison of gabapentin enacarbil, pramipexole, ropinirole and rotigotine in moderate-to-severe restless legs syndrome. Curr Med Res Opin. 2014;30(11):2267-2278
18. Collister D, Pohl K, Herrington G, Lee SF, Rabbat C, Tennankore K, et al. The DIalysis Symptom COntrol-Restless Legs Syndrome (DISCO-RLS) trial: a protocol for a randomized, crossover, placebo-controlled blinded trial. Can J Kidney Health Dis. 2020:7:2054358120968959.
19. Xia M, He Q, Ying G, Fei X, Zhou W, He X. Clinical Efficacy and Safety of Massage for the Treatment of Restless Leg Syndrome in Hemodialysis Patients: A Meta-Analysis of 5 Randomized Controlled Trials. Front Psychiatry. 2022:13:843263
20. Sinclair PM. Interventions for chronic kidney disease-associated restless legs syndrome. Int J Evid Based Healthc. 2018;16(3):182-184.