Original Article

Evaluation Of Usefulness Of Ropinirole In The Treatment Of Post Covid Restless Leg Syndrome – A Homogenous Quasi-Experimental Feasibility Study.

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Abstract

Background: Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a widely known, prolonged, multifactorial limb movement disorder wherein patients have an insatiable desire to move their legs. This is frequently associated with abnormal, non-painful sensations that begin at rest and improve with activity and pain may be the distressing symptom in a few. Ropinirole, a dopamine agonist, is a proven drug for this disease.

Methods: In this study of thirty-two post covid restless leg syndrome, selected by well-established criteria, a course of ropinirole 2 mg in the night was given for three weeks. The drug compliance was maintained more than 95% by telephonic interview. The pain scores (VAS 0- 10), Likert scores of satisfactions, were observed after three weeks and three months.

Results: The scores significantly decreased after three weeks which maintained the same and an insignificant decrease after three months. The median score decreased from 7 to 3 (three weeks) to 2 in three months. The Likert satisfaction scores improved to 1.81 from three (p value= 0.00). There was improvement in scores from three weeks to three months. There were no side effects.

Conclusion: In this single centre, quasi experimental study on the efficacy of ropinirole on post covid restless syndrome, we found the drug dosage of 2 mg in the night for three weeks is effective in the control of symptoms. The drug gives better satisfaction which prolonged to three months even if the drug is stopped in three weeks. There were no clinically significant side effects.

Key words: covid, restless leg syndrome, ropinirole, pain, satisfaction.

INTRODUCTION:

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a widely known, prolonged, multifactorial limb movement disorder wherein patients have an insatiable desire to move their legs. This is frequently associated with abnormal, non-painful sensations that begin at rest and improve with activity. There is a diurnal pattern of symptoms worsening at night. Insomnia exists, as well as a correlation with involuntary jerky movement patterns of the legs during sleep[1]. Restless leg syndrome is underdiagnosed, and treatment is often delayed. The disorder can begin in childhood, but it is often not diagnosed until the third decade of life. Syndrome of restless legs are worse at rest and sleep. Coronavirus infection in humans began in December 2019 in the Chinese province of Wuhan and has since spread throughout the world, infecting millions and killing lakhs. Even though many drugs and nutrition are being researched to target the disease, there are not much description about its complications and their management. Sleep problems affect 34% of COVID-19 patients overall. A multi - centre study in Spain found that 35% of 1,142 COVID-19 people recovering from the hospital had poor sleep quality after 7 months. The Pittsburgh Sleep Quality Index was used in an Egyptian study of 182 participants 6 months after COVID-19 infection. A history of diabetes, oxygen administration, and mechanical ventilation were found to be risk components in 65% of the participants. The typical symptoms of patients who had recovered from COVID-1 at 6 months were fatigue as well as muscle weakness and sleep struggles. Given the impact of COVID-19 on quality of sleep, a few recommendations, such as sustaining a regular sleeping schedule and a relaxed atmosphere, as well as stress reduction at night, are critical to preventing or mitigating the impacts brought by the pandemic. There are a few studies causing exacerbation of restless leg syndrome after a covid infection. [2-7]The first medication which was approved by the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe primary RLS was ropinirole, a dopamine agonist. This drug has been shown to be safe and efficient in managing the

movement disorders of RLS and enhancing sleep quality in many large-scale clinical trials[8]. Hence in this study, we tried to find out the usefulness of the drug ropinirole in controlling the symptoms of RLS which surfaced after a covid infection.

METHODOLOGY:

Study primer:

The study was undertaken in a hospital in South India. After ethical committee approval and patient consent the work was initiated (IRB STH 105/2021 – 11/04/2021) The study was conducted according to the declaration of Helsinki. The intervention is an established one and the drug has been in use for many years safely for the same indication. The risk is minimal according to the ICMR guidelines.

Inclusion and exclusion criteria:

The patients who were diagnosed as RLS according to established criteria after a recent covid infection were included. Those who were willing to take part in the study and to take the drug with more than 80 % compliance were only included. The patients who had multiple co morbid illness who had any neurological disease, neuropathy prior and unwilling to participate were excluded. Any patient who had such symptoms before his/her covid infection.

Sampling and statistics:

The study was planned as a homogenous quasi experimental study. Hence the plan was to include 30 patients who met the criteria described above. But 32 patients were included in the study**.** The descriptive statistics was used to describe the mean and SD. The chi square test and the Friedman tests were used for analyses of non-parametric data. A p value ofless than 0.05 was considered significant. The patients should have a recent covid infection and should have recovered completely from the same.

Data collection:

The patients who met the essential criteria described below after a covid infection were selected. The diagnosis was confirmed by two physicians.

1. Uncontrollable urge to move the lower extremities, as well as unpleasant and uncomfortable sensations, may occur.
2. The desire to move the extremities decreases during the day but increases in the evenings and at night. The symptoms appear at rest, as well as during periods of sleep and inactivity.
3. The urge to move the lower extremities can be relieved partially or completely by ambulation or stretching the legs. The symptoms are mild or absent as long as the activity is continued.
4. The urge to move the lower extremities is stronger in the evenings, making sleep impossible. As a result, the patient is frequently tired during the day.
5. They should have discomfort and pain and be able to describe in terms of 0- 10 numerical rating scale of pain.

These symptoms should not be confused with other behavioural conditions, such as tardive dyskinesia and muscle spasms.

A routine Complete blood count, liver and renal function tests including a thyroid profile was done. After patient selection, they were advised to take Ropinirole (Adrole 2 mg XL – Icon life sciences- India) in the night daily for a period of three weeks. The basic demographics like age, sex and weight were noted. The pain scores were assessed on Day 0, 21(three weeks) and three months (12 weeks). The day zero by meaning on the day of reporting and advised to start the drug. The same day they were advised to start the intervention. Any other systemic illness which does not affect the study was noted.

All patients were advised to report at three weeks and 12 weeks. The drug was administered for only three weeks. Any side effects or new symptom, video calling was planned. The phone calls were made to instruct patients to be compliant in the intake of the drug regularly in the night.

A commonly used 5-point Likert scale example was used to measure satisfaction:

1. Very satisfied,
2. Satisfied,
3. Neither satisfied nor dissatisfied,
4. Dissatisfied,
5. Very dissatisfied.

The pain scores and the Likert scores were noted on day 1, after three and six weeks. Any side effects, noncompliance was noted. If the patient has persistent symptoms with the use of the drug after one week the rescue analgesic in the form of tramadol tablet was considered. All data were entered in a excel proforma, transferred to SPSS software for analyses. (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). The null hypothesis is that the there is no difference between pain scores at 0 time and the rest two times.

RESULTS AND ANALYSES:

All the thirty patients completed the study with more than 95 % compliance regarding the intake of the drug**.** The basic demographic features and the descriptive statistics is tabled below. The median post covid days is 25.

Table 1 Showing Demographic Data And The Post Covid Days On Presentation;

	N	Minimum	Maximum	Mean	Std. Deviation
Age	32	36	65	51.53	7.062
Weight	32	21	80	65.72	11.211
Post covid days	32	20	90	34.22	21.098
Valid N (listwise)	32				

The number of males is significantly more than the females (see table 2)

Table 2 Showing Demographic Data Of Gender.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	male	23	71.9	71.9	71.9
	female	9	28.1	28.1	100.0
	Total	32	100.0	100.0	

Regarding the VAS pain scores, there was a significant reduction between 0 day, three weeks and three months. The median value was 7 which decreased to 2 and then 1 at three weeks and three months respectively.

Table 3 Showing VAS Scores At 0, Three Weeks And Three Months.

	N	Mean	Std. Deviation	Minimum	Maximum	. 25th
Vas0	32	6.59	1.073	5	9	6.00
vas3weeks	32	2.03	.897	0	3	1.25
vas3mths	32	1.56	.716	1	3	1.00

Table 4 Showing Median Scores At Different Times.

	Percentiles	
	50th (Median)	75th
Vas0	**7.00**	7.00
vas3weeks	**2.00**	3.00
vas3mths	**1.00**	2.00

The difference between 1 and 2, 1 and 3 are significant statistically but between 2 and 3 and is not significant. (See table 5)

Table 5 Showing The Statistical Significance Of VAS

	Null Hypothesis	Test	Sig.	Decision
1	The categories of Vas0 occurwith equal probabilities.	One-SampleChi-Square Test	.017	Reject the null hypothesis.
2	The categories of vas3weeksoccur with equal probabilities.	One-SampleChi-Square Test	.026	Reject the null hypothesis.
3	The categories of vas3mths occur with equal probabilities.	One-SampleChi-Square Test	.010	Reject the null hypothesis.

Regarding Likert satisfaction scores, the results are similar to VAS scores. (see Tables 6 – 8)

Table 6 Showing The Differences In Likert Scores Between The Groups.

	N	Mean	Std. Deviation	Minimum	Maximum	. 25th
likert0	32	4.09	.641	3	5	4.00
likert3wks	32	2.22	.706	1	4	2.00
likert3mths	32	1.53	.621	1	3	1.00

Table 7 Showing The Differences In Ranking In Likert Scores Between The Groups.

	Mean Rank
likert0	3.00
likert3wks	1.81
likert3mths	1.19

Table 8 – Statistical Significance In Likert Scores.

N	32
Chi-Square	59.862
df	2
Asymp. Sig.	.000

There were no clinical side effects in any of the patients.

DISCUSSION:

The covid 19 struck the with countless mortalities and multisystem morbidities. The treat protocol varied with institutions and countries. Given the impact of COVID-19 on quality of sleep, a few suggestions are critical to preventing or mitigating the effects induced by the pandemic, including maintaining a healthy routine and a relaxed atmosphere[7], as well as relieving stress at night. Modifications in metabolism, mood disorders, and their drug therapy, including the use of antidepressants, can all raise the likelihood of developing sleep disorders like Restless Legs Syndrome (RLS). Exerciseat a low to moderate intensity is advisable to avoid immunosuppression and the increased risk of COVID-19 contamination. Ondo et al. have described in a case study series that ropinirole is effective in around 60 % of patients. There were some rashes and minimal side effects with the use of the drug. We did not get any significant side effects to cause stoppage of the drug usage. The telephonic conversation was continued to confirm the compliance of the drug intake. Nakamura et al have described RLS a s a variant affecting the anal region and we purposely omitted such variantsin the inclusion and exclusion criteria. Buchfehrur et al described so many methods to correct the disorder, and clearly described the use of dopamine agonists as the first choice. In our study we used the same drug to counter the disease symptoms and get efficient results. Opioids should indeed be considered for RLS patients, particularly individuals who have failed other treatments, because they are extremely efficient in severe cases. When monitored closely, they can be extremely safe and long-lasting for long-term therapy. They should also be seriously considered for medical therapy withaugmentation because they are very efficacious at alleviating the worsening symptoms associated when dopamine agonists are reduced or eliminated[12]. In our study we did not have failures with the use of dopamine agonists and there was no need for a rescue opioid in our study cases. RLSss were investigated after COVID-19 vaccination[13], and the findings suggested that RLS could be one of the unanticipated adverse symptoms after COVID-19 vaccination. More research is needed to confirm the link between RLS and COVID-19 vaccination[13]. We did not go into this aspect of the disorder. We had our limitations that this is not a controlled trial with placebo for ethical reasons. The sample size is a quasi-experimental with thirty-two patients in a single centre. A multi centric randomized controlled trial will further establish our results.

CONCLUSION:

In this single centre, quasi experimental study on the efficacy of ropinirole on post covid restless syndrome, we found the drug dosage of 2 mg in the night for three weeks is effective in the control of symptoms. The drug gives better satisfaction which prolonged to three months even if the drug is stopped in three weeks. There were no clinically significant side effects.

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