



Clinical Study on Dyskinesia in Parkinson's Disease

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ABSTRACT: *In this clinical observational study on dyskinesias and motor fluctuations which was conducted in a medical college hospital, about 100 patients with Parkinson's disease were studied. Hoen and Yahr staging, AIMS Scale, Although several scales assess selected attributes of PD-dyskinesias, no comprehensive rating tool exists. Available rating scales were evaluated by the investigators and patient focus. Lateral segment^[1] of the globus pallidus is overactive in dyskinesias in Parkinson's disease. In the earlier stages of Parkinson's disease before the emergence of motor symptoms when significant dopaminergic neuronal loss is counterbalanced by endogenous compensatory mechanisms which are proposed. These are both dopaminergic focused on enhancing effects or exposure to existing dopamine and non dopaminergic being focused on reducing the activity of indirect striatal output pathway. Enhancement of compensatory mechanisms are responsible for the motor complications {Dyskinesias}^[2] with levodopa. Novel and attractive disease modifying approach to PD would alleviate the symptoms.*

KEYWORDS: *DYSKINESIA, L-Dopa, Motor fluctuations*

HIGHLIGHTS:

Dyskinesias are artefacts in the ONstate on treatment with levodopa. Dopamine agonist should be preferred rather than levodopa.

I. INTRODUCTION

Involuntary movements--or dyskinesias--are a debilitating complication of levodopa therapy for Parkinson's disease, and is experienced in most patients. Despite the importance of this problem, little was known about the cause of dyskinesia until recently; however, this situation has changed significantly in the past few years. Our increased understanding of levodopa-induced dyskinesia is not only valuable for improving patient care, but also in providing us with new insights into the functional organization of the basal ganglia and motor systems^[3].

Dyskinesia affects ~30 to 40%^[4] of patients with Parkinson's disease. Younger age, young age of onset and severity of PD are major intrinsic non-modifiable risk factors for dyskinesia, female gender is another factor but not independent of other factors. Genetic expression and plasticity may determine pre-disposition to age of onset of PD^[5] and dyskinesia, these are currently non-modifiable factors arising due to an interaction of intrinsic and extrinsic factors. Lower initial body weight and weight loss during the course of the disease increase the risk of dyskinesia. Levodopa dose per kilogram body weight is a more significant risk factor than absolute levodopa dose. L-DOPA (L-3, 4-dihydroxyphenylalanine) remains the most effective drug for the treatment of Parkinson's disease. However, chronic use causes dyskinesia^[6], a complex motor phenomenon that consists of two components: the execution of involuntary movements in response to drug administration, and the 'priming' phenomenon that underlies these movements' establishment and persistence. A reinterpretation of recent data

suggests that priming for dyskinesia results from nigral denervation and the loss of striatal dopamine input, which alters glutamatergic synaptic connectivity in the striatum. The subsequent response of the abnormal basal ganglia to dopaminergic drugs determines the manner and timing of dyskinesia expression. The combination of nigral denervation and drug treatment establishes inappropriate signalling between the motor cortex and the striatum, leading to persistent dyskinesia. . Early use of longer acting non-levodopa (i. e. dopamine agonists) medications delays the onset of dyskinesia. Interaction between body weight, levodopa dose and mode and duration of drug delivery is a significant modifiable factor. treatment options for the prevention of dyskinesia induction and for the suppression of established dyskinesia are limited. This situation is made more difficult by a poor understanding of the Pathophysiology of the processes underlying both the priming for dyskinesia and the manifestations of involuntary movements. Loss of tonic stimulation of striatal dopamine receptors in PD and its replacement by pulsatile dopaminergic stimulation ^[7] using short acting drugs has been proposed as leading to the abnormalities that cause dyskinesia induction. As a consequence, the concept of continuous dopaminergic stimulation (CDS) was introduced to explain why longer acting dopamine agonists do not produce the same intensity of dyskinesia.

Levodopa treatment for the bradykinesia of Parkinson's disease (PD) is initially effective, but after approximately 5 years, 50% of PD subjects develop "wearing off ^[8]", motor fluctuations and dyskinesia. Therapeutic interventions are then directed at minimising bradykinesia, dyskinesia, "off time" and motor fluctuations. The effectiveness of these interventions. Clinical rating scales ^[9] have their well appreciated limitations, including the inter-rater variability and limited scope for continuous monitoring. While diaries have become important in measuring PD fluctuations, patients find it difficult to report the nature, severity and timing of change in motor states.

To sum up the management of the dyskinesia

- adjusting the dose of your levodopa to avoid large fluctuations in the amount of dopamine in your system
- taking levodopa in a continuous infusion or an extended release formulation
- taking amantadine extended release (Gocovri), which was recently approved to treat dyskinesia
- for tardive dyskinesia, taking a newly approved drug — valbenazine taking levodopa in smaller doses more often
- taking your levodopa 30 minutes before a meal, so the protein of your food doesn't interfere with absorption
- getting exercise, such as walking and swimming, as prescribed by your doctor
- using stress management techniques, since stress is known to make dyskinesia worse
- using dopamine receptor agonists through monotherapy — only in the very early stages of Parkinson's before developing dyskinesia
- undergoing deep brain stimulation, which is a surgical treatment for severe symptoms

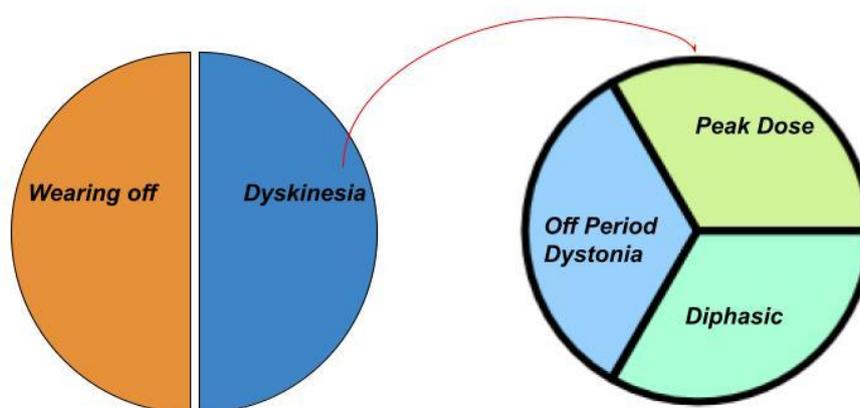
II. MATERIALS AND METHODS:

Study population: Includes parkinson's disease patients attending outpatient clinic of trinaveli medical college hospital.

Although several scales assess selected attributes of PD-dyskinesias, no comprehensive rating tool exists. Available rating scales were evaluated by the investigators and patient focus groups. Modifications were finalized into the (Unified Dyskinesia Rating Scale UDysRS). The UDysRS has four parts: I: Historical Disability (patient perceptions) of On-Dyskinesia impact (maximum 44 points); II: Historical Disability (patient perceptions) of Off-Dystonia impact (maximum 16 points); III: Objective Impairment (dyskinesia severity, anatomical distribution over seven body regions, and type (choreic or dystonic) based on four activities observed (28 points); IV: Objective Disability based on Part III activities (maximum 16 points)

It was tested against rapid alternating movements (bradykinesia), AIMS (dyskinesia) and the scores obtained from the UPDRS III and IV clinical rating scales.

III. OBSERVATION:



The median age of 100 patients with parkinsons disease was 60.4 years.

Dyskinesias are predominantly peak dose, diphasic or off-period dystonia

Among 100 patients with Parkinson's disease included in this study, almost all of them received L-dopa since the availability of other dopamine agonists are not there in this tertiary care hospital.

Among them 30% of them were experiencing treatment induced dyskinesias and 40% response fluctuations.

Prevalence of motor complications by disease duration, treatment duration and Hoehn and Yahr stage

Duration of >5yrs----15%

<5yrs----6%

>10 yrs---65%

	Mean	SD
Age in years	60	10.3
Disease duration in years	8.2	5.3
Age at onset (in years)	58	5.6
Duration of treatment with levodopa	6.8	4.7
Dose of levodopa (mg/day)	316	
Hoehn and Wyahr stage	3.2	1.2

As per the staging by HOEHN AND YAHR

1 or 1.5 --No motor complications

2 or 2.5 --40% motor fluctuations, 30% dyskinesia

4 or 5 ---70% had motor fluctuations and dyskinesia

Percentage of Parkinson's disease

	<i>Disease duration</i>		
	<5 years	6-10 years	>10 years
<i>Motor Fluctuations</i>			
Patients on levodopa	18	39	57
Patients with good response on levodopa	22	59	72
<i>Dyskinesia</i>			
Patients on levodopa	4	18	57
Patients with good response on levodopa	5	19	63

SUBTYPES OF MOTOR FLUCTUATIONS AND DYSKINESIAS

Wearing off fluctuations-34%

Sudden off period -3%

TYPES OF DYSKINESIA

Peak dose -25%

Diphasic -5%

Off period dystonia -10%

Patients who are prone to develop dyskinesia are having the disease for a longer duration, long treatment duration, high dose of levodopa, greater disability, greater disease severity, 4 or 5 of Hoehn and Yahr staging and had a good response to L-dopa and were receiving more than 300 mg of L-dopa.

Dyskinesia range from tremor, chorea, ballisms, athetosis, dystonia, and myoclonus and otherwise called hyperkinetic movement disorders.

The DATATOP study^[10] in which a large cohort of patient with parkinsons disease were followed with regular appointments by movement disorder experts also reported high rates of motor fluctuations and dyskinesias with 30% and 50% patients respectively, developing these complications with levodopa<2yrs. (parkinsons study group1996)

Differences between studies indicate that certain variables can influence the occurrence of motor fluctuations and dyskinesias on levodopa treatment. They have partly been attributed to different dosages of levodopa and initial lack of use of peripheral decarboxylase inhibit

IV. CONCLUSION:

Levo dopa is the gold standard therapy for parkinsonsdisease. Levodopa induced dyskinesia is defined as involuntary, purposeless predominantly choreiform movements. Levodopa induced dyskinesia corresponds to the times of peak plasma levodopa concentration and resolves with the reduction of individual levodopa doses. OFF states in PD manifest with dystonia, toe curling, foot inversion. Choreiform dyskinesia manifest with a biphasic pattern surfacing at the beginning and the end of levodopa peak. However limiting or deferring levodopa treatment tends to compromise parkinsonism control. Oral dopamine agonists are not as efficacious as levodopa and have undesirable side effects as impulse control disorders, hallucinations and sleep attacks.

Preclinical studies have suggested a number of directions that might be utilized to prevent dyskinesia in PD. However, much of what is proposed is empirically-based and we still do not have a good understanding of why dyskinesia appears, why it persists or how to bring the movements under control. Certainly, the use of CDD can reduce dyskinesia intensity but other factors also influence its appearance and it is these that we need to study at the preclinical level if effective therapies are to be developed. Some believe that PD patients will prefer to be ON with dyskinesia than OFF, reality is that patients will prefer to be ON without dyskinesia. To achieve this goal research on LID should continue.

When levodopa doses were adjusted dyskinesia was not bothersome. Marked improvement or resolution of dyskinesia in 65% of patients. 20% of severely dyskinetic patients neither lowering levodopa dose nor put on amantadine adequately controlled the dyskinesia without substantially increasing parkinsonism. 15% of the patients lost follow up.

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