



Original Research Article

Effect of caloric vestibular stimulation on brain neurochemicals in rotenone induced mouse model of Parkinson's disease

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ABSTRACT

Introduction: It is learnt that Parkinson's disease has no specific standard treatment, without side effects. Hence, it is very essential to discover a natural therapy which promises less or minimum side effects in delaying or preventing Parkinson's disease (PD).

Objective: This study was taken-up to demonstrate the effectiveness of caloric vestibular stimulation on the brain neurochemicals in rotenone induced mouse model of Parkinson's disease.

Materials and Methods: The study included 24 healthy and adult male Swiss albino mice. Their body weight was between 25 - 40g. Mice were randomly divided into four groups, wherein each group was containing 6 rats. Cold water treatment was used in the study as specified in literature as hot water (40° C) causes irritation in the middle ear cavity of the mice. The following neurotransmitters like Acetylcholine, serotonin, dopamine and GABA were estimated by using kit method procured from Sigma Chemical Co.

Results: The results of the study suggest a positive impact of vestibular stimulation in Parkinson's disease management.

Conclusion: The study results are in accordance to the earlier studies showing a positive impact of vestibular stimulation on the brain neuro-transmitters in rotenone induced mouse model of Parkinson's disease. Therefore, the study demands further research to learn the mechanism of action of vestibular stimulation in the management of Parkinson's disease.

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1. Introduction

Though the exact cause for the Parkinson's disease is not clear yet, but considered as the second common est disease causing the motor function impairment. Parkinson disease affects approximately 1% of the population among the age group of 65 years, wherein at about 85 years of age the increase is up to 4% to 5% of the specific population.¹ As there is no standard treatment for the disease without any side effects,² it is essential to find out a natural therapy with minimum or less side effects to delay or in preventing Parkinson's disease (PD). This study is importance as Parkinson's disease (PD) burdens an increasing number of our nation's elders

and their families. Vestibular stimulation is known to modulate cognitive processing, enhance learning and spatial memory.³ Interestingly, vestibular dysfunction is more prevalent in Parkinson's disease.⁴ Earlier studies reported the existence of connections between the vestibular system and basal ganglia.⁵ Implementation of noisy and galvanic vestibular stimulation may show an improvement in the motor deficits of PD.⁶ So vestibular stimulation may be considered as a neuro - physiological approach and a palliative therapy for cognitive impairment and motor dysfunctions in Parkinson's disease. Hence, vestibular stimulation can be idea l method of application on the aged Parkinson's patients possessing no side effects.⁷ The ideal and most effective type of vestibular stimulation in Parkinson's disease could be identified by applying different types of vestibular stimulation in rat PD model and studying

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the cognitive, behavioral and neurodegenerative changes. Our extensive review of literature has shown that till date no studies related to vestibular stimulation in India exists, as a mode of treatment for Parkinson's disease. Our preliminary studies had clearly shown vestibular stimulation to be effective in learning, cognition, verbal and spatial memory, both in humans and in animal studies. Hence, this study was taken-up to learn the effectiveness of caloric vestibular stimulation on brain neurochemicals in rotenone induced mouse model of Parkinson's disease.

2. Materials and Methods

2.1. Animals

The study included 24 healthy and adult male Swiss albino mice. Their body weight was between 25 - 40g. Standard laboratory conditions were provided to mice with required food and water ad libitum. The study was conducted according to the guidelines of The Indian National Science Academy. The same was used for data management and interpretation and all efforts were made to reduce the animal number and their suffering.

Mice were randomly divided into four groups.

Group 1 (n=6): Control mice - olive oil (1.0 mL/Kg b.w) as vehicle i.p for 30 days daily.

Group 2 (n=6): PD mice - rotenone (3 mg/kg b.w) i.p for 30 days daily.

Group 3 (n=6): Hot water vestibular stimulation group- rotenone (3 mg/kg b.w) i.p daily and hot water vestibular stimulation on alternate days for a period of 30 days.

Group 4 (n=6): Cold water vestibular stimulation group- rotenone (3 mg/kg b.w) i.p daily and cold water vestibular stimulation on alternate days for a period of 30 days.

2.2. Caloric vestibular stimulation

The middle ear cavity of the mice was irrigated with hot water (40°C) and cold water as specified in literature. 0.5 ml of water was taken in 5 ml syringe with the needle removed. The ear was irrigated with water drop by drop, using the syringe. Gently the earlobe of mice was shaken. The procedure was continued with the other ear.⁸

2.3. Outcome measures: Estimation of brain neurotransmitters

After 30 days of the experimental period, the animals were fasted overnight and sacrificed by cervical decapitation. The brains were excised immediately and the brain tissue was homogenized in ice-cold n-butanol solution and used for estimation of biochemical parameters. All the test protocols were carried out between 10:00 am to 12:00 pm. Acetylcholine, dopamine, serotonin and GABA were

estimated by using kits, purchased from Sigma Chemical Co.

2.4. Estimation of reduced glutathione (GSH)

GSH was estimated by the method explained by Moron et al. which is a standard method.⁹

2.5. Study setting

The study was conducted at Little Flower Medical Research Centre, Angamaly, Kerala, India.

2.6. Ethical consideration

The study got the approval from the institutional animal ethical committee of Little Flower Medical Research Centre, Angamaly, Kerala, India.

2.7. Data analysis

Data analysis was done by applying SPSS 20.0 version. The significance of the difference between the groups was observed by using One way ANOVA followed by Tukey HSD post hoc test. Probability value <0.05 was considered to be significant.

3. Results

Group 2 and 3 had showed a significant increase ($P < 0.001$) in the levels of acetyl choline, when compared with group 1 (control). Wherein, there was no significant difference in the levels of acetylcholine between the groups 4 and 1. There was a significantly low levels of acetyl choline was noticed in group 3 and 4 in comparison to group 2 ($P < 0.001$). The levels of acetyl choline was significantly lower than group 3 in group 4 ($P < 0.001$). The levels of dopamine showed a significant decrease ($P < 0.001$) in group 2, 3, 4 than group 1. The levels of dopamine levels showed significant increase in group 3 and 4 when compared to group 2 ($P < 0.001$). When compared with group 3 the Dopamine levels in group 4 showed a significant increase ($P < 0.001$). The groups 2, 3 and 4 showed a significantly higher Serotonin levels ($P < 0.001$) when compared with group 1. The Serotonin levels in group 3 are lower when compared to group 2, which was not statistically significant. There was a significantly lower levels of Serotonin in group 4 when compared to group 2 ($P < 0.001$). The Glutamate levels showed a significant decrease in group 2 ($p < 0.001$) and 3 ($P < 0.001$) when compared with group 1. Glutamate levels showed a significant increase in group 4 when compared with group 1. There was a significant increase in Glutamate levels in group 3 and 4 when compared to group 2 ($P < 0.001$). Group 4 showed a significant increase in the Glutamate levels when compared to group 2 ($P < 0.001$). There showed a significant increase in the GABA levels of group 2 ($P < 0.001$), 3 ($P < 0.001$) and 4 ($P < 0.001$). The

Table 1: Brain neurotransmitter levels in control and intervention groups

Groups	Group 1	Group 2	Group 3	Group 4	F value
ACH (mole/minute/mg tissue)	0.0863± 0.003508	0.129± 0.00646	0.1033± 0.00830	0.08133± 0.002431	86.1953
Dopamine (ng/g tissue)	0.1858± 0.0045643	0.1259± 0.002446	0.1404± 0.001898	0.1611± 0.001570	494.9078
Serotonin (ng/g tissue)	0.1254± 0.003724	0.1608± 0.002318	0.1516± 0.00591	0.1364± 0.00140	105.8853
Glutamate (ng/g tissue)	0.2147± 0.006626	0.16267± 0.01036	0.1943± 0.007139	0.282± 0.01030	198.4111
GABA (ng/g tissue)	0.1540± 0.00228	0.205± 0.007522	0.1318± 0.002300	0.1412± 0.00578	254.2808

(Data was expressed as mean and SD)

GABA levels of group 3 and 4 showed a significant decrease ($P<0.001$) when compared to group 2. The GABA levels of group 4 was significantly higher ($P<0.01$) when compared to group 3.

4. Discussion

The study was conducted to learn the effectiveness of caloric vestibular stimulation on brain neurochemicals in rotenone induced mouse model in Parkinson's disease. Positive impact of vestibular stimulation was observed on the neurotransmitters. Vestibular dysfunction, which is associated with risk of falling, was observed in both Parkinsonian patients and atypical Parkinson's disease. The Galvanic vestibular stimulation (GVS) is learnt to activate the vestibular afferents and these changes in the vestibular input exert s strong influence on the standing balance and posture of the subject. GVS activates extrapyramidal structures such as basal ganglia, limbic system, pedunculopontine nucleus, spinal cord through the vestibular nerves. These leads to an increase in the axial motor function and further improve the postural instability of the subject.⁹ Parkinsonian patients there was a prevalence of tremor, dizziness, tinnitus, gait unbalance and falls. Alteration was observed in the peripheral vestibular system and the caloric test.¹⁰ In Parkinson's disease postural sensory integration is controlled by pedunculopontine nucleus- thalamic, not the cortical cholinergic innervations. Impairment of this section and their thalamic efferents causes postural instability in Parkinsonian patients.¹¹ Binaural galvanic vestibular stimulation (GVS) learnt to improve the anterior bending angle in the patients with Parkinson's disease.^{12,12} Vestibular nuclei excitability was reduced in Parkinsonian patients which can be modulated by inducing DOPA.¹³ We noticed an impairment in the processing of vestibular information in Parkinsonian patients those affected by the lateral trunk flexion. This impairment was partially responsible for the abnormality in patients' posture.¹⁴ Frontal-basal ganglionic and frontal-parietal systems dysfunction affects visual and spatial abilities in Parkinson's disease.¹⁵

Earlier studies suggested that, vestibular stimulation may be considered as a natural method of treatment for treating Parkinson's disease.¹⁶ India has low prevalence of PD yet very good at research performance in PD and possess 16th rank in global context, in the year 2002-2011.¹⁷ Depression, anxiety, anhedonia, psychosis, cognitive disorders, apathy, suicidal behavior are common in Parkinson's disease.¹⁸ Patients with early PD performed significantly worse in the tasks involving memory, executive functions, and attention.¹⁹ It was observed that PD patients when compared with normal subjects showed delay in switching of the saccade from one target to another, proving that the basal ganglia are not just involved in the somatomotor loop but also are involved in the oculomotor loop of the frontal sub cortical circuit.²⁰ Increased speech impairment, restless leg syndrome (RLS),²¹ impulse control disorders,²² both obstructive and restrictive patterns of respiratory dysfunction were very common in PD.²³ The decrease in the response of blood pressure and heart rate to the autonomic stimulation reveals the presence of cardiac autonomic dysfunction in PD patients.²⁴ It was reported that the reduction in the combined effect of the muscle strength, decreases visual sense, proprioception and narrow base support leading to the imbalance in PD.²⁵ Ayurvedic treatment like panchakarma (cleansing or eliminating therapy) followed by a mixture of cow's milk, Withania somnifera, Hyoscyamus reticulatus seeds, Mucuna pruriens and the roots of Sida cordifolia were used to improve the daily activities of the patients with PD.²⁶ It was also learnt that a exercises with a systematic program can improve the UPDRS scores, daily activities and also gait of PD patients.²⁷ The wireless vibratory feedback system called as PD shoe and partial weight supported treadmill gait training (PWSTT) like physical therapies were effective in treating difficult symptoms of PD like freezing and gait disturbances.²⁸

Vestibular System plays a vital role in everyday life, contributing to a surprising range of functions from reflexes to the highest levels of perception and consciousness. Vestibular stimulation is known to be

one of the most popular and newest therapies used to treat the developmentally delayed children. The extensive preliminary studies had shown that the application of controlled vestibular stimulation by using swing not just serves as an intervention for the learning disability but can also to relieve cancer pain, stress, promotes sleep, improves immunity and treats endocrine disorders.²⁹ Cold water vestibular stimulation suppresses the stress induced changes in immunological parameters in Wistar albino rats.³⁰ Hot and cold vestibular stimulations are beneficial in maintaining lipid profile of Wistar albino rats.³¹ Hot water caloric vestibular stimulation improves cognition in scopolamine induced partial amnesia Wistar albino rats.³²

5. Conclusion

The results of the study suggest that there is a positive impact of vestibular stimulation and can be used in the management of the Parkinson's disease. There is a need for the extensive research in this area to understand the mechanism of action of the vestibular stimulation used in the management of PD.

6. Conflicts of interest

None.

7. Source of funding

Self-funding.

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