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Original Article

IMPACT OF CALORIC VESTIBULAR STIMULATION ON CO-ORDINATION IN PARKINSON DISEASE INDUCED MICE

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ABSTRACT

Objective: This study was undertaken to evaluate the effect of vestibular stimulation on motor coordination in Parkinson's disease (PD) induced mice.

Methods: 18 healthy adult male Swiss albino mice were used in this study. Vestibule was stimulated by caloric vestibular stimulation (CVS). Pesticide Rotenone was used to induce Parkinson's disease (PD). Motor coordination was assessed by the fall-off time and the activity score using the rotarod and actophotometer, respectively.

Results: In the rotarod test, there was a significant increase in the fall-off time ($p<0.01$) in the CVS PD group (131.63±18.34) on the 30th day when compared to the PD group (95.33±15.17). In the actophotometer, the activity score improved in the PD CVS group on the 15 (235±47.09) and 30th days (251.38±25.76), while there was no improvement in the PD group. This shows the significant effect of caloric vestibular stimulation on motor coordination in Parkinson's disease.

Conclusion: This study confirms that caloric vestibular stimulation with hot water resulted in the improvement of motor coordination in PD. Hence this study certainly merits further studies with a higher sample size to confirm the effect of caloric vestibular stimulation on the enhancement of motor coordination in individuals with Parkinson's disease.

Keywords: Parkinson's disease, Vestibular stimulation, Motor coordination, Rotarod, Actophotometer

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INTRODUCTION

Parkinson's disease is a neurodegenerative brain disorder that leads to tremors, stiffness, and difficulty with walking, balance, and coordination. The symptoms begin early and worsen over time. Depression, behavioral changes, and sleep problems occur as the disease progresses. Men are 50% more affected than women. The most common age of Parkinson's is 60 y but sometimes it may occur a little early in 50 y due to specific gene mutations [1].

Nerve cells in the basal ganglia, which control movement, become impaired in Parkinson's disease. The basal ganglia secrete dopamine neurotransmitters; therefore, if they are damaged, they generate less dopamine, resulting in Parkinson's movement issues. Production of norepinephrine, the principal chemical messenger of the sympathetic nervous system, which controls numerous bodily functions such as heart rate and blood pressure, is also affected [2, 3]. Due to this, fatigue and postural hypotension may occur in Parkinson's disease. Lewy bodies are present in the brain cells of Parkinson's patients, which are clumps of the alpha-synuclein protein. After daily sessions of caloric vestibular stimulation, a case study revealed that there was a 50% reduction in both motor and non-motor symptoms of Parkinson's disease [4]. A previous study stated that vestibular stimulation in Parkinson's disease leads to the improvement in motor control by increasing functional neural connectivity. CVS has been shown to activate several ascending cortical and subcortical circuits in people with Parkinson's disease. Its induction method distinguishes it from all other known pharmacological and other neuro-modulatory techniques, which are non-endogenous and chemically/anatomically targeted. Cortical involvement and neurovascular coupling are the key processes involved in PD when combined with the diffuse clinical symptoms shown here. CVS stimulation induces oscillations in cerebrovascular dynamics, which is suggestive of 'pontine involvement. Many previous studies suggested going for large-scale clinical evaluation to have a higher level of understanding of this [5, 6]. The aim of the present study was to evaluate the effect of hot water vestibular stimulation on motor coordination in Parkinson's disease (PD) induced mice assessed by roto rod and actophotometer.

MATERIALS AND METHODS

This study was approved by the institutional animal ethics committee (IAEC) of Saveetha Medical College and Hospital. [approval number SU/CLAR/RD/017/2016]. The research was conducted in compliance with CPCSEA guidelines (Committee for the purpose of control and supervision on experimentation on animals). Every attempt was made to keep the number of animals utilized and their suffering to a minimum.

Animals

In this study, 18 healthy adult male Swiss albino mice with body weights ranging from 25 to 40 grams were procured from the Central animal house of Saveetha medical college. All the animals were acclimatized in the Department of physiology for a period of 1 w. Mice were maintained in regular laboratory settings, with free access to food and water. Mice were divided into three groups at random:

Group I (n=6): Control mice: no drugs or intervention was given

Group II (n=6): Parkinsonism was induced by the administration of rotenone and (PD group).

Group III (n=6): PD induced+caloric vestibular stimulation (CVS PD) with hot water for 30 d

Chemicals and drugs

Rotenone and Dimethyl sulfoxide (DMSO) were obtained from Sigma Aldrich; olive oil was commercially obtained.

Rotenone-induced PD model

There are various animal models available for Parkinson's disease. In this study, we used the rotenone-induced PD model by injecting rotenone at a dose of 2.5 mg/kg body weight rotenone intraperitoneally for 9 d to induce the PD in mice [7, 8].

Method of administration of rotenone

Rotenone solution was first prepared as a 50× stock in 100% dimethyl sulfoxide (DMSO) and diluted in medium-chain triglyceride and olive oil to obtain a final concentration of 2.5 mg/kg rotenone in 98% Olive oil, 2% DMSO. Vortex the solution creates a stable emulsion of the DMSO containing rotenone and olive oil. The solution was made fresh 2–3 times/week and stored in an amber septa vial protected from light and inverted several times before each injection to eliminate the possibility of settling [9].

Caloric vestibular stimulation

The middle ear cavity of the mice was irrigated with hot (40° degree centigrade) water. 0.5 ml of water was taken in a 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 so that water reaches the inner ear. The procedure was continued with the other ear [10].

Protocols of parameters

Tests for motor coordination parameters were carried out in the facility of the Department of Pharmacology, Saveetha University All the test protocols were carried out between 9:00 am to 12:00 pm. Animals were habituated as per the training protocol for all the test parameters.

Motor coordination was assessed by

Rotarod test

A horizontal metal rod coated with rubber with a diameter of 3 cm is coupled to a motor with a speed range of 1 to 40 rotations per minute (rpm). The rod is 50 cm long and is separated into four portions by plastic discs, allowing four mice to be tested at the same time. To keep the animals from jumping off the roller, the rod is set at the height of roughly 50 cm above the tabletop. Before each session, the animal's body weight was measured. Before each test session, each mouse had to be trained [11, 12].

Training

During the training phase, the mice were allowed to ride on the roto rod for 3 min, with a 5-minute intertrial interval for three days. On days two and three, record the latency to fall for each trial.

Test session

The mouse was placed onto the rotating cylinder to start the trial and allowed to ride on the rod until the mouse falls off the cylinder and stops the timer. The riding time (and the rpm) of each mouse was recorded by starting the cylinder at a low speed (4 rpm) and the speed was increased gradually. The apparatus was cleaned with 70% ethanol [fig. 1, 2].

Rotarod

Fig. 1: Animal riding on the rotorod

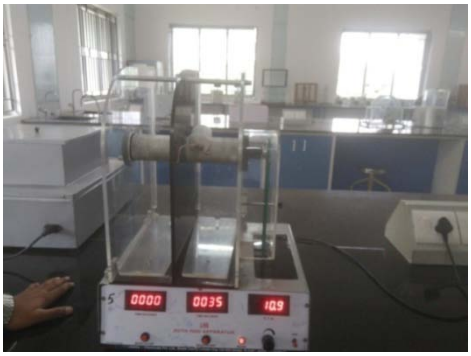

Fig. 2: Fall off time and speed of the rotating rod (rpm)

Actophotometer

Photoelectric cells were used in this device, which is coupled to a circuit with a counter. When the animal cuts off the beam of light falling on the photocell, a count was made. The animal moves in a square arena in an actophotometer. Before the test, each mouse had to be weighed. The mice were individually placed in the activity cage for 5 min after the equipment was turned on. All the animals' basal activity scores were recorded [13, 14] [fig. 3, 4].

Fig. 3: Animal activity in actophotometer

Fig. 4: Actophotometer with the activity score

Statistical analysis

The collected data were analyzed with IBM SPSS statistics software 27.0 version. Descriptive statistics were done. The values were expressed as mean±SD to find out the significant difference between the various groups, the multivariate analysis by Kruskal Walli's test was done followed by the Mann-Whitney U test. For the repeated measures (0^{th} day, 15^{th} day and 30^{th} day) the Friedman test was used. The probability value of $p<0.05$ was considered a significant level.

RESULTS

There was no significant change in the body weight of the animals in all three groups (control, PD only, and CVS PD group [table 1].

Roto rod was used to evaluate balance and coordination by measuring the fall-off time in experimental animals. The fall-off time has decreased consistently ($p<0.01$) in PD-induced mice on the 15th and 30th days when compared to the control group. There was a significant increase in the fall-off time ($p<0.01$) in the CVS PD group on the 30th day when compared to the PD group [table 1]. In the actophotometer, the activity score of the control group was 286.5 at the start of the study, which improved to 301.25 (5%) on the 15th day. On the 30th day, the score decreased to 229.25(20%) from baseline. In the PD group, the mean activity score remains almost the same 213.167 on the 0 and 15th days. It declined to 207.33 on the 30th day (3%). In the CVS PD group, the mean activity score improved by 11% (210-235) on the 15th day from baseline and it further improved on the 30th day (251.37) by 19% [table 1].

Table 1: Effect of vestibular stimulation on body weight, fall-off time, and activity score in all the three groups

Groups	Day	Body weight (g)	Fall off time (s)	Activity score (numbers)
Control	0th d	32.5±2.5	221.25±44.42$^{\$\$}$	286.5±29.74$^{\$\$}$
	15th d	32.30±2.25	232.7±42.03$^{\$\$}$	301.25±30.93$^{\$\$}$
	30th d	32.78±1.56	303±21.94$^{\$\$}$	229.25±23.06
PD only group	0th d	31.80±3.38	98.17±37.09**	213.17±70.05
	15th d	30.77±3.35	98.17±35.14**	213.1±50.14**
	30th d	29.72±3.42	95.33±15.17**	207.33±44.64
CVS PD group	0th d	33.24±2.14	98.38±40.27	210±43.98
	15th d	31.95±2.05	116±41.11	235±47.09$^{\#}$
	30th d	31.88±2.05	131.63±18.34$^{\#\#}$	251.38±25.76$^{\#\#}$

Data are expressed as mean±SD. Significance between the groups are indicated as a) control group and PD only group (*p<0.05, **p<0.01, ***p<0.001), b) control and CVS PD groups ($^{\$}$p<0.05,$^{\$\$}$p<0.01,$^{\$\$\$}$p<0.001), c) PD only group and CVS PD groups ($^{\#}$p<0.05,$^{\#\#}$p<0.01,$^{\#\#\#}$p<0.001)

The body weight of animals in all three groups measured at the beginning of the study is more or less similar and there is no statistically significant difference between them.

There is no change in body weight within the control group on the 0, 15, 30th day. While in the other two groups, there is a very minimal change in weight of the mice (6 % reduction in PD-induced mice and 4% in the CVS PD group), the reduction is not statistically different.

Studies conducted in Germany by M. Alam *et al.* and in Pittsburg by Jason *et al.* observed that there was a reduction in body weight proportional to the dose of rotenone [15, 16].

When compared within the groups, the activity score was more or less the same for the PD group and PD CVS group at baseline. The activity score improved in the PD CVS group on the 15 and 30th days, while there was no improvement in the PD group. The results were statistically significant.

This shows the obvious effectiveness of the vestibular stimulation on motor activity in PD induced group. The activity score in normal mice was decreased over time, which may be due to the adaptation of the animal to the environment inside the actophotometer, and motor activities were decreased. Rotenone depletes dopamine in the posterior striatum and prefrontal cortex, leading to metabolic insufficiency in the nigrostriatal dopaminergic neurons, according to a study on homogenized brain tissue. Because they get direct glutamatergic input from diverse routes, such as the cortex, the subthalamic nucleus (STN), and the prepontine tegmentum, dopaminergic neurons are more vulnerable to external and endogenous insults (PPTg). In dopaminergic neurons in the substantia nigra (pars compacta), glutamate inputs cause an increase in intracellular sodium concentration. Na/K-ATPase activity and ATP consumption were boosted to lower intracellular sodium levels. Dopaminergic synapses require an enhanced mitochondrial activity for the generation of high-energy molecules in order to keep dopaminergic neurons in a constant tonically active state. Dopamine deficiency makes it difficult to initiate movement [17].

There is an increased activity score in the experimental group (CVS PD group) throughout the experiment. This shows the obvious effectiveness of the vestibular stimulation on motor activity in PD induced group. But the obtained values are not statistically insignificant. This may be due to a shorter treatment period of 1 mo. The nucleus tractus solitarius, the dorsal motor vagal nucleus, and the nucleus ambiguous/parambiguous all receive projections from the vestibular nuclei [18]. The ventrolateral medullary reticular formation, the nucleus raphe Magnus, and the lateral medullary tegmentum all receive projections from the vestibular system [19]. These connections permit information about body motion to the pathways mediating autonomic and emotional responses. Because of the above vestibular projections, the hot water stimulation of the vestibular nucleus in turn, causes motor stimulation and arousal in the animal [20, 21]. This could have led to an increase in the activity score observed in the CVS PD group animals.

CONCLUSION

This study categorically confirms that the caloric vestibular stimulation with hot water enhances motor coordination, learning, memory, and behavior in PD-induced mice when assessed using a rotarod actophotometer. Hence this study certainly merits further studies with a higher sample size to confirm whether caloric vestibular stimulation can be recommended for enhancement of motor coordination, learning, memory, and behavior.

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Nil

AUTHORS CONTRIBUTIONS

Ram Mohan N was the principal investiagator and was instrumental in bringing out the concept and in designing the study. Kayalvishi and Rashmi Ramanathan helped in Literature search and manuscript writing. Jeevithan analysed the data, interpreted the results and helped in manuscript writing. Archana guided the study throughout from conception of the study till completion.

CONFLICT OF INTERESTS

Declared none

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