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Original Article

Caloric Vestibular Stimulation Alleviates the Motor Dysfunctions in a Mouse Model of Parkinson's Disease

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ABSTRACT

Background: Parkinson's disease (PD) is one of the most common degenerative disorders of the ageing brain. Currently, there is no cure for PD and most of the available treatments only aim to reverse the dopamine deficiency and relieve its symptoms. Caloric vestibular stimulation (CVS) is believed to help in relieving motor symptoms of PD. Hence, the present study is planned to evaluate the effect of CVS on behavioral changes in PD Mice. **Methods:** Twenty-four healthy male Swiss albino mice divided into four groups (*n*=6) were used for the study. PD was induced by giving an intraperitoneal injection of MPTP for 5 consecutive days. Bilateral CVS was given with hot water (temperature 40°C) for 15 days. Changes in behaviour (locomotor activity, grip strength, motor coordination, immobilization time) were measured on day 1 and day 15 and the results were statistically analysed. **Results:** The PD group showed a significant decrease in locomotor activity, muscular strength (fall on time), grip strength and immobilization time when compared to the control group, whereas CVS prevented the symptoms of PD when compared with the PD group. **Conclusion:** Caloric vestibular stimulation was effective in alleviating behavioral alterations in Parkinson-induced mice.

Keywords: Grip strength, Immobilization time, Locomotor activity, Motor coordination, Parkinson's disease.

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INTRODUCTION

Parkinson's Disease (PD) is the second most common age-related neurodegenerative disease characterized by tremor, rigidity, slowness of movement, postural imbalance, and other non-motor symptoms such as cognitive impairment, depression, anxiety, sleep disorders, and apathy to name a few.[1] PD is one of the most common neurodegenerative diseases, caused by degeneration of dopaminergic neurons in the substantia nigra pars compacta thereby lowering the amount of dopamine available for neurotransmission in the corpus striatum. Subsequently, there is an accumulation of Lewy bodies in the dopaminergic neurons, further contributing to the disease.[2] Age, environmental factors, genetics, and oxidative stress could be the cause of PD. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model has been the most used model for explicating damage to the nigrostriatal pathway in PD.[3] The chief treatment options available now are drug therapy that includes the widely used levodopa (a dopamine precursor), dopamine receptor agonists, Catechol-O-Methyltransferase (COMT) inhibitors, and Monoamine Oxidase (MAO) inhibitors.[4] Although the drugs were effective but long-term usage contributed to other side effects in older patients which include dizziness, confusion, hallucinations, psychosis, and agitation.[5] Postural hypotension and somnolence were other adverse effects reported with the use of levodopa.[6]

Studies have demonstrated that neuropathology of PD, such as Lewy bodies is present in the central vestibular system.[7] According to electrophysiological and neuro tracker investigations, vestibular information is transferred to the striatum, which in PD lacks dopaminergic input.[8] Some early studies of vestibular function in PD suggested deficits in the vestibulo-ocular (VORs) and vestibulospinal reflexes.[7] The vestibular system, controls posture and balance and is tightly linked to the body's entire physiology.[9] The vestibular system controls reflexes cognition and coordination and is therefore referred to as "The Sixth Sense".[10] In recent years' stimulation of the vestibular system has been in use for diagnosing neurological disorders,[11] treating dementia, relieving depression and anxiety,[12] regulating neurotransmitters associated with ageing.[13] Deep brain stimulation (DBS) emerged as a new and effective treatment for the motor symptoms and dyskinesias of PD.[14] Galvanic vestibular stimulation helped in alleviating some of the motor symptoms of PD,[15] but many patients have reported discomfort during the procedure.[7]

In the present study Caloric, Vestibular Stimulation (CVS) is used to stimulate the vestibular apparatus. It is a simple and non-invasive procedure that is shown to improve the motor and non-motor symptoms of PD in pre-clinical experiments.[16] The primary goal is to determine the impact of bilateral CVS on behavioural outcomes in PD-induced Swiss albino mice.

MATERIALS AND METHODS

Chemicals

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was purchased from Sigma Aldrich, USA for the present study.

Animals

A total of 24 healthy male Swiss albino mice weighing 25-30 gm were used for the study after obtaining ethical clearance from the AIMST University Animal Ethics Committee (AUAEC/FOM/2020/04). Animals were individually housed in spacious polyacrylic cages in university animal house and maintained at controlled temperature and humidity under a 12 h light/dark cycle. Food and water were available to the animals' *ad libitum*. Animals were allowed to acclimatize to the animal house before performing any tests on them. All the experiments, interventions and recordings were done between 9 am to 5 pm so that the circadian rhythm Is not disturbed and influence the readings.

Experimental Design

Swiss albino mice were randomly divided into four groups of six animals each.

Group I: Control group

Group II: PD group

Group III: CVS for 15 days

Group IV: PD + CVS for 15 days

Group I was considered as a normal control. The animals in group II and IV were administered with an intraperitoneal injection of MPTP (30mg/kg body weight) in sterile saline, once daily for 5 consecutive days to induce dopaminergic neuron death in the substantia nigra/ to induce PD.[17] The animals in group III and IV were given vestibular stimulation for 15 days after confirming the mice developed PD in group IV. Behavioural assessment was done at the before and end of the experimental procedures.

Caloric Vestibular Stimulation

The middle ear cavity of mice was irrigated with 42°C water, which caused a convection current in the semicircular canal. Approximately 2.0 mL of water was drawn into the syringe. The mouse was secured in a supine position with its head slightly inclined. Warm water was expelled from the tube at a rate of 0.1 mL/sec after the head was twisted.[13,18] In this research, bilateral vestibular stimulation was administered daily between 9 am and 12 pm for 15 days as mentioned in the experimental design.

Behavioural Assessment

***Locomotor activity*:** The mice's locomotor activity was studied using the actophotometer (Jainsons, India). Mice are placed in the center arena and their locomotor activity was noted for 10 mins continuously. The movement of the animals interrupts the light coming from the photocell. Every time there is an interruption of light it is recorded as a count by the digital counter.[19,20]

***Grip Strength*:** Grip strength was studied using a wire grip test to assess muscle strength. A wire was fixed horizontally between two platforms Each animal was hung with its paws on the middle of the wire, and the duration of time the mice could hold on to the wire before falling was recorded. The height above the ground level was kept at a minimum to avoid any injuries from falling and additionally cotton and sponge were placed on the ground as cushion. Prior training was given to all the mice before the actual testing. The fall-off time was recorded in all the groups.[4,20]

***Motor coordination assessment*:** Motor coordination in the mice was evaluated using a digital Rota-rod. It is a four-panel techno device with a timer. Mice were tested based on their ability to stay on a Rota-rod apparatus that was rotating at a speed of 20-25 rpm. All the mice were trained before subjecting them to the testing. On the day of the test, each mouse had three trials with a rest time of 5 min between each trial. The fall of time was recorded for all the trials and the mean of 3 trials was considered as the reading.[21]

***Forced swim test*:** Immobilization time was assessed by the forced swim test. In this test, a tank was prepared housing water at a temperature of 24°C-30°C. The water level was maintained at a depth to ensure that the rodent's tails and feet did not touch the bottom of the tank. The mice were put into the tank one at a time and allowed to swim. The time between when the mouse stopped swimming and started sinking was recorded. Each mouse was removed immediately as it began to sink, dried and put back into cages. The water tank was cleaned as the accumulation of faeces and urine could cause bacterial contamination.[22]

Statistical analysis

Data were expressed in mean ± SEM and analyzed by one-way ANOVA, followed by Tukey's post hoc test using GraphPad Prism software. A *p*-value less than 0.05 was considered significant.

RESULTS

Locomotor activity: The PD group showed a significant decrease in locomotor activity when compared with the control group (P <0.001). The locomotor activity showed a significant improvement in the PD + CVS group when compared with the PD group (P <0.001) and the control group (P <0.05). The group that received CVS alone did not show any significant changes when compared with the control group and showed significant differences in locomotor activity (P <0.001) when compared with the PD group (Figure 1).

Grip Strength: The effect of vestibular stimulation on grip strength is given in Figure 2. Grip strength was significantly decreased in the PD group when compared with the control group (P<0.001). Caloric vestibular stimulation significantly improved the grip strength in the PD + CVS group when compared with the PD group (P<0.001) and the control group (P<0.01). Mice in the CVS alone group showed a significant improvement in the grip strength when compared with the PD group (P<0.001) but no differences when compared with the control.

Motor coordination assessment: The effect of vestibular stimulation on latency to fall (sec) on rotarod performance is given in Figure 3. The mean fall-off time of the PD group was significantly decreased (P<0.001) when compared with the control group. PD + CVS group showed considerable improvement when compared with the PD group (P<0.001) and the control group (P<0.05). Fall off time in CVS alone group was significantly increased when compared with the PD group (P< 0.001) and no difference when compared with the control group.

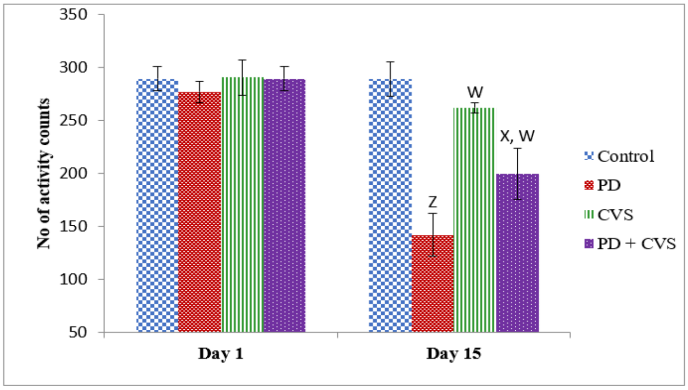

Figure 1: Impact of CVS on locomotor activity. Values are expressed as mean ± SEM (n=6).
^{x}p<0.05, ^{z}p<0.001 when compared with that of the control group; ^{w}p<0.001 when compared with that of the PD group. (One-way ANOVA followed by Tukey's *post-hoc* test).

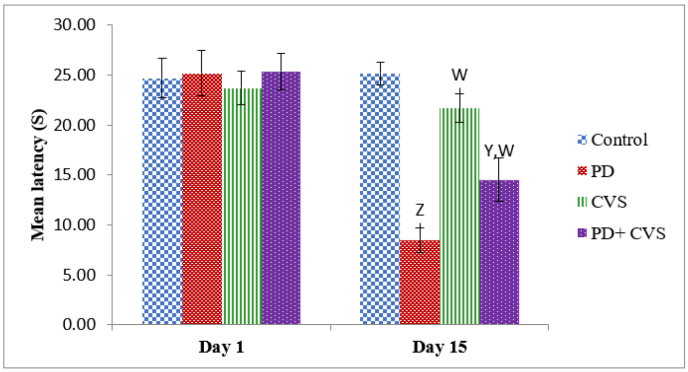

Figure 2: Impact of CVS on wire grip. Values are expressed as mean ± SEM (*n=6*). $^{Y}p<0.01$, $^{Z}p<0.001$ when compared with that of the control group; $^{W}p<0.001$ and when compared with the PD group. (One-way ANOVA followed by Tukey's *post-hoc* test).

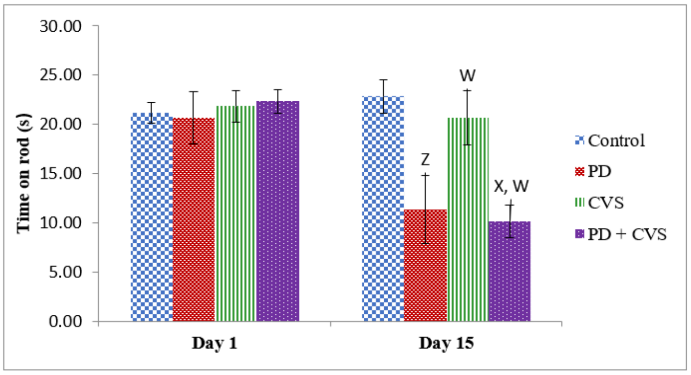

Figure 3: Impact of CVS on fall off time. Values are expressed as mean ± SEM (*n=6*). $^{X}p<0.05$, $^{Z}p<0.001$ when compared with that of the control group; $^{W}p<0.001$ when compared with the PD group. (One-way ANOVA followed by Tukey's *post-hoc* test).

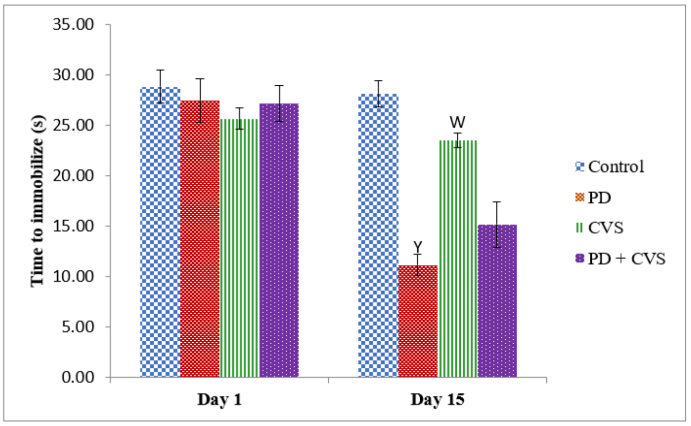

Figure 4: Impact of CVS on immobilization time. Values are expressed as mean ± SEM (*n=6*). $^{Y}p<0.01$ when compared with that of the control group; $^{W}p<0.001$ when compared with the PD group. (One-way ANOVA followed by Tukey's *post-hoc* test).

Immobilization time: The effect of vestibular stimulation on immobilization time as recorded in the forced swim test is given in Figure 4. PD group showed a significant decrease in the immobilization time when compared with the control group. No significant change was observed in the PD + CVS group when compared with the PD and control groups. CVS alone group showed a significant increase ($P<0.001$) in immobilization time when compared with the PD group.

DISCUSSION

In this research, CVS improved locomotor activity, muscle strength, motor coordination, immobilization time and memory in PD-induced mice, indicating its ability to ameliorate motor deficits that were induced by PD. The characteristic movement disorders are seen in PD-include bradykinesia, rigidity, and resting tremors are all caused due to the loss of dopaminergic neurons of substantia nigra pars compacta.[23] In the present study, the neurotoxin MPTP was injected intraperitoneal for 5 consecutive days to destroy the dopaminergic neurons. Being a lipophilic drug, MPTP can cross the blood-brain barrier. MPTP is metabolized to the intermediate 1-methyl-4-phenyl-2,3-dihydropyridinium species ($MPDP^+$) in the brain by glial monoamine oxidase-B (MAO-B), which is then oxidised to the lethal version MPP^+.[3] MPP^+ is released into the extracellular space by astrocytes, where it is taken up by dopaminergic neurons. Once MPP^+ accumulates in dopaminergic neurons, it largely promotes neurotoxicity by blocking complex I of the mitochondrial electron transport chain, leading to ATP depletion and oxidative stress induced by superoxide and nitric oxide, followed by neuronal death.[24-26] Other types of vestibular stimulation have been shown to improve motor function and postural instability in Parkinson's disease and hypotonic cerebral palsy, which in turn improved locomotion.[27] By stimulating the vestibular nerves through galvanic vestibular stimulation in Parkinsonism axial motor capabilities were improved.[28] The CVS triggers the vestibular afferents nerves which activate the basal ganglia and limbic system via the cerebellar vermis. The efferent connection from the basal ganglia, reaches the spinal cord through the pedunculopontine nucleus to control motor movements.[29] Thus, CVS activates the extrapyramidal connections to improve motor coordination and activity in PD mice.

Vestibular stimulation can augment various neurotransmitters, and this may also play a key role in enhancing motor activity. In a study by Sailesh and Archana vestibular stimulation has limited the changes in the dopamine and GABA levels.[30] Jinu *et al.*, have shown in their study that bilateral caloric vestibular stimulation in the dementia model, had the potential in modulating and regulating acetylcholine release, balancing glutamate level and acetylcholinesterase inhibition and thereby improving motor coordination and anxiety level.[31] Another possible mechanism could be by increasing the serotonin levels as vestibular stimulation has been reported to increase serotonin release and thereby delay brain ageing.[32] Similar increase in serotonin was reported in another study where serotonin was restored to normal post-CVS administration in MPTP-induced PD.[30] Serotonin has a positive effect on GABA and glutamate signaling and they are used as potential therapeutic agents to improve cognitive decline and various symptoms in Alzheimer's disease.[33]

In the present study, PD-induced mice showed a decrease in locomotor activity, muscle strength, motor coordination, immobilization time and memory all of which are evident from the declined test results as seen in the behavioral studies. The intervention of CVS has considerably improved the motor symptoms in the mice which can be seen in the improved performance of the animals on the actophotometer, rotarod, wire grip test, forced swim test and Morri's water maze. Recent studies are also supportive of CVS administration, where CVS has increased dopamine levels thereby relieving the motor symptoms in experimental mice.[34]

CONCLUSION

In the present study, CVS improved the motor symptoms and inhibited the MPTP-induced neuronal damage in the mice. CVS has most

probably increased dopamine levels by shielding the neurons from further degeneration and ameliorating the neuropathology caused by MPTP.

No damage or change was noticed in the behaviour of mice in the group that only received CVS demonstrating that CVS administration is safe and causes no adverse effects. CVS can be used as an adjunct in the treatment of motor deficits in the early onset of Parkinson's disease. The molecular mechanism by which CVS confers neuroprotection must be further investigated.

ABBREVIATIONS

CVS: Caloric Vestibular stimulation; **COMT:** Catechol-O-Methyltransferase; **DBS:** Deep Brain Stimulation; **GABA:** Gamma Aminobutyric Acid; **MAO:** Monoamine Oxidase; **MAO-B:** Monoamine Oxidase-B; **$MPDP^+$:** 1- Methyl-4-Phnyl-2,3 Dihydropyridinium; **MPTP:** 1- Methyl-4-Phenyl-1,2,3,6- Tetrahydropyridine; **PD:** Parkinson Disease; **VORs:** Vestibulo- Ocular reflexes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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