Original Article

Effects of Virtual Rehabilitation and Constraint Induced Movement Therapy on Brain Derived Neurotrophic Factor Mediated Motor Improvement in Stroke Patients

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ABSTRACT

Objectives: To carry out a comparison between serum BDNF levels as well as enhancement in upper limb motor function in terms of gross movement, pinch, grip, primary grasp, pre and post intervention in the study and control groups.

Study design And Setting: It was a Randomized Control Study conducted from March 2015 to March 2016 at Holy Family Hospital Rawalpindi in collaboration with the Multidisciplinary research laboratory at Islamic International Medical College, Rawalpindi.

Methodology: In this study; forty stroke patients were randomly designated to either the study group or the control group. Upper limb activity capability which was quantified by Action Research Arm Test (ARAT) and serum Brain Derived Neurotrophic Factor (BDNF) was measured in both control and study group. The control group underwent traditional upper limb physiotherapy for 16 sessions. The study group underwent Constraint Induced Movement Therapy for the upper limb in combination with the use of motion capture video gaming technology for 16 sessions each of twenty minutes duration. Before and after completion of intervention sessions; ARAT and serum BDNF were measured and compared in both control and study groups.

Results: Serum BDNF levels was significantly improved in study group as compare to control group ($p<0.001$). ARAT showed significant improvement in study group participants as compare to control groups ($p<0.001$).

Conclusion: Virtual rehabilitation was an efficacious method for Neuroplastic enhancement in stroke patients.

Keywords: Action Research Arm Test, Brain Derived Neurotrophic Factor, Neuroplasticity, Stroke.

INTRODUCTION:

Stroke is the leading cause of debility and motor function impairment throughout the world affecting 350,000 individuals each year. [1] The prevalence of this debilitating disorder has surpassed 4.8% in Pakistan.[2] There are two chief defects that lie at the root of the etiology of stroke; one being "Throm boem bolism" of arterial vessels of the brain, and the other, disruption of the flow of blood in the cerebrovascular system. Stroke due to inadequate blood flow to the cerebral tissues claims 87% of the total head-count of stroke whereas stroke caused by cerebrovascular bleeding ("spontaneous intracerebral and subarachnoid hemorrhage") accounts for the rest.[3] Motor function debility is one of the main manifestations of stroke, being able to recover motor function (upper extremity motor function)after surviving the initial onslaught of the disease via physiotherapy has a resultant encouraging influence on upper limb motor activity, a consistent measure of which is the action research arm test (ARAT).[4]

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Neuronal growth and healing, formation of new neuronal connections, strengthening of protective mechanisms in nerve cells especially following brain damage caused by deprivation of adequate blood flow, and generalized improvement of neuronal health and vitality has been closely linked to a peptide based growth factor known as Brain-derived neurotrophic factor.[5] BDNF has been shown to reduce the degree of cerebral infarction and aid natural salvage of damaged nerve cells.[6]Re-establishment of motor function after stroke is known to rely on the formation of new axonal and dendritic connections and other inherent, damage-control modifications and mechanisms within the nervous system known as "neuro-plasticity".[7]Rehabilitative techniques that demand self-directed, goal oriented, dynamic and repeated movements have shown to result in better, "plasticity based" enhancement of neuronal health after damage incurred by stroke.[8]

Constraint-induced movement therapy is a technique of physical therapy in which the patient is made to constrain the unaffected limb and is forced to make use of the weakened

limb for the majority (90%) of the time that he/she is awake. This form of therapy also demands that the activities carried out by the patient should be goal oriented and task specific (like movement of the impaired arm), with gradually increasing intensity based on the patient's progress ; a type of conditioning of behavior known as "shaping".[9]

An emerging trend in the field of stroke rehabilitation that has gained attention in the recent years is "Virtual Rehabilitation" which essentially aims to cause structural and functional rewiring of the parts of the brain that are responsible for consolidation of memories, learning and motor function by stimulating the "mirror-neuron system".[10, 11, 12] "Nintendo Wii™" has been one of most widely used video-game technologies; as it is low-cost and user friendly. It requires that the player/s carry out the various commands of the game in the form of an on-screen persona or "avatar" and in doing so, the immersive stimuli are able to activate the mirror-neurons, which in turn, initiate neuroplastic changes that eventually result in recovery of motor function. Another reason behind the "Nintendo Wii™" being the most popular form of Virtual Rehabilitation technology is the ability of the user to change and adjust the degree of required dexterity and speed of motion according to his/her own requirements.[13]

Various assortment tests such as the Motor Assessment Scale (MAS), Fugl-Meyer (Upper extremity component) Assessment scale (FMA-UE), Wolf Motor Function Test (WMFT), and Action Research Arm Test (ARAT) are reported for the quantification of upper extremity motor function in stroke patients.[13] The ARAT stands out as it is explicitly intended to be time-efficient (an average of 10 minutes being required for administration) and this aspect renders it more desirable than other upper extremity assessment scale alternatives.[14]

Since the efficacy of novel virtual rehabilitative techniques in stroke survivors are still relatively unexplored, the current study intended to carry out a comparison between serum BDNF levels as well as enhancement in upper limb motor function in terms of gross movement, pinch, grip, primary grasp, pre and post intervention in the study and control groups.

METHODOLOGY:

This project was carried out at Holy Family Hospital Rawalpindi in alliance with Islamic International Medical College Rawalpindi after acquiring approval from the Ethics Committees from both establishments. It was a randomized control trial for the duration of one year (from March 2015 to March 2016). 40 stroke patients were selected for this study, who were then randomly designated (by manual balloting) to either the study group or the control group. The inclusion criteria were; first incident of stroke, age between 30 to 60 years, weakened motor capacity of one arm, a time duration of no more than 4 months since the episode of stroke, a basic comprehension of computer/video game commands and radiologically declared stroke by CT-scan or MRI. The exclusion criteria were; other neural disorders, impaired cognizance, dementia or epileptiform disorders, linguistic barriers that would affect the ability to understand the intervention regimen, compromised visual acuity visual, musculoskeletal impediments that could limit movement, and an inability to perform voluntary arm movements.

After acquiring written informed consent, certain baseline demographics and stroke relevant variables of each subject were recorded, including age, sex, blood pressure, affected cerebral hemisphere, type of stroke and handedness. Upper limb "activity capability" was quantified by ARAT, on a scale of 0 to 57. Serum BDNF was measured after taking blood samples.

The intervention for the study group was structured to include CIMT for the upper limb using motion capture video gaming technology (Nintendo Wii™) for four times, 20 minute sessions a week for four weeks (total 16 sessions). The subjects wore a specialized heavy mitt on the uncompromised hand, thereby restricting its use during the intervention. The degree of how challenging each game was, adjusted based on each individual subject's ease of motion and the deftness of the debilitated arm. The target activities of the intervention comprised of a combination of adduction, abduction, extension and flexion of the shoulder joint, wrist joints, pronation and supination of the forearm, finger rolling, pinching, slicing motion, gripping, and arm swinging. The improvement of the subjects on the basis of how the games were played, deftness of command execution and swiftness and agility of movement was recorded throughout the duration of intervention and with each individual's improvement in these parameters, the degree of challenge that the game demanded was increased in a step ladder pattern. The participants were expected to restrict the use of their healthy limb for the majority of waking hours during the day and were asked to keep a track of the number of hours for which they complied with this command on a daily basis.

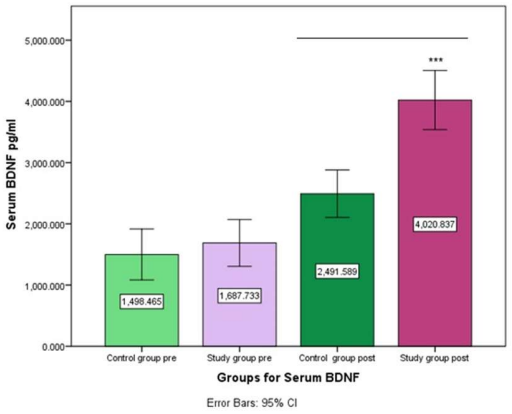
The control group underwent traditional upper limb physiotherapy for 16 sessions (4 sessions for 4 weeks) of 20 minute duration and there was no restriction based on handedness of the training. The control group candidates were made to carry out activities like reaching and pointing, lifting weighted objects with the affected side and various other commands involving the use of both sides of the upper limb like stabilizing a bottle with the healthy hand and attempting to unscrew the cap with the weakened hand and vice versa. Improvements in activity capacity and fluidity of motion were recorded throughout the training period and the skill level demanded by the task commands was increased in a step-ladder pattern accordingly.

Once the period of intervention was over, both the control and study group were evaluated for upper limb motor activity capability (via the ARAT scale) and for serum BDNF, blood samples were drawn. The blood samples taken for serum BDNF level measurement both before and after the intervention phase were first centrifuged to separate the serum and the serum samples were then stored at a temperature of negative 80 degrees Celsius. For quantification of serum BDNF levels, quantitative sandwich ELISA technique was employed. The storage of serum samples and the ELISA procedure was carried out in the multi-disciplinary lab at Islamic International Medical College Rawalpindi. For analyzing the raw numerical data, SPSS 21 software was employed. Results were presented as mean + SD. A p value of < 0.05 was taken as statistically significant. For the comparison of mean serum BDNF results and ARAT total as well as subtest scores between before and after the intervention phase, paired sample t-test was used.

RESULTS:

The difference between the mean post-intervention serum BDNF levels between the study and control group was highly significant (p<0.001) as shown in the figure I. The mean post intervention ARAT scores of study and control group had a statistically significant difference (p<0.001) as seen in table I. All four subtests of ARAT i.e., grasp, grip, pinch and gross movement showed highly significant improvement between the control and study groups.

Figure : Pre- and Post-intervention comparison of the Serum BDNF levels in the control and study groups



***Highly statistically significant between study and control groups p<0.001

DISCUSSION:

Stroke is the leading cause of motor function impairment worldwide, affecting 350,000 individuals each year.[1] Motor function of the stroke survival patients can be recovered up to a varying extent via rehabilitation, depending upon the cause and area of the brain involved. In the current study subjects in both the control and study groups showed marked elevation in serum BDNF levels after the 28 day period of receiving their respective forms of intervention. The difference between the mean serum BDNF values of the control and the study group was highly significant. These changes are supported by numerous studies showing evidence of plasticity driven motor improvement following interventions involving neuro-rehabilitative practices especially those based on exposure to surroundings rich in multimodal stimuli.[15]

Certain studies explored the effect of introducing exogenous BDNF to the ischemic cerebral tissue to look for evidence of functional motor recovery. Ploughman et al in a trial testing the effect of "skilled reaching" in rats found that "BDNF contributes to motor recovery following focal ischemia".[16] It is therefore suggested that the greater the levels of circulating BDNF following an intervention, the greater the effectiveness of said intervention in inducing activity-dependent neuroplastic cerebral reorganization and the greater the subsequent improvement in motor function.

Data regarding circulating BDNF levels has been varied. A trial conducted by Zoladz J.A et al to assess the effect of endurance training on the plasma concentration of BDNF found pre-intervention levels of plasma BDNF to be 10.9+2.3 pg x ml (-1) in young healthy men.[17] Lang et al while studying the "association of BDNF serum concentrations with central serotonergic activity" found Serum BDNF levels of 16.407+7.6 in men and 17.077+7.8 ng/ml in women; a trial comprising 109 healthy individuals (62 men and 47 women).[18] However; It has been shown that BDNF is most active during the "prenatal period" when the development of neuronal circuitry is under its control and then later on in life during the formation of new memories and in processes involving cognition and motor function.[19] Cerebrovascular and neurodegenerative disorders have shown to have a negative impact on the expression of this neurotropin reflected by low circulating levels of BDNF; an event that can be used as a "neurological biomarker" for stroke, Alzheimer's

Table I: Comparison between the mean subtest scores of ARAT pre and post intervention in the study and control groups

Outcome measures	Control group pre-intervention	Study group pre-intervention	p value	Control group Post-intervention	Study group post-intervention	p value
ARAT X (0-57) + S.D	16.80+ 2.707	16.20+3.942	0.578	36.80+ 6.940	48.30+5.768	<0.001***
Grasp X (0-18)	4.90+1.774	4.20+2.567	0.323	10.90+3.401	14.65+2.300	<0.001***
Grip X (0-12)	3.65+0.999	4.05+ 1.395	0.303	7.70+1.218	10.25+1.293	<0.001***
Pinch X (0-18)	6.45+1.932	6.40+1.569	0.929	12.00+2.513	15.40+1.930	<0.001***
Gross movement X (0-9)	1.80+1.735	1.90+2.292	0.877	6.37+1.300	8.00+1.214	<0.001***

disease, Parkinson's disease and cerebral palsy among others. An elevation in serum BDNF in the face of such neuronal disorders could point towards the effectiveness of treatment.[20]

There have been few human studies employing CIMT augmented by Virtual Rehabilitation and even fewer that have used serum BDNF as a barometer for gauging neuroplasticity driven motor recovery in the sub-acute phase of stroke. However, the highly significant increase in the serum BDNF levels in the study group compliments the findings of the animal trial conducted by Livingston-Thomas in which a neuro-rehabilitation regimen clinically similar to CIMT was carried out in Endothelin-1 induced stroke model rats.[21]

Single subject study was carried out by Slijper et al which showed that the motor function strength and agility of the upper limb shows significant improvement after intervention of 5 weeks of video-game centered physiotherapy, assessed by ARAT scores. These findings are in concurrence with the current study's results.[22]

Ample literature showed improvement in specific subtests of ARAT like the one conducted by Christie et al.[23] It focused on showcasing the efficiency of Nintendo Wii as a safe and effective device for neuro-rehabilitative purposes. In this study, the only sub-test of ARAT in which the 9 subjects showed significant ($p = 0.03$) improvement was the "Grip" sub-test.[23] The EVREST trial conducted by Saposnik et al, could be used as a justification for the improved ARAT scores in the current study as it highlighted the direct link between improved upper limb motor capacity and potentiating of not only newly formed synaptic connections in the brain but the salvage of old, reversibly damaged neuronal connection as well, caused by repeated, goal oriented activity, which is the foundation of Virtual rehabilitation.[24]

Indeed, the progress made by the study group candidates of the current study in terms of carrying out fluid and well-coordinated movements by the end of the intervention phase could be attributed to the positive impact of interactive video-gaming on hand-eye coordination, findings which can be corroborated with the trial conducted by Kullman at the Arizona State University which showed marked improvement in the dexterity, grip strength and hand-to-eye-coordination in surgeons who were subjected to Nintendo Wii gameplay.[25]

It is important to note that trials that have used "Wiihabilitation" alone as a means of causing motor function improvement have not contributed on upper limb motor capability improvement as those which have employed a combination of interactive video gaming technologies and standard physiotherapeutic techniques such as CIMT.[26-27] These findings are very encouraging for the current study's result as it too employed a modified physiotherapeutic regimen of CIMT plus Virtual Rehabilitation which proved to be instrumental in bringing about highly significant motor function improvement in its study group participants.

Neuroplastic enhancement led by growth factors such as BDNF seems to respond quite significantly to novel physiotherapeutic approaches such as Virtual rehabilitation if used as an aide with standard techniques such as Constraint Induced Movement Therapy. It is an efficacious and sound method of keeping stroke survivors engaged in and compliant with physiotherapy approaches by inculcating interest and encouraging self-directed therapy time while at the same time bringing about actual, worthwhile motor function improvement; a feat not yet matched by traditional rehabilative techniques . This study does, however, leave room for further exploration, at scale that is much larger, and that which engages a greater demographic of stroke survivors.

CONCLUSION:

Virtual rehabilitation was an efficacious method for Neuroplastic enhancement in stroke patients.

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