STUDY INVESTIGATING MOTOR IMPROVEMENT IN CEREBRAL PALSY PATIENTS FOLLOWING SENSORY STIMULATION

A Dissertation submitted in partial fulfillment of the requirement for the Degree of Doctor of Medicine in Physiology (Branch – V) Of the Tamilnadu Dr. M.G.R Medical University, Chennai -600 032

Department of Physiology

Christian Medical College, Vellore,

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CERTIFICATE

This is to certify that the thesis entitled "**Study investigating motor improvement in cerebral palsy patients following sensory stimulation** " is a bonafide, original work carried out by Dr. Pijush Kanti Bagchi, in partial fulfillment of the rules and regulations for the M.D – Branch V Physiology examination of the Tamilnadu Dr. M.G.R. Medical University, Chennai to be held in April- 2015.

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DECLARATION

I hereby declare that the investigations that form the subject matter for the thesis entitled "**Study investigating motor improvement in cerebral palsy patients following sensory stimulation**" were carried out by me during my term as a post graduate student in the Department of Physiology, Christian Medical College, Vellore. This thesis has not been submitted in part or full to any other university.

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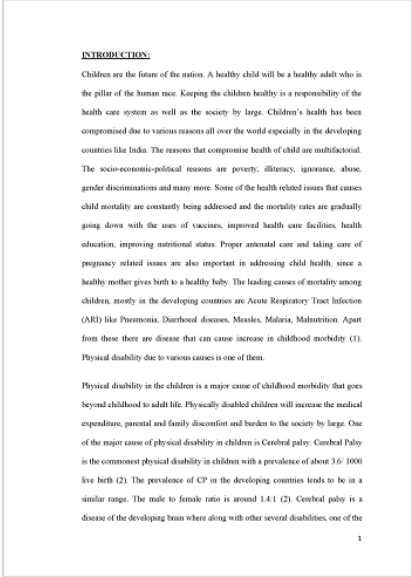

INTRODUCTION:

Children are the future of the nation. A healthy child will be a healthy adult who is the pillar of the human race. Keeping the children healthy is a responsibility of the health care system as well as the society by large. Children's health has been compromised due to various reasons all over the world especially in the developing countries like India. The reasons that compromise health of child are multifactorial. The socio-economic-political reasons are poverty, illiteracy, ignorance, abuse, gender discriminations and many more. Some of the health related issues that causes child mortality are constantly being addressed and the mortality rates are gradually going down with the uses of vaccines, improved health care facilities, health education, improving nutritional status. Proper antenatal care and taking care of pregnancy related issues are also important in addressing child health, since a healthy mother gives birth to a healthy baby. The leading causes of mortality among children, mostly in the developing countries are Acute Respiratory Tract Infection (ARI) like Pneumonia, Diarrhoeal diseases, Measles, Malaria, Malnutrition. Apart from these there are disease that can cause increase in childhood morbidity (1). Physical disability due to various causes is one of them.

Physical disability in the children is a major cause of childhood morbidity that goes beyond childhood to adult life. Physically disabled children will increase the medical expenditure, parental and family discomfort and burden to the society by large. One of the major cause of physical disability in children is Cerebral palsy. Cerebral Palsy is the commonest physical disability in children with a prevalence of about 3.6/ 1000 live birth (2). The prevalence of CP in the developing countries tends to be in a similar range. The male to female ratio is around 1.4:1 (2). Cerebral palsy is a disease of the developing brain where along with other several disabilities, one of the

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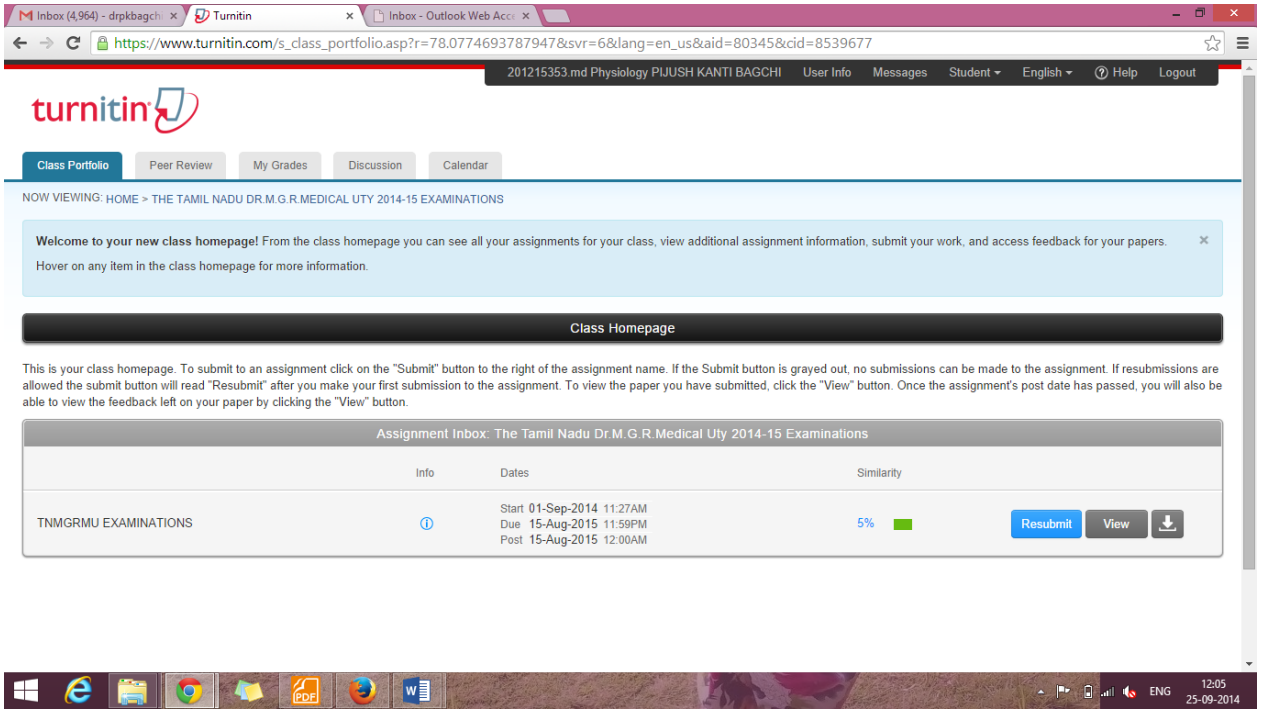
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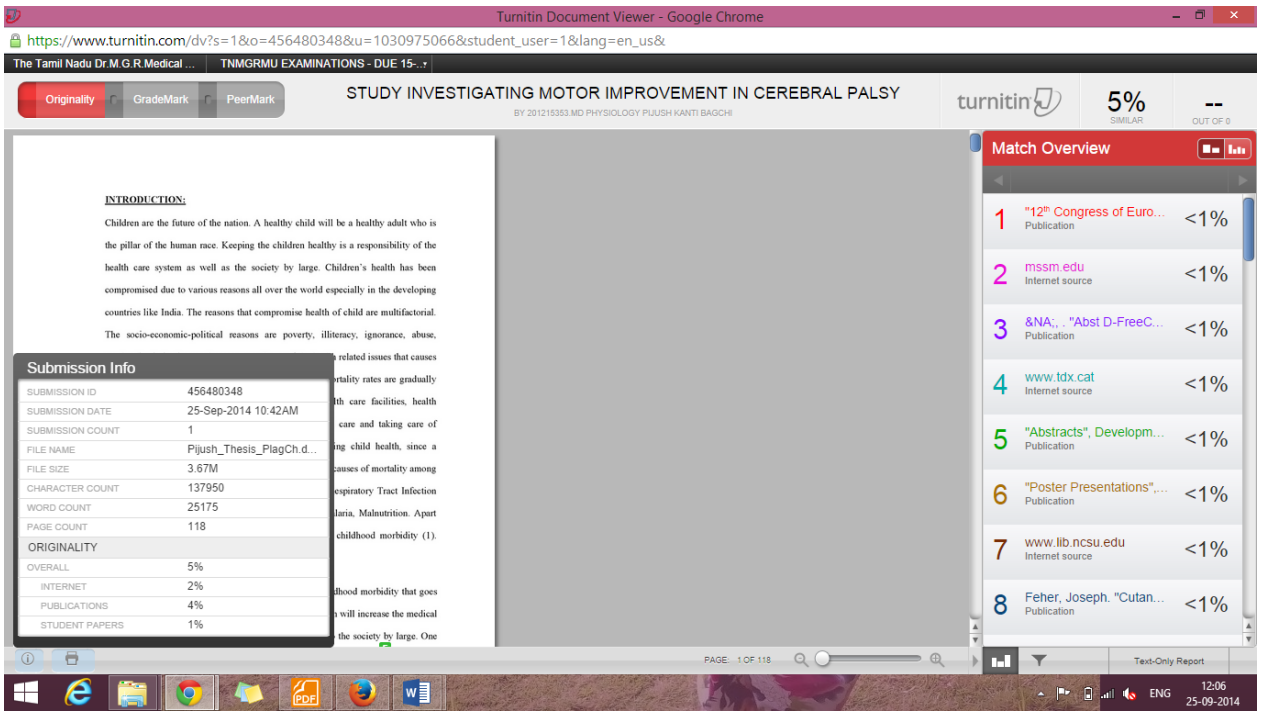
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TABLE OF CONTENTS

ABSTRACT

Study Investigating Motor Improvement in Cerebral Palsy Patients Following Sensory Stimulation

Background: Cerebral palsy is the commonest cause of physical disability in children, with no cure till now. Extensive sensory input to the motor cortices and to the motor descending pathways raises the potential of using sensory stimulation of the extremities to produce neuroplasticity to improve motor function in cerebral palsy patients.

Objectives: To investigate the effect and usefulness of local palmar vibration therapy in improving motor hand function of cerebral palsy children.

Methods: A single blinded, randomized controlled trial (Registry number CTRI/2013/05/003700) was designed to investigate the effect of local vibration therapy, a sensory input, on the change in motor hand function in cerebral palsy children. Thirty eight cerebral palsy children were screened and 23 were recruited as per the inclusion and exclusion criteria, randomised and allocated to treatment and control groups. Twenty children completed the study. The control group received standard conventional therapy. The intervention group, in addition, received bilateral localized 50 Hz palmar vibration therapy daily for 5 min, 5 days per week, for 4 weeks.

Results and Discussion: Interim analysis revealed no statistically significant difference in the change in hand function or activities of daily living between the groups. However, intra-group analysis revealed significant improvement of hand dexterity of both dominant and non-dominant hands in the intervention group but only

of the dominant hand in the control group, which is suggestive of a beneficial effect of vibration therapy in the intervention group. Further, the bilateral improvement in hand function in the intervention group, reveals that the protocol used in the study for the application of vibration therapy, has no effects of inter-hemispheric cortical inhibition on the non-dominant cortex. The findings of the interim analysis defend the appropriateness of studying the role of sensory stimulation as a mode of therapy, to enhance hand dexterity in Cerebral palsy children.

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Children are the future of the nation. A healthy child will be a healthy adult who is the pillar of the human race. Keeping the children healthy is a responsibility of the health care system as well as the society by large. Children's health has been compromised due to various reasons all over the world especially in the developing countries like India. The reasons that compromise health of child are multifactorial. The socio-economic-political reasons are poverty, illiteracy, ignorance, abuse, gender discriminations and many more. Some of the health related issues that causes child mortality are constantly being addressed and the mortality rates are gradually going down with the uses of vaccines, improved health care facilities, health education, improving nutritional status. Proper antenatal care and taking care of pregnancy related issues are also important in addressing child health, since a healthy mother gives birth to a healthy baby. The leading causes of mortality among children, mostly in the developing countries are Acute Respiratory Tract Infection (ARI) like Pneumonia, Diarrhoeal diseases, Measles, Malaria, Malnutrition. Apart from these there are disease that can cause increase in childhood morbidity (1). Physical disability due to various causes is one of them.

Physical disability in the children is a major cause of childhood morbidity that goes beyond childhood to adult life. Physically disabled children will increase the medical expenditure, parental and family discomfort and burden to the society by large. One of the major cause of physical disability in children is Cerebral palsy. Cerebral Palsy is the commonest physical disability in children with a prevalence of about 3.6/ 1000 live birth (2). The prevalence of CP in the developing countries tends to be in a similar range. The male to female ratio is around 1.4:1 (2). Cerebral palsy is a disease of the developing brain where along with other several disabilities, one of the major disability

is motor dysfunction. It is the motor disability that makes these patients crippled and dependent on others. Depending upon severity, even performing work for just daily living sometimes becomes impossible for them. The cause of this disease is multifactorial. Some of the causes are preventable to some extent and some are not. There are several modes of management which are currently available but none of them offers a cure. Management of cerebral palsy includes management of motor dysfunction along with other disabilities like spasticity, speech disorder, dystonia etc. Improvement of motor dysfunction requires multi-speciality approach. But no one therapy alone is sufficient to manage cerebral palsy. Cerebral palsy is the static encephalopathy produced by injury to the developing brain in the perinatal period. Clinically it is mainly a disease of posture and movement, although there are other co-morbidities. CP is topographically classified-into Hemiplegia, Diplegia, Triplegia and Quadriplegia (2). To improve the functional ability of these patients, motor improvement is crucial. Hence treatment of CP is aimed at improving motor functions through a multidisciplinary approach involving physiotherapy, occupational therapy, pharmacotherapy and surgery. The normal development of motor functions seen in the normal growing child is restricted in the CP child. A contributing factor for this is the reduced sensory feedback the child gets, as the interactions of the CP child with the surrounding environment is limited.

Vibration is a form of sensory stimulus which has been investigated as a modality of therapy in many conditions like CP, Stroke and Parkinsonism (3–7). Whole Body Vibration has been reported to produce motor improvement in CP patients, and local site specific vibration has been found to reduce spasticity in CP children (8,9). The exact mechanism by which the beneficial effect of vibration is produced is still not elucidated.

Extensive to and fro connections exist between the sensory and motor areas of the brain cortex. The motor cortex receives input from the adjacent sensory cortices, namely the primary sensory cortex and the sensory association areas of the parietal lobe. Further, 40% of the Corticospinal tract fibres (Motor descending pathways) originate from the somatosensory cortices, and only the rest arise from motor cortices (10,11). The presence of the extensive sensory input to the motor cortices and to the motor descending pathways raises the potential of using sensory stimulation of the extremities to produce neuroplasticity and to improve motor function. Would regular application of painless sensory stimuli to the palms of cerebral palsy patients enhance the excitability of the motor cortex and produce reorganization of the sensory and motor cortices through the phenomenon of neural plasticity, leading to improved motor functions in these patients? Published literature reports studies, where localized electrical stimulation increased excitability and reorganization of the motor cortex. This suggests that localized site-specific vibration of the hands alone may contribute to improved motor function of the hands. The present study addressed this question by randomizing cerebral palsy patients of age group 6 - 15 years, into control and intervention groups. Standard treatment was given to both groups. In addition, vibratory stimuli was applied to both palms of the intervention group. The extent of improvement of hand function, as assessed by the Box and Block Test in the two groups, has been compared. Further, the change in Activities of daily Living, measured using Modified Barthel Index, has been compared. The present study is an interim analysis of an ongoing randomized controlled trial, approved by the Institutional review Board and registered under Clinical trial registry of India.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

CEREBRAL PALSY:

Cerebral palsy (CP) is a term used to describe a group of disorders causing physical disability in children and adults. It is a heterogeneous group of clinical syndromes which is characterized by dysfunction of motor and posture due to insult to the developing brain due to various causes. Cerebral palsy is a non-progressive disorder of the nervous system and a static encephalopathy, but the clinical features change as the brain matures over time. The clinical presentation is dynamic. CP may present during infancy with delayed motor development milestones (12). Impaired motor function in CP is thought to be due to decreased motor recruitment in the central nervous system and also due to changes in the muscle morphology as a secondary effect of motor dysfunction (13).

HISTORY OF CEREBRAL PALSY:

The term cerebral palsy has been known to the world since very ancient time. It was used to describe the people with physical disability mainly due to motor dysfunctions. Cerebral palsy has also been found in literature in the history Cerebral palsy has been documented in historical records of civilisations. These sources, however, are based on suspicion since clinical documentations were lacking at that time. An engraving of a picture of a person with a crutch on a tombstone dating back to 15^{th} to 14^{th} century BC is considered by historians to depict a person afflicted with cerebral palsy. Probably the oldest case of suspected cerebral palsy comes from the evidences on the mummy of an Egyptian pharaoh called Siptah who ruled around 1196 to 1190 BC (14). He died at an early age with features of a disease consistent with cerebral palsy.

The history of medical literature also refers to a “cerebral palsy like disease” as a known entity. The Greek medical literature uses the term palsy to denote paralysis. They have described paralysis or weakness of the limbs in their literature. Roman history also suggests diseases similar to cerebral palsy. One of the Roman emperor called Claudius probably had a disease which from its description had resemblance with Cerebral palsy (14).

The history of modern medicine finds the first documentary representation of CP in the work of Hippocrates in "Corpus Hippocraticum" (14). The proper definition and description of cerebral palsy was given by William John Little at the beginning of ninetieth century. He was the first person to engage himself in the study of cerebral palsy to a great extent. He came out with many new concepts of cerebral palsy. He for the first time, threw some light on the aetiology or risk factors of the disease. He suggested that prematurity and problems during delivery could be responsible for the disease. Later, spastic diplegic CP was named after him as Little’s disease (14). Subsequently, William Gowers found a relationship between problem in delivery and the occurrence of paralysis in newborns and mentioned the disease as “birth palsy”. Based on his observation he also made a classification of “birth palsy” as peripheral and cerebral.

After William John Little, the person who reviewed the disease maximally was William Osler (1849–1919). He classified the problem and linked the causation of the disease with problems at the time of delivery. However, he along with many investigators made mistakes like erroneously linking the disease with some non-related diseases like poliomyelitis (14).

Renowned psychiatrist Sigmund Freud (1856-1939) who practised initially as a neurologist worked further on the aetiology of the problem and found it as a problem occurring before birth or at the time of delivery or after the baby is born. He described the clinical features of the disease and linked it to the sites of brain damage.

During the twentieth century many people worked on cerebral palsy and many new approaches to therapy, including surgery, came to focus. One of the important classification system of cerebral palsy called Gross Motor Function Classification System (GMFCS) was developed in 1997 by Robert Palisano *et al* (15).

The significant developments in the understanding of CP that followed since then, are all due to the contributions of these three personalities in the field of cerebral palsy: William Osler, Sigmund Freud and Robert Palisano.

EPIDEMIOLOGY OF CP:

Cerebral Palsy (CP) is the commonest physical disability in children with a prevalence of about 2-2.5/ 1000 live births (16–18). The prevalence of CP in the developing countries tends to be in a similar range (18,19). In India, the figure is around 2- 2.8/ 1000 live births (19). A recent study conducted by the Centre for Disease Control and Prevention (CDC) in 2008 has shown few other important epidemiological facts about cerebral palsy such as that the disease is more common in males than females. The study also found that spastic type CP is more common and accounts for 77.4% of the cases. Epilepsy (41%) and Autistic Spectrum Disorders (ASD) (6.9%) were found to be important common co-morbidities as per the study (17). A group of different studies which were conducted at different time points, in different places like Europe, Sweden, United Kingdom and Ireland all made the same observation that incidence of

cerebral palsy is much higher in babies with low birth weight than in babies whose birth weight is normal (20,21). Moreover, the incidence of severe neuromotor disability of around 10% was seen in babies born at or below 25 weeks of gestation (22). One review of several studies showed that 12% of babies born at or below 26 weeks of gestation and 8% of babies born at or below the birth weight of 800 gm developed cerebral palsy (23). It has also been found that the risk of cerebral palsy is higher in babies who are born with a birth weight at or below the 10^{th} percentile of normal than babies whose birth weight is within 25^{th} – 75^{th} percentile of normal. The risk of developing cerebral palsy is lowest in babies who are born with a birth weight of more than one standard deviation above the mean (24,25). However, recent studies show that there is a decreasing trend in the risk of developing cerebral palsy, even in premature and low birth weight babies, probably due to advanced and better perinatal care in recent times (26,27).

AETIOLOGY OF CEREBRAL PALSY:

The causation of cerebral palsy is multifactorial (28). Majority of them occur due to problems during either foetal development or the neonatal period (29). However the cause of the condition still remains unknown in most cases of established CP (30). The injury to the developing brain may be prenatal, natal or postnatal. The causes can be due to congenital, genetic, inflammatory, infectious, anoxic, traumatic and metabolic disorders. Prenatal maternal chorioamnionitis, infection, drug or alcohol abuse, maternal epilepsy, hyperthyroidism, severe toxaemia, third trimester bleeding, prematurity and Cystic Periventricular Leukomalacia are some of the risk factors for developing Cerebral palsy (12,18). Prematurity alone was found to be present in 78% of the cases followed by intra uterine growth retardation and intra uterine infection in

34% and 28% of the cases respectively. Antepartum haemorrhage and placental pathology were found in 27% and 21% of cases. Multiple pregnancy as a causation of cerebral palsy was found to be present in 20% of cases (28). There has also been reports of association of maternal alcohol intake during pregnancy with development of cerebral palsy in the baby (31–33). Maternal heavy smoking and vaginal infection were also found to be associated with cerebral palsy (34). The following pathological conditions described below are established risk factors for cerebral palsy.

Hypoxic Ischemic Encephalopathy (HIE):

Frequently, cerebral palsy is described as being associated with perinatal asphyxia. However, hypoxia related injury alone does not contribute much in the causation of CP (35–38). HIE is a group of disorders where due to hypoxic insult to the brain at an early age, neuronal damage occurs leading to abnormal neurological functions manifested as seizures, unconsciousness, depressed body tone and reflexes and even cardio-respiratory malfunctioning which may be fatal. There are some markers of outcome of HIE that have a positive correlation with the development of CP (39). The disorders that are linked to the development of CP are seizures, hypotonia, multiple organ dysfunctions, severe persistent low APGAR score and coma (40).

Congenital problems:

Congenital abnormalities including structural brain defects, chromosomal aberrations, genetic abnormalities are also potential risk factors for developing cerebral palsy (41–46). Congenital deformities are present more commonly in cerebral palsy patients; 53% in quadriplegic CP and 35% in Non-quadriplegic CP (47). Both central nervous system and Non- central nervous system deformities are found in patients with

cerebral palsy (43). Babies born with breech presentation are also at risk of developing cerebral palsy (48,49).

Prematurity:

Prematurity is the single most important cause of cerebral palsy. Prematurity associated pathological conditions are mainly responsible for this. Premature babies who usually suffer from Periventricular leukomalacia (50), Bronchopulmonary dysplasia, intracranial haemorrhage (51) are more prone to develop CP.

Cerebrovascular accidents:

Cerebrovascular accidents in the form of cerebral thromboembolism or intracranial haemorrhage or stroke may lead to cerebral palsy in the babies. Intracranial haemorrhage though less frequent, may occur in patients with coagulopathy and they are more prone to develop the CP and about 28% of the cases have associated neurodevelopmental abnormalities (52). Thalamic haemorrhage is common in infants with some predisposing factors like cerebral venous thrombosis due to infections and congenital heart diseases. The thalamic haemorrhage may lead to neurodevelopmental disorders after infancy (53).

Multiple births:

The risk of developing CP increase in case of multiple pregnancy as in the case of twins and other higher order pregnancies (54). The reasons for this can be attributed to low birth weight and congenital anomalies of the foetus. Cord around the neck and dysfunctions of vascularity are also more common in multiple births which in turn

contributes to the development of CP (55). Even death of a foetus in a twin increases the risk of development of CP in the other due to thromboembolic insult (54).

Maternal infections:

Various infections of the mother during antenatal period are risk factors for the baby in developing cerebral palsy. Many complications to babies may occur like infection in the foetus or in the new born including septicaemia and meningitis. These diseases can cause neurodevelopmental disorders. Both bacterial and viral infections are responsible for the risk. Common infections that occurs in mothers are Syphilis, Toxoplasmosis, Varicella infection, Rubella, Cytomegalovirus (CMV) and Herpes infection (TROCH infections). The microbes causing all these diseases can cross the placental barrier and cause infection or damage to the foetus. This is a risk factor for developing cerebral palsy. Other bacterial agents can also cause serious infections to the mother. Mother may give history of having developed chorioamnionitis. This is again a risk factor for developing CP (56,57). The association can also be attributed to other complications occurring in the neonate as a consequence of maternal infection and these can also increase the risk for developing CP. The complications in the newborn due to maternal chorioamnionitis are perinatal hypoxia, neonatal meningitis, convulsions. High fever in the mother at the time of delivery due to any infections also increase the risk of developing cerebral palsy (57,58).

Obstetric complications:

Different maternal obstetrics complications like Premature rupture of membrane, antepartum haemorrhage, placental insufficiency, hypoxia, traumatic delivery,

Meconium stained liquor causing meconium aspiration syndrome, may contribute to the risk of the baby developing CP (59).

Perinatal infections in baby:

Neonatal septicaemia and meningitis, TORCH infections affect the nervous system. As a complication of these diseases, neurological dysfunctions may occur which may lead to development of CP. Even infections by non-bacterial pathogens like viruses and fungus, can cause cerebral palsy (60,61).

Trauma:

Trauma to the brain due to any reason may damage the developing brain and may predispose to development of cerebral palsy (59).

Genetic disorders:

Thrombophilia, as evidenced by the presence of factor V Leiden or Antiphospholipid antibody in mother or in the baby, has got a role in the aetiology of CP (62). Cytokine polymorphism is also a risk factor (59).

Drug induced:

Cerebral palsy may occur in babies whose mother had taken different drugs which can cross placenta and affect the foetus with its teratogenic effect (59).

Bilirubin encephalopathy:

Neonates for the first seven days of life have underdeveloped blood brain barrier. So substances which normally cannot pass through the blood brain barrier, will cross the

neonatal blood brain barrier to eventually reach brain tissue. Bilirubin in unconjugated form, is one such substance which can cross the Blood Brain Barrier and destroy the neurons and supporting cells in the brain of neonates, whenever its serum level becomes very high due to any cause. Due to many reasons serum level of bilirubin may go up in neonates causing pathological jaundice. One of the main causes of pathological jaundice is Rh incompatibility, where the sensitized Rh negative mother's anti D antibodies destroys the baby's red blood cells causing severe haemolytic jaundice. This is an example of unconjugated hyperbilirubinemia and this high level of unconjugated bilirubin can cross the Blood Brain Barrier and get deposited in brain structures like basal ganglia and nuclei of the brain stem. The unconjugated bilirubin destroys the neuron and the neuroglial cells in these regions causing bilirubin encephalopathy. One of the major and severe consequence of this is kernicterus. The survivor develops severe neurodevelopmental dysfunctions. The babies may develop choreo-athetoid cerebral palsy later in life (1,2).

Other metabolic disorders:

Prenatal maternal metabolic problems like iodine deficiency, different hormonal disorders like hypothyroidism of the mother can be risk factors for developing cerebral palsy (2,63).

Hypoglycaemia and vitamin K deficiency in the baby in the natal and post natal period can also be metabolic risk factors, other than kernicterus, for developing CP (64).

Maternal prenatal medical/ surgical problems:

Seizure disorders in the mother, vascular insufficiency in the form of thromboembolic disorders causing hypoxic effects, psychosomatic disorder in mother, anti-

phospholipid syndrome, babies born through in-vitro fertilization, maternal traumatic injuries may lead to development of cerebral palsy in the baby (59).

PATHOLOGY OF CEREBRAL PALSY:

The pathological finding in cerebral palsy patients are confined mostly to the central nervous system. The muscle morphology also becomes defective according to some studies (13). The peripheral nervous system is spared in CP. The observed pathological changes in cerebral palsy due to different aetiologies (59) are:

i) Hypoxic injury

ii) Diffuse neuronal damage

iii) White matter injury

iv) Periventricular leukomalacia

v) Neuronal necrosis

vi) Cerebral haemorrage in different areas

vii) Intraventricular haemorrhage

viii) Subependymal parenchymal destructions

ix) Infarction of cerebral cortex

x) Gliosis

xi) Status marmoratus

xii) Brain structural malformation

PATHOPHYSIOLOGY OF CEREBRAL PALSY:

Pathogenesis of cerebral palsy is injury to brain due to various reasons, by various mechanisms at cellular level. The neuronal injury and subsequent different pathological changes are due to hypoxia, ischaemia, infection or inflammation. The destruction of cells is caused by inflammatory mediators, free radicals, microglia mediated free radical destructions and calcium mediated tissue injury (50). Cytokine and other proinflammatory mediators cause destruction of tissues (65). The reactive oxygen species and nitrogen species mediated cellular damage, the neurotransmitter like glutamate mediated excitotoxicity are also other reasons for neuronal cell death (65). The tissue destruction can cause demyelination and destruction of premyelinating oligodendrocytes (50,65).

CLASSIFICATION OF CEREBRAL PALSY:

Cerebral palsy is classified based on different types of neuromuscular abnormalities. They are spastic, dyskinetic (with chorea, athetosis and dystonia), ataxic (simple and diplegic), hypotonic and mixed. Spastic CP is the commonest type seen and accounts for 70%-75% of all cases. Topographical classification of spastic CP patients is into Hemiplegia, Diplegia, Triplegia and Quadriplegia patients (12).

Spastic Cerebral Palsy:

The patient presents with hypertonia and signs and symptoms of upper motor neuron type of lesions. The increased tone prevents the patients from carrying out motor functions like impaired gross and fine motor movements. Motor skills are less developed in these patients. They get tired easily and suffer from fatigability. The spasticity itself causes some exaggerated motor signs which actually are signs of upper

motor neuron lesion and prevents the patient from carrying out normal motor functions. Exaggerated deep tendon reflexes, planter or patellar clonus, excessive tone of both flexor and extensor group of muscles are seen during stressful voluntary action. The spasticity is further aggravated in stress. The normal movement and posture are greatly affected. The complex movement of any particular action cannot be executed properly. Continuous increased tone in the patient, except during sleep may make the concerned extremity rigid and deformed (2,12,13,18).

Spastic Monoplegic CP: This type is relatively less common than the other topographically classified varieties of cerebral palsy. The spastic monoplegia involves single limb with impaired voluntary motor performance and increased tone and also signs of upper motor neuron lesions.

Spastic diplegic CP: This is one of the common types of cerebral palsy. While many of the studies report spastic diplegia as the commonest (30-40%), some studies report an occurrence of 22% and as the second commonest type of CP, after spastic quadriplegia (2,12). Spastic diplegia occurs due to various aetiologies including periventricular leukomalacia, cystic changes, infarction, and prematurity, metabolic or endocrinal abnormalities and infections (2). The clinical features include spasticity of both lower limbs with symmetrical or asymmetrical involvement. The upper limbs may or may not be affected. In some cases of spastic diplegia the upper limbs are affected to a greater extent than others. The associated abnormality like sensory loss is common, whereas seizure is seen less and intellectual activity is less impaired. The voluntary motor activity of both lower limbs are greatly affected. Sitting, walking and other activities using lower limbs, like dressing, are difficult for them. They suffer

from spasticity related complications, and morbidity like contracture and deformities which further limit their activities (2,12,66).

Spastic triplegic CP: This is again a relatively less common type of cerebral palsy. The motor functions of three of the limbs are impaired.

Spastic quadriplegic CP: This involves motor functions of all the four limbs. Patients are more severely affected than the other types. The associated brain pathologies detected through neuroimaging are disorders like prematurity, low birth weight (67), brain dysgenesis, infarction, periventricular leukomalacia, cystic encephalomalacia and many structural brain defects like schizencephaly. Genetic, metabolic and endocrinal abnormality can give rise to Quadriplegic CP. Ischemic events or infection can also be responsible for development of this type of CP (2). The children suffer from various comorbidities like seizure disorders, musculoskeletal deformities, speech abnormalities, visual disturbances and low intelligence. They are prone to develop recurrent respiratory tract infection or pneumonia due to recurrent aspiration of food content into the respiratory tract owing to pseudo bulbar palsy (2,12). Spasticity, contracture, deformity and severe motor disability are common (68,69).

Spastic hemiplegic CP: One half of the body is typically involved in this type of cerebral palsy. Cerebrovascular accidents like infarction due to thrombosis and embolism may give rise to spastic hemiplegia (70–73). Hypercoagulability, infection, placental abnormality, congenital heart disease and vascular malformations are some of the contributing factors for thromboembolic incidences (74,75). The patients usually present after infancy with one sided motor weakness and hemiplegic posture. There is deformity of the affected side of the limbs due to contracture of the muscles. They have a hemiplegic gait which becomes more prominent during walking. There

is more tone of the flexor group of muscle (12). There is also associated comorbidity due to recurrent seizures and visual impairment (75). Facial nerve palsy is also common in this group of patients (12). Sensory system may also be affected in some cases (76). The patients may have cognitive disturbances as well (77,78).

Dyskinetic Cerebral palsy:

This type of CP patients predominantly has involuntary movement disorders. The affected babies might have had perinatal hypoxic insult. Kernicterus due to neonatal unconjugated hyperbilirubinaemia and consequent bilirubin encephalopathy also causes dyskinetic CP. Genetic or metabolic abnormalities can also be attributed to its development (2). The babies present with lethargy and decreased movement. But involuntary movements are common in the form of chorea or athetosis. This type may further be classified based on the predominant movement disorder associated with them, like dystonic or choreoathetotic. The pathological brain lesions and resultant extrapyramidal effects are due to involvement of the basal ganglia or thalamus.

Choreoathetoid type of dyskinetic CP is classified based on the predominant movement disorder associated with it, of either chorea or athetosis. Patients with choreiform symptoms have rapid, jerky, involuntary movement of part of the body. Patients sometimes also presents with ballismus, a more severe type of chorea (79).

Dystonic type of dyskinetic CP patients present with dystonia or abnormal tone, along with pyramidal tract lesions. They usually have limb involvements as well. Dystonic CP can present with a normal tone or with hypotonia but in some form the tone may also be increased. There is rapid or slow, involuntary, repetitive, twisting limb movements which may get intensified with emotional stress. They also have

abnormality of speech and cognition. The dystonia also varies with change of body position, emotional status or sleep (12).

Ataxic Cerebral palsy:

Ataxic cerebral palsy is associated with dysfunction of cerebellum or sensory nervous system (79). The coordination and gait are abnormal along with other abnormal motor functions. Delayed developmental milestones are present. They also have speech and cognitive impairment. The problem may be due to perinatal insult or genetic abnormalities. Ataxic CP can be of two types depending on presentation and the associated comorbidities like simple ataxic CP and ataxia with diplegic CP.

Hypotonic Cerebral Palsy:

Hypotonic CP is also sometimes named as Atonic CP which is characterized by profound decrease in tone of the muscles. The patients are severely disabled and cannot even stand up by themselves. The developmental milestones are markedly delayed. The dependency level is very high. They also have poor cognitive ability. Structural brain malformation, agenesis, microcephaly are some of the aetiological factors (2).

CLINICAL FEATURES OF CEREBRAL PALSY:

Clinical features of cerebral palsy are varied and depend on clinical staging and classification and severity of the disease at presentation. The afflicted babies present with delayed developmental milestones. Though the disease is non-progressive, its clinical presentation changes over time. Primarily, cerebral palsy is a disease of motor system and posture. But it can affect the functions of central nervous system globally.

Motor impairment may be accompanied by sensory and autonomic impairment but the peripheral nervous system is usually spared (80–82). The clinical presentation can also be due to involvement of other systems, as complications affecting those are common.

The symptoms actually vary with regard to certain factors, like the age at which the patient presents, the classification of the disease, severity and dependency.

i) History of risk factors
ii) Inability to perform motor functions for the age
iii) Increased tone, spasticity
iv) Dystonia
v) Involuntary movement
vi) Not gaining weight
vii) Delay in speech
viii) Hearing problem
ix) Problem in vision
x) Excessive tightness of limb muscle
xi) Convulsions – recurrent
xii) Poor academic performance

The signs are again dependent on the age at presentation and type of CP and severity of the disease. The cerebral palsy is usually diagnosed after infancy and mostly after third year of life. Since the developmental milestones for a normal developing child varies with age, the clinical signs are also variable. Delayed developmental milestone at any age is one important sign of the disease.

CO-MORBIDITIES OF CEREBRAL PALSY:

Though cerebral palsy is mainly a disease of motor function and posture, there are several other comorbidities which coexists in several patients (75 %) (12). The following comorbidities have been identified (83).

i) Cognitive impairment: 50 % of all patients suffering from Cerebral palsy also suffer from some form of cognitive and intellectual impairment. Quadriplegics are more prone to develop cognitive disability than other. They also have some form of speech and language disability and also other learning disorders (83).

ii) Seizure disorders: 25 % of patients have epilepsy or seizure disorders. This is more common in quadriplegic, hemiplegic and atonic CP. They also have some associated learning disability (83).

iii) Behavioural problems: They also have some behavioural disorders in about 25 % of cases (83).

iv) Sleep disturbances: 20 % of the CP patients have sleep disturbances (83).

v) Speech disorders: This is found in about 25 % of cases and that can be attributed to pre-existing poor cognition and deafness. The poor oral and pharyngeal muscle activity and incoordination are responsible for the disorder (83,84).

vi) Visual disturbances or blindness: Blindness as a comorbidity in CP patients are found in about 10 % of cases. Visual cortical lesion, refractive errors, retinal diseases and squint are found in patients (85,86).

vii) Deafness: 4 % of the patients are deaf or have other forms of hearing loss. Sensorineural hearing loss is common in patients with kernicterus (87). There may be lesion in the auditory cortex due to hypoxic insult (88).

viii) Autism: Many of the patients of CP (6.9 %) have autism spectrum disorders. It is more common in atonic CP than in other varieties (89).

ix) Urinary diseases: Bladder control problems are present in 25 % of cases of CP. Urinary urgency, hesitancy, poor capacity, stress incontinence, detrusor instability and neurogenic bladder are not uncommon (90–93).

x) Drooling: Due to weakness of the oropharyngeal muscle there is poor control of mouth closure and 20 % of the patients present with drooling.

xi) Feeding difficulties: Poor motor control of oropharyngeal muscle due to severe motor disabilities, 7 % of the patients have some form of feeding difficulties and may require even gavage feeding for survival (83).

xii) Pulmonary diseases: The patients suffer from pulmonary diseases due to recurrent aspiration of food and resultant aspiration pneumonitis. This is due to incoordination of muscles of palate and pharynx. The thoracic cage and spinal deformity is also responsible for recurrent pulmonary diseases. Pulmonary diseases are one of the leading cause of death in cerebral palsy patients (94).

xiii) Musculoskeletal disorders: 75 % of the patients have feeling of pain due to a battery of reasons. 30 % of cases have hip displacement. 30 % of CP children cannot even walk at all (95). There is also presence of several deformities of limbs, thoracic cage and spine (96).

xiv) Osteopenia: The cerebral palsy patients suffer from osteopenia due to lack of movement, muscular weakness and nutritional deficiency of

micronutrients (97,98). The patients have low bone mineral density and are prone to experience fractures for the same reason (99).

xv) Malnutrition: Feeding difficulty, gastro intestinal diseases like gastro oesophageal reflux disorders, recurrent aspirations, constipation makes the patients prone to develop malnutrition and consequent stunting of growth and growth failure (100–103).

xvi) Dental abnormalities: Recurrent reflux of stomach acid content makes the patient prone to develop dental diseases (104).

FUNCTIONAL CLASSIFICATION OF CEREBRAL PALSY:

Cerebral palsy is classified by a number of classification system based on dependency and severity. Gross Motor Function Classification System (GMFCS) is one of the most popular scale to classify CP (105). It classifies CP into five levels in ascending order of severity. Another classification system based on how the cerebral palsy children use their hand function to initiate motor activity is referred to as the Manual Ability Classification System (106).

DIAGNOSIS OF CEREBRAL PALSY:

CP is mainly diagnosed clinically with supportive evidence from radiological studies and many other different investigations, but investigations can neither exclude nor confirm the diagnosis (16).

A careful history and clinical examination is pivotal in diagnosis. Abnormal neurological signs, impaired motor development, delayed developmental milestones, abnormalities in tone and posture, signs of comorbidities will suggest a provisional diagnosis along with presence of positive history and risk factors. Investigations like

screening for blood coagulation disorders and screening for metabolic disorders are important. Other investigations which can exclude other diseases or support the diagnosis of cerebral palsy will help in reaching a definite diagnosis.

Magnetic resonance imaging (MRI): Brain lesions can be picked up by magnetic resonance imaging (107,108). MRI is also more informative than CT scan.

Electroencephalography (EEG): Patients with epilepsy or seizure disorders are investigated using EEG (73).

Cranial Ultrasonography: This is also used to diagnose neonatal stroke along with other modalities of investigations (73).

Lumber puncture: Patients with resistant convulsions are investigated by lumber puncture to rule out other neurological disorders.

Testing for genetic and metabolic diseases: Screening for genetic and metabolic diseases are also done (87).

Children with CP are also investigated for visual and auditory abnormalities. Brain stem Evoked Potential is measured. Testing using ophthalmoscope is also carried out to find comorbidities.

MANAGEMENT OF CEREBRAL PALSY:

There is currently no cure for CP and treatment is mainly supportive to improve quality of life by improving functional ability either by improving motor function or by the use of assistive devices or techniques (109). Management of cerebral palsy is

multidisciplinary (110). The participation of departments of Paediatrics, Neonatology, developmental paediatrics, paediatric sub specialities, Neurology, Orthopaedics, Surgery, Physical Medicine and Rehabilitation, Ophthalmology, otorhinolaryngology, psychiatry is necessary for holistic approach in managing the disease. The management plan and approach also differ among patients since the presentation and the complaints and the disabilities are different in different patients of different type and classification of illness. The plan of management is prioritized for speech and language development, communications skill development, educational improvement, improvement of activities of daily living, attaining a close to normal appearance, improvement of growth and nutrition and overall betterment of motor functions.

Medical management: Medical management includes drug therapy mostly to decrease spasticity. Abnormally increased tone is treated by muscle relaxants like Diazepam, Dantrolene and Baclofen (111). Other drugs like Trihexyphenidyl, Scopalamine, Glycopyrrolate are used as anticholinergic drugs for different problems like drooling in CP (112–114). Botulinum toxin is used to reduce spasticity (87,115,116).

Surgical management: To relieve spasticity the commonest surgical procedure done is selective dorsal rhizotomy (117). To improve deformities tendon release surgeries are also done called muscle-tendon surgeries (118).

Orthopaedic therapy: Plaster of Paris casting of the affected limb is done to relieve spasticity in case of deformity. But definite evidence of improvement is yet to be confirmed (119).

Physiotherapy: Physiotherapy is one of the mainstays of management for rehabilitation. Muscle strengthening exercises, stretching, active exercise for both

upper and lower limb, trunk control exercises and gait training are part of physiotherapy. There are also some other techniques that are used to improve motor performance like Bimanual training, constraint induced movement therapy, Goal directed training, context focused therapy, self-care management and fitness training (13).

Occupational therapy: The patients are rehabilitated with the help of occupation therapy training. These include improving balance in different postures like sitting, standing and kneeling. Balance is improved by different techniques. Gross motor skills are improved by active exercise and these include rolling, sitting, standing and transfer activities. The hand function is very important for rehabilitation for better quality of life and for activities of daily living and many more. Hand functions can be improved by several methods to improve reach, facilitate grasp, pinch, hand manipulation of objects and hand writing. Activities of daily living (ADL) training is one of the most important part of therapy since this helps in elevating the quality of life of patients and in helping them to have a near normal appearance. The ADL training involves all the daily necessary activities of life like maintaining personal hygiene, bathing, eating, dressing, toilet training and also training to improve motor function to facilitate mobility, chair or bed transfer, walking, climbing stairs and even training on wheel chair for those who are unable to sustain mobility in spite of all available measures (13).

Behavioural and cognitive therapy: Since about 50% or more of the CP children have cognitive and intellectual impairment and many of them have behavioural problems, cognitive therapy is employed for them. Behavioural therapy is also useful in

correcting many behavioural problems in cerebral palsy children including management of drooling along with pharmacological therapy (120).

Play: different types of age appropriate play is also part of occupational therapy (121).

Speech therapy is employed for patients with dysarthria and motor dysfunction involving oropharyngeal muscles.

Psychiatric therapy: Patients with psychiatric problems are assessed by a psychiatrist and different problems like temper tantrums, depression, and agitation are treated by both pharmacological therapy as well as non-pharmacological therapy like psychotherapy and behavioural therapy.

Deep brain stimulation therapy can be used for dystonic cerebral palsy, but the supportive evidences are not strong (122).

Some other therapies are also tried on cerebral palsy patients without a promising result. Neuromuscular electrical stimulation, threshold electrical stimulation, functional electrical stimulation (FES), hyperbaric oxygen therapy, sensory integration therapy, massage therapy, hydrotherapy, neurodevelopmental therapy are some of the examples which are not recommended due to either lack of definitive evidences or because of other available better therapies (123).

Supportive therapy: Supportive therapy in the form of psychological therapy, counselling, and social support are important in relieving psychological stress, social stigma of both the patients and the parents and the family at large. Counselling is done to explain to the parents about the disease, causation, management, outcome and

prognosis. It also relieves parent's anxiety and improves the quality of care of the child (121).

Vibration therapy: There are evidences that show that vibration therapy can improve motor functions in cerebral palsy patients. But there are also reports that suggest that the results of vibration therapy are not promising. The vibration therapy can be given either as whole body vibration or localized vibration (3–5,124,125).

PROGNOSIS OF CEREBRAL PALSY:

The prognosis of cerebral palsy depends on the stage of the disease and the associated comorbidities. The milder form of the disease has better prognosis than the severe form of the disease. Associated comorbidities like seizure disorders, status epilepticus and other related complications worsen the prognosis.

ROLE OF IMPROVEMENT OF HAND FUNCTION IN THE MANAGEMENT OF CEREBRAL PALSY:

Cerebral palsy is managed by multidisciplinary approach (110). None of the single therapy alone is sufficient to manage these patients. Aim of management is to give a near normal status to patient as far as possible. That is why different approaches are sought to improve different parameters of the disease condition. Improving motor function is one of the most important aims in management since this is essential for becoming self-efficient to carry out work for earning a living. To improve quality of life and activities of daily living, ensuring a good hand function is one of the essential elements that need to be addressed. Studies show that about 83 % of the patients of CP have motor involvement of the hands. 36 % of patients have clinical contracture and 69 % of patients of CP have poor clinical hand functions (126). The impaired hand

function is definitely an important factor for poor quality of life and morbidity. Activities of daily living need a good hand function for obvious reasons. Improving hand motor function is thus important in CP.

Improving hand function and improvement of ADL

The Activities of Daily Living (ADL) is a tool to assess the motor performance of the patients in day to day activities. It includes ADL training and assessment. The parameters assessed for ADL are maintenance of personal hygiene like brushing, cleaning face, washing hands, personal grooming, shaving or combing hair, bathing and managing toilet activities. Feeding, dressing and many more activities are also included (127). An individual needs a reasonably good motor functioning of the body, especially good motor function of hands to perform these daily activities The gross manual dexterity is one of the independent predictors of the motor hand function activity of cerebral palsy patients (128).

PHYSIOLOGY OF HAND FUNCTION IN RELATION WITH CP:

Motor system of hand:

Motor system of hand includes both upper motor neuron (UMN) and lower motor neuron (LMN) system that control the hand function.

The lower motor neuron (LMN) system comprises of the alpha motor neurons present in the anterior horn of spinal segments C5 to T1, whose axons compose the motor branches of the brachial plexus and form the motor innervations of muscles of upper extremity. The main motor nerves are median nerve, ulnar nerve and radial nerve. Axillary nerve and musculocutaneous nerve also contribute to the motor supply of

upper extremity. The nerves supply all the skeletal muscles of upper extremity. The hand is also supplied by these same nerves which supplies all the small muscles of hand which are important in executing coarse and fine movements of hand and fingers. Lower motor neuron system, is intact and unaffected in cerebral palsy patients (2).

Upper motor neuron system of hand starts from the cerebral cortex itself. The motor cortices are responsible for the motor functions and control of the body. The primary motor cortex is situated in the pre-central gyrus (Brodmann's area 4) in the frontal lobe. The cells are arranged there in a columnar organization. There are six layers of cells in the cerebral cortex. The external and internal granule cell layers receive inputs from thalamus and also from other cortical regions. From the external and internal Pyramidal cell layer efferent tracts originate (10). The motor cortex is somatotopically organized. There is a large area of representation of hand in the motor homunculus. The supplementary motor area projects to primary motor cortex. The premotor cortex projects to the primary motor cortex, brainstem reticular formation and spinal cord (11).

Lateral corticospinal tract is formed by the axons of UMNs, whose cell bodies are in the cerebral cortex. 31 % of these fibres originate from neurons in the primary motor cortex (from Brodmann's area 4). The cell bodies of these neurons form the pyramidal cells of cortical layer V which includes Betz cells (giant pyramidal cells). 29 % of fibres originate from neurons of premotor & supplementary motor areas (from Brodmann's area 6) and 40 % of fibres arise from the neurons of primary somatosensory areas (Brodmanns's area 3, 1, 2) and somatosensory association areas of parietal lobe (from Brodmann's areas 5 and 7). Each area of the cortex is somatotopically organized. So the UMN axons which will ultimately be responsible

for motor activity of hand will come from the motor hand area. Hand area has got larger area of representation than other areas in both somatosensory and motor cortices. The axons of the UMN then descend down as corona radiata. The corona radiata converge and pass down through the posterior limb of the internal capsule and descend down to the brain stem. There it passes through cerebral peduncles of the Midbrain and then through Ventral Pons. Then it descends further and forms the Pyramids of the Medulla. At the level of the lower part of medulla, 85 % of the fibres cross over to the opposite side (at the level of Pyramidal decussation). The crossed fibres then descend down further into the spinal cord to form the lateral corticospinal tract, which is important for voluntary control of fine, skilled and precise movements of hand and also foot and digits. The remaining 15 % of the fibres are uncrossed. They descend as anterior corticospinal tract ipsilaterally. These fibres control the axial and proximal girdle muscles. They are involved in controlling the posture and stability of trunk muscles for smooth distal limb activities (10,11,129).

The lateral corticospinal tract descends in lateral column of spinal cord and ultimately terminates by synapsing with alpha motor neurons of anterior horn of the spinal cord which supplies the distal limb muscles. These alpha motor neurons which supply the distal limb muscles, form the dorso-lateral group of anterior horn cells (129). The lateral corticospinal tract fibres terminate in almost the entire cord, but mostly at cervical and lumbosacral enlargements. That is why motor activity of hand mostly depends on the integrity of lateral corticospinal tract. The anterior corticospinal tract, on the other hand, descends in the anterior column of the spinal cord. Some of the fibres of the anterior corticospinal tract cross in spinal cord to terminate on contralateral alpha motor neurons which supply contralateral axial and proximal girdle muscles (10,11,129). UMN is affected in cerebral palsy (2).

Sensory system of hand:

The sensory system of the hand, which detects sensory inputs such as touch, pain, temperature, proprioception and vibration and carries the information about these somatic sensations to the cerebral cortex, comprises of a three-order neuron system. The receptor that detects these sensations are present in the skin and subcutaneous tissues of hands (130). The receptor transmits the information picked up and transduced by it, to the first order neurons of the sensory pathway. The information is further transmitted to the second order neurons which passes on the information to the third order neurons which terminate in the Primary somatosensory cortices.

Cutaneous receptors: Different types of cutaneous receptors are present in the body which carry bodily senses. The sensory receptors are of different types such as the mechanoreceptors, nociceptors and thermoreceptors. Each receptor is specialised to detect mainly a specific modality of sensation. Free nerve endings which are minimally specialized receptors, send impulse through axons of C, Aδ fibres. They are slowly adapting receptors and carry pain, temperature and crude touch from skin of whole body. Their threshold of activation is high. Mechanoreceptors present over palm are Merkel's disc, Meissner's corpuscle, Ruffini's corpuscle and Pacinian corpuscle. Each of the receptor differs in their property of activation, position, shape and size. Merkel's discs are encapsulated nerve ending. Impulse from Merkel's disc is carried by the Aβ fibres. They are present in all over skin and carries touch and pressure. They are slowly adapting receptor and their activation threshold is low. Meissner's corpuscles are present between the dermal papillae and found in the glabrous skin. Signal from them are carried by the axons of Aβ fibres. They are rapidly adapting receptors and carry touch, pressure and vibration at a frequency of 20 – 50

Hz. Their threshold of activation is also low. The density of Meissner's corpuscle in glabrous skin of hand is high. They have receptive field of 2-3 mm in diameter in the finger tips and 10 mm over palm. The Pacinian corpuscles are encapsulated, onion like structure present in the subcutaneous tissue. They can be activated by deep pressure and vibration at a frequency of 60- 100 Hz. Impulse is carried by the axons of Aβ fibres. They are rapidly adapting receptors and activation threshold is low. Ruffini's corpuscles are also situated deep into the skin and activated by stretching of the skin. They are slowly adapting receptors and activation threshold is low. Impulse from Ruffini's corpuscle is carried by Aβ fibres (11,129,130). The mechanoreceptors converts mechanical energy to electrical energy. The receptive field over superficial skin has got many highly sensitive points due to presence of Meissner's corpuscles and Merkels's disc, whereas Pacinian corpuscles and Ruffini's corpuscles have single point of maximally sensitive receptor field in the deeper layer (129). Touch, pressure and vibration over the mechanoreceptors produce receptor potential which is a nonpropagated, depolarizing, graded potential. When the graded potential reach a threshold level, it can produce an action potential in the first node of ranvier and the impulse is transmitted proximally through the sensory nerve (11).

Vibration is a sensory stimulus that is produced by the sinusoidal oscillation of any object placed over the skin. These oscillations are sensed by a pulse code by the cutaneous mechanoreceptors. With each cycle of oscillatory sinusoidal wave, one action potential is developed. Then the sensory nerve action potential transmits the vibratory signal. The vibration frequency is signalled by the action potential frequency (129). Vibration at 50 Hz which is the intervention used in the present study stimulates Meissner's corpuscles (10,129).

Sensory nerves carry information from the sensory receptors. The receptor potential which is formed by the action of vibration stimulus is transmitted to the sensory nerve and the developed action potential travels through the axons of the peripheral nerves, like the median nerve, ulnar nerve, radial nerve and others. The axons of the sensory nerves carrying vibration sensation from the receptor, form the first order neurons, whose cell bodies are present in the dorsal root ganglion. The central axon of these pseudo unipolar neurons enter the spinal cord through the dorsal root and from lamina III to VI ascends in the posterior column of spinal cord. These dorsal column fibres synapse with neurons of nucleus gracilis and nucleus cuneatus in the medulla. The axons arising from nucleus gracilis and nucleus cuneatus form the second order neurons, which cross over to the opposite side at the Great sensory decussation of medulla and ascend up as the medial lemniscus to synapse with the third order neurons in the ventro posterolateral nucleus of the thalamus. The axons of the third order neurons then project up to terminate in the primary somatosensory cortex (S1) which projects to the secondary somatosensory cortex (S2) and to the sensory association cortices. The sensory cortex is also somatotopically organized like the motor cortex and hand area has got a greater area of representation in the cortex (10,11,129).

Relationship between sensory and motor cortices:

There are extensive to and fro connections between the motor cortices and sensory cortices. The primary motor cortex (M1) receives somatosensory afferents. The motor cortex receives inputs from the somatosensory cortex. The somatosensory input is relayed in such a fashion that it comes from an area which is homologous to the motor cortex. Since both the sensory and motor cortex are somatotopically organized, the sensory outputs from one area of sensory cortex transmits tactile and proprioceptive

information which projects to the same functional area of representation of that region in the motor cortex. So the somatosensory area for hand representation sends tactile and proprioceptive inputs to the motor hand area which when excited causes movements of muscles of hands. The inputs do not come directly to the motor cortex from the somatosensory area. It is relayed through thalamic relay nucleus. The ventral posterolateral nucleus of thalamus is also somatotopically mapped like the somatosensory and motor cortices. So the relay is also organized somatotopically from somatosensensory area of hand representation to the area of hand representation in the thalamus to the corresponding hand area of primary motor cortex (10).

Another observation that may show the sensory-motor connection is elicitation of M2 wave in EMG. If a peripheral muscle is stretched or stimulated, two different waves of different latencies are seen in the EMG. A short latency M1 response followed by a long-latency M2 response is generated. The M1 wave is the short latency response which is produced due to monosynaptic connection of Ia afferents to the spinal motor neurons. The M2 response is generated as the sensory signal is transmitted via the motor cortex. In patients with Klippel-Feil syndrome the M2 wave is seen bilaterally, if one limb is stimulated. The corticospinal neurons in Klippel-Feil syndrome branch out abnormally and they supply the spinal motor neurons bilaterally. So the sensory motor connection at the motor cortical level can be evidenced by the generation of M2 wave (129,131).

There is contribution of neurons of somatosensory areas to the descending motor pathways also. 40 % of fibres arise from the neurons of primary somatosensory areas (Brodmanns's area 3, 1, 2) and somatosensory association areas of parietal lobe (from Brodmann's areas 5 and 7). Each area of the cortex is somatotopically organized.

These neurons project to the dorsal horn of the spinal cord and also to medullary dorsal column nuclei. Their function is to send a positive sensory feedback to the motor cortex for a smooth movement. They respond to a change of limb position, rate of movement and magnitude of muscular force of contractions during movement (10).

Assessment of hand motor function:

Motor functions of hand can be evaluated clinically by assessing the bulk, tone and power of the hand muscles. However, this would be a subjective method. More objective and reproducible methods of evaluation of hand function are by using different scales like Box and Block test for manual dexterity (132), Fine finger dexterity test (Purdue Peg-board Test) (128), Manual Ability Classification System (MACS) (106,133), Toronto Rehabilitation Institute–Hand Function Test (TRI-HFT), Grasp and release test, Sollerman hand function test, Jebsen hand function test, Minnesota manual dexterity test, Action Research Arm Test (ARAT), GRASSP, AuSpinal (134), Jamar dynamometer, and handheld dynamometer (135).

Box and block test for manual dexterity:

The Box and Block test for manual dexterity is a simple, easy to assess, inexpensive test to assess manual dexterity or the hand functions in patients. Box and Block test results positively correlate with the MACS results in cerebral palsy patients (136). It is useful in assessing hand function in other conditions also, like Brachial plexus injury (137). This test has been validated in children in the age group of 6 – 19 years (128,132). There are also reports of studies which have used the Box and Block test to accurately assess hand function in CP children (128,136,138) of 6-19 years.

Approaches to improve motor functionality:

There are many approaches that can be adopted to improve motor functions in patients having motor impairment. The motor impairment range from flaccid paralysis of muscles, to hypertonia and spastic paralysis of muscles, to contractures of limbs. The strategies are pharmacological therapy like administration of drugs that decrease tone of skeletal muscle and thus decrease hypertonia and spasticity (111). This in turn will facilitate the movement of muscles with ease. Drugs like centrally acting muscle relaxants are used for this purpose. Botulinum toxin is another option for the same purpose (87,115,116). There are non-pharmacological therapies to take care of spasticity as well. Exercise, different types of physiotherapy, different modes of occupational therapy can help in relieving hypertonia. Another option is surgical therapy which actually takes care of the limbs which have been severely deformed due to contractures developing secondary to prolonged neglected hypertonia. Tendon release surgeries relieve the contracture and improve the range of mobility (118). Selective dorsal rhizotomy is also done for treatment of spasticity (117). Serial casting can also relieve spasticity and contracture.

Apart from management of spasticity, improving power of muscle is crucial for motor performance. Techniques like Bobath neurodevelopmental approach assist the child with cerebral palsy to get rid of abnormal postural tone and also improve control of posture (13). Motor performance can be improved by active exercises. Active exercise improves muscle power.

Physiologically, strategies to improve motor performance may be classified as those measures that strengthen the upper motor neuron system, those that tackle the lower motor neuron system and techniques that target the skeletal muscles themselves.

Upper motor pathways can be enhanced by increasing the recruitment of motor cortical neurons for a given task. This can be achieved by strengthening the synaptic connections that impinge on the motor cortical neurons and increasing the excitability of the pool of motor cortical neurons.

Cerebral palsy is a disease of the upper motor neurons. There is damage to the developing brain due to various aetiologies. The injury causes damage or death of the neurons in brain. Thus the motor cortical neurons are affected in CP. The resultant weakness of the limbs, reduces limb movements which further decreases the excitability of the surviving motor cortical neurons of the CP patient due to the prolonged disuse of the limb. The absence of the normal volley of proprioceptive inputs from the paralysed limb to the cortical neurons would contribute to this (139). Thus the purpose of improving brain function is to strengthen the viable as well as the damaged neurons of the motor cortices so that their functional output can be improved. So increasing motor cortical excitability is one way to restore the existing upper motor neuronal activities. Motor cortical excitability can be increased by different ways. One way of achieving this is by increasing the activity of the concerned muscles or increasing the movement of the involved limbs, which by a feedback mechanism can increase the excitability of those motor cortical areas which have the upper motor neuron control of the concerned muscles or limbs. The phenomenon by which the functional properties of the motor cortical neurons are altered is called Motor cortical plasticity (140). Motor cortical excitability can also be increased by sensory stimulation of the involved limb or part of the body. This phenomenon is called Cross system plasticity (140).

NEUROPLASTICITY

Neuronal plasticity is the ability of neurons to change their property of response to stimulation. The mature neurons of the adult human brain are not capable of cell division or regeneration, with the exception of the hippocampal neurons. However, the human brain is capable of changing the structural and functional organization of the existing neurons and this is possible at any age. Neuroplasticity occurs naturally to cope with different changes in external or internal environmental of the body. It occurs to achieve various purposes. It can help different brain activities like cognition. The property of neuroplasticity can be exploited therapeutically to treat several conditions like traumatic brain injury, neurological brain impairment, insomnia and various psychological disorders. It probably forms the basis of Cognitive Behavioural Therapy (141). Previously it was difficult to study neuroplasticity owing to lack of proper tools to study. Hence animal models were used to study neuroplasticity initially. But with the advent of recent advances in technology like Transcranial Magnetic Stimulation (TMS), studying of neuroplasticity has been made easier. TMS is a non-invasive, painless technique that can be used to study the mechanism of neuroplasticity. Proof of principle studies show that application of TMS can even induce or modulate cortical plasticity in humans. With the help of TMS and TMS-EEG co-registration neuroplasticity is studied (142). In TMS-EEG co-registration the TMS pulse is given on the head and at the same time EEG is recorded. This it can provide information about the cortical excitability directly and instantaneously. It also can give ideas about the dynamics of brain functions (142).

Though both adult brain and the developing brain of child are capable of modulating brain wiring, it is more prominent in an infant's brain. The mature adult brain can

undergo dynamic plastic changes in in response to different sensory inputs originating from the environment or from within the body. In addition, mature adult neurons can also modulate in response to efferent demands and also in response to behavioural changes (142). The neural networks of human brain executes specific functions but also may be modulated. Though one specific area of cortex is designated for the functions of a particular part of the body, it can modulate itself to take charge of the control of other parts of the body by strengthening or weakening pre-existing synaptic connections of those cortical neurons. Babies learn new skills and information by the property of plasticity of neurons. In this process, the neurons can form new synapses, may branch out and form new synapses to strengthen connections. Neuronal connections may also be removed by natural selection due to paucity of stimulation or other reasons in infants. In fact, pruning of synaptic connections occur markedly after birth till the adult brain develops (143). The strength of the neural connections will deteriorate in the absence of sensory inputs. The classic paper by Hubel and Wiesel in 1965 experimentally showed for the first time that sensory inputs are necessary for formation of synaptic pathways of vision in new born kittens (144). This is essentially an example of neuronal plasticity.

Though naturally occurring reinforcement or deterioration is common in infants and children, adults also exhibit considerable neuronal plasticity. This becomes evident in circumstances where adults are learning new things or un-learning existing patterns of behaviour or connections. Learning new skills, memorising new facts, recovering functions of limb after damage are all examples of neural plasticity. Plasticity can occur in neocortex in both sensory and motor areas. Memory is the prototype area of learning where plasticity has been described maximally through different experiments (129). The physiology of plasticity has been described through many mechanisms. The

types of plasticity is based on the different types of mechanisms. Due to short term or long term reorganizations in the connections and behaviour of neurons, circuits, synapses and overall network, adaptability to new sensory stimulation occurs. It is also possible to memorize new information, recover lost limb functions, acquire new skills and development through the phenomenon of neuronal plasticity (142).

The neural plasticity is of different types based on different mechanism of actions (102,129,142,145). A classification of plasticity has been portrayed in **Figure 1**.

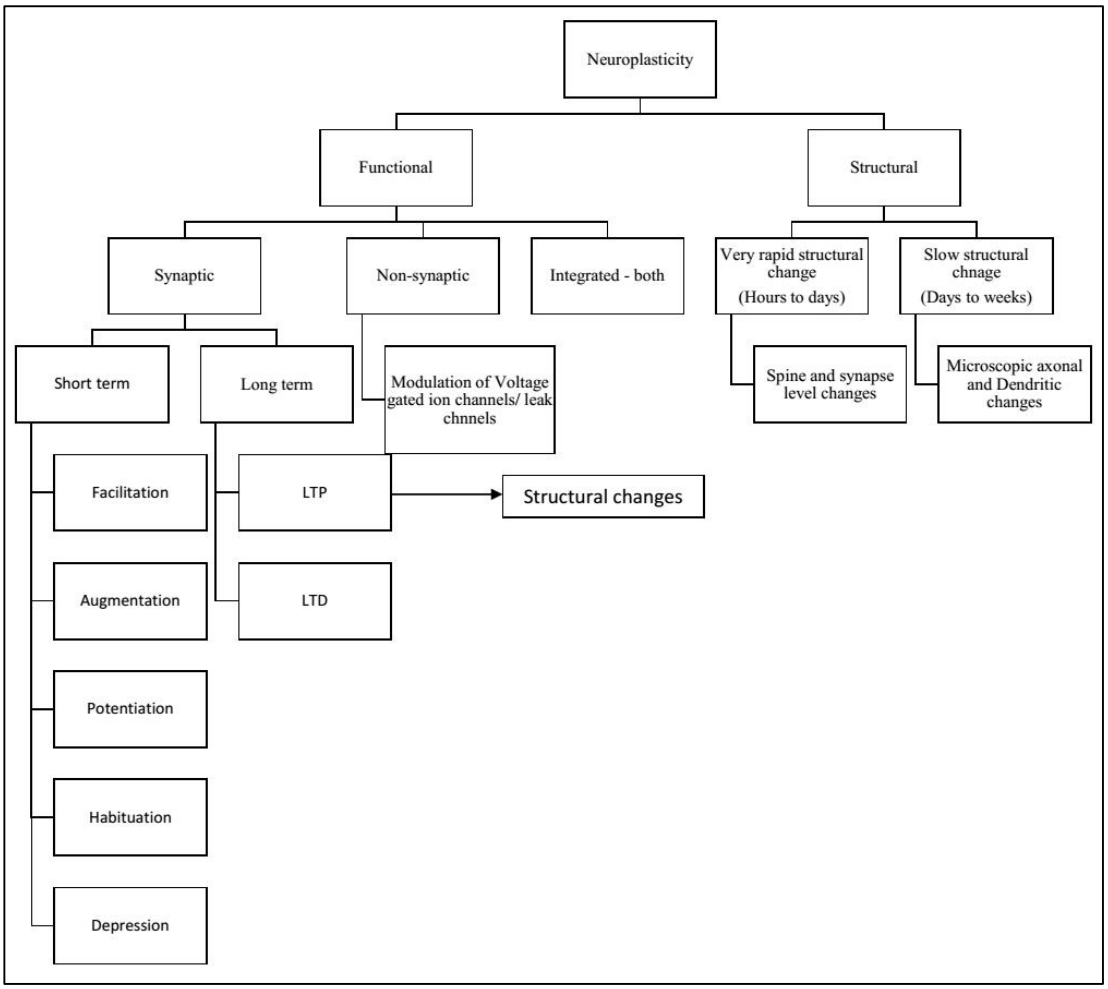

Figure 1: Classification and mechanism of neuroplasticity. (LTP: Long term potentiation; LTD: Long term depression)

Neuroplasticity has been broadly classified into functional and structural. Functional neuroplasticity can be synaptic, non-synaptic or both. Synaptic connection strength is reinforced and amplified or there could be synaptic weakening through neuroplasticity. Reinforcement occurs in an existing neuronal structural network. The structure of neuron, synapse and network connection remain same. The synaptic change occurs by changing the pattern and strength of electrical transmission. These changes occur by different mechanisms.

Based on time taken for changes to develop, functional neuroplasticity can be classified into short term potentiation and long term potentiation. It can also be categorised based on the type of change produced at the synapse by the functional plasticity, into long term potentiation and long term depression.

Cellular mechanisms of Synaptic plasticity can be divided into two. It can be through electrical and chemical changes producing changes in synaptic transmission leading to synaptic plasticity. Another is morphological or structural changes of synaptic connections involving increased protein synthesis and where new dendrites are formed or synaptic contacts are removed (129).

The onset of developing long term plasticity is very rapid but the effect of enhanced synaptic strength stays for long time. Unlike short term potentiation this occurs at post synaptic level and develops after a presynaptic neuron is stimulated repeatedly. Short term potentiation occurs at presynaptic level. The cellular events that occurs at the level of presynaptic neuron, can increase or decrease the strength of synaptic transmission. The synapse is a junction of a presynaptic neuron and a post synaptic neuron. Changes that occur in the pre-synaptic neuron and thereby causes changes in the strength of synaptic transmission is said to occur at the level of presynaptic neuron.

It reflects presynaptic changes. Changes in Intracellular Ca^{2+} is the main factor for development of all the different types of synaptic plasticity and there will not be any synaptic plasticity in absence of Ca^{2+} (129,145,146). Short term potentiation typically lasts for 10 seconds to several minutes. Repetitive stimulation of neuron can increase or decrease the strength of synaptic transmission for a short period of time. They are of different types based on the period of their action.

- Facilitation is a type of functional synaptic plasticity where the effect is seen for 10-100 milliseconds.
- Augmentation lasts for several seconds.
- Potentiation lasts for 10 seconds to several minutes.

Another variant of short term functional plasticity is depression which occurs if the frequency of stimulation is increased. Habituation, on the other hand occurs in response to a low frequency stimulation. The mechanism of action of short term synaptic plasticity is due to increase in intracellular Ca^{2+} concentration due to prior repetitive tetanic stimulation. The action potential that follows tetanic stimulation causes considerable increase in intracellular Ca^{2+} in the presynaptic neuron. The increase in strength of synaptic transmission is due to enhanced release of neuroactive peptide from the presynaptic neuron through exocytosis secondary to high level of intracellular Ca^{2+}. Habituation, on the other hand occurs due to decreased quantal release of neurotransmitter in response to a repeatedly applied benign or harmless stimulus (145).

Hebbian-like Long term potentiation (LTP) increases the neuronal synaptic strength of transmission. Here the changes occur in the post synaptic neuron. There is increased post synaptic potential developing in response to a stimulus applied subsequent to a

train of impulses that pass through the synaptic connections. The onset of developing this type of plasticity is very rapid but the effect of enhanced synaptic strength stays for long time. Unlike short term potentiation this occurs at post synaptic level and develops after a presynaptic neuron is stimulated repeatedly. Mechanism of development of LTP is either NMDA receptor mediated (NMDA receptor dependent) or NMDA receptor independent. NMDA receptor, AMPA receptor and Metabotropic Glutamate receptors are expressed in the post synaptic membrane. Complex interactions among these receptors at the cellular and molecular level brings about LTP (129,142,146).

Sometimes there is also weakening of synaptic strength, a phenomenon known as long term depression (LTD). The mechanism of action and types of long term depression can be mediated by different receptors. It can be NMDA receptor-dependent LTD (NMDA-LTD), Metabotropic glutamate receptor-dependent LTD (mGluR-LTD) and LTD through cannabinoid type 1 (CB1) receptors (CB1-LTD). The main intracellular event which is responsible for long term synaptic plasticity is changes in concentration of intracellular Ca^{2+}. A very sharp rise of intracellular Ca^{2+} for very short period of time initiates long term potentiation, while moderate increase in intracellular Ca^{2+} level which sustains for a long period of time initiates long term depression. Changes in Intracellular Ca^{2+} is the main factor for development of all the different types of synaptic plasticity.

Another form of functional synaptic plasticity is metaplasticity which is a type of non-Hebbian plasticity. It is a form of homeostatic plasticity. Here there is overall gross modulation of synaptic transmission and excitability of neuron. The changes are based on experience. The mechanism of action of metaplasticity is not yet known properly.

Involvement of neuroglial cells and release of tumour necrosis factor-alpha have been postulated. The global nature of this form of plasticity is called ‘plasticity of synaptic plasticity’ (147).

Functional plasticity can also be non-synaptic where there is change and modulation of conductance of ion channels in the neurons. The transmission of neuronal action potential or synaptic potential requires expression of ion channels and their activation. One of the important type of channel involved in the transmission of the action potential are the voltage gated ion channels. Other ion channels play an important role for maintaining the resting membrane potential and hence the excitability of neurons (11,129,145). The modulation of these channels can change the membrane potential and can modulate the neuronal transmission. Modulation of neuronal transmission can change the excitability of the concerned brain area and allow neuroplasticity to occur (148).

GABAergic neurons are inhibitory neurons and exhibit high level of plasticity. They are responsible for overall gross changes in the neuronal excitability in brain. The plasticity in these neuronal circuit plays a crucial role in somatosensory cortex (146,149).

Neuroplasticity can also occur structurally. Various structural changes like synapse number, formation or deletion of neuronal branches and many more are responsible for structural neuronal plasticity. Other different changes are changes in anatomical connections between neurons, Changes of connections of synapses, structural changes in neurons like changes of structures of axons and dendrites, their branching type, number and also plasma membrane of neuron. Structural changes will also modulate the cortical excitability. Structural changes of plasticity is also time dependent in

different parts of the central nervous system. Synaptic structural changes and changes of structure of dendritic spine can occur very rapidly, from hours to days. But macroscopic structural changes involving axonal projections and also dendritic spine take place relatively slowly, from days to weeks (129,142,146). Reinforcement of neuronal connection through formation of new synaptic connections, increases the excitability of brain. Similarly, removal of one or more synapses from the circuit can decrease the strength of neural transmission of impulse. Plasticity also occurs by remodelling an existing pathway to a different circuit. Structural plasticity is more common in adults where they help in formation of new neural connections. The formation of structural plasticity is a complex procedure and involves many factors.

Neurotransmitters may play an important role in establishing structural plasticity. They may act as a neurotropic factor that helps in the genesis of new connections and change in structural organization of neurons or they simply can modulate the electrochemical activities in the circuit and thereby facilitate neuronal transmission (146).

One of the known processes of structural plasticity is through synaptic rewiring. This is more relevant in the formation of long term memory. When there is damage of a pre/post- synaptic part of a neuron due to any reason, the synapse formed by that part becomes non-functional and eventually deleted from the network. The remaining part of the damaged neuron now can make new connection by strengthening of a pre-existing synaptic connection which had been kept inhibited up till now by the synapse of the neuron which was damaged. Damage of that neuron releases the other synapse from inhibition or allows strengthening of this previously weakened synapse (143). Synaptic rewiring may also be possible by formation or deletion of dendritic spines,

sprouting of new branches, rearranging new network in an existing connection, reconnecting quiescent neuronal branch, making a new connection, generating new dendritic spine and synapse (146).

Another form of experience dependent plasticity that occurs in human brain is Spike time dependent plasticity. This also is a form of hebbian type of learning and is time dependent (146,150). This involves different cellular mechanisms. This has a time dependent change of excitability of post synaptic neuron to stimulation in the presynaptic neuron. Spike time dependent plasticity (STDP) occurs in two forms of which one is excitatory and the other is inhibitory. Pre-leading post firing, where the presynaptic spikes comes before the post synaptic action potential, causes excitation of post synaptic membrane and causes long term potentiation. This is usually NMDA receptor mediated LTP. Here the post synaptic membrane receives repeated firing form the pre synaptic membrane before the post synaptic membrane fires. If the presynaptic impulse spikes comes about 0 -20 milliseconds before the onset of post synaptic spike, the resultant post synaptic potential is potentiated (146,151). Another form of STDP is related to long term depression. The depression of post synaptic potential occurs when the temporal sequence of the stimulus is pre leading post firing. Here the post synaptic action potential starts before the repeated presynaptic spikes come. If the interval between the two is 0 to 20-50 milliseconds, there is depression of resultant post synaptic action potential. This causes long term depression and it is either NMDA receptor mediated or cannabinoid receptor mediated LTD (146). The classical mechanisms are NMDA receptor mediated LTP and LTD, NMDA receptor mediated LTP and cannabinoid receptor (CB1) mediated LTD and metabotropic glutamate receptor (mGluR) mediated LTD (146).

The effect of neural plasticity in increasing or decreasing excitability of brain in one or different areas is possible because of connectivity of brain. The neuronal connections of brain is organised in different ways (142,152). The inter relation of this organization helps in creating plasticity in brain areas. The brain connectivity is mainly based on two principles. Neurons in the brain segregate themselves in an area and execute same function together in that area. Here one group of neurons are responsible for the control and functions of one area. This principle is called segregation (152). Another is called integration, where more than one group of neurons exert a global function by organizing themselves with neuronal connections. Their actions are coordinated among themselves. Integration is relevant for cognition and behaviour. Brain connectivity has also been described in space and time (152). The spatial connectivity comprises of axonal interconnection within an area of cortex or between the different layers of the cerebral cortex. The axons can also connect two or more different cortical areas. When plasticity occurs in the neurons or synapse of these connections, it is called cross system plasticity (140).

Types of brain connectivity can be of anatomical connectivity where physical connections of neuronal networks are present and functional connectivity. Functional connectivity of brain is time dependent (153). The effective connectivity is liaison between the anatomical and functional connectivity. All the two types of connectivity of brain are interrelated to each other (142,153). Their relationship and temporal causation is not fully understood. Different models describe the relationship differently. Some propose that stimulation can induce rapid structural connectivity first, followed by development of functional plasticity following exposure to subsequent stimuli. Others argues that it is probably functional plasticity that rapidly

occurs first following stimulation, and subsequent stimuli forms the structural component of connectivity (142).

Techniques to study effective connectivity include functional Magnetic Resonance Imaging (fMRI), Electroencephalography (EEG), Transcranial magnetic Stimulation (TMS) Magneto encephalography (MEG) and Positron emission tomography scan (11,142).

Sensory stimulation in improving motor function:

Improvement of motor functions can be gained by exploiting the property of neural plasticity. One of the known fact about motor cortical plasticity is that repeated movement of a part of a body can increase the motor area of representation of that part in the motor cortex. Likewise, prolonged dis-use of a limb or part of a limb can cause regression of size of the motor cortical area of representation. Similarly area of somatosensory representation of a limb moves to the surrounding areas if that limb or part of it is removed. Moreover, somatosensory map of adjacent areas can encroach to that cortical area which used to be the sensory map of the non-used limb. Interestingly, if a part of the somatosensory cortex which represents a particular part of body is removed, the somatosensory map of that part gets shifted to the adjacent areas (11,129). This is an excellent example where the body naturally exploits the phenomenon of cortical plasticity to restore the functions of a damaged cortical area.

There are extensive to and fro connections between the motor cortices and sensory cortices. The primary motor cortex (M1) receives somatosensory afferents. The motor cortex receives inputs from the somatosensory cortex. The somatosensory input is relayed in such a fashion that it comes from an area which is homologous to the motor

cortex. Since both the sensory and motor cortex are somatotopically organized, the sensory outputs from one area of sensory cortex transmits tactile and proprioceptive information which projects to the same functional area of representation of that region in the motor cortex. So the somatosensory area for hand representation sends tactile and proprioceptive inputs to the motor hand area which when excited causes movements of muscles of hands. The inputs do not come directly to the motor cortex from the somatosensory area. It is relayed through thalamic relay nucleus. The ventral posterolateral nucleus of thalamus is also somatotopically mapped like the somatosensory and motor cortices. So the relay is also organized somatotopically from somatosensensory area of hand representation to the area of hand representation in the thalamus to the corresponding hand area of primary motor cortex (10).

So repeated stimulation of somatosensory cortex by afferent impulses generated by the application of vibration stimulus to a peripheral part of the body, can increase excitability of the representative area of the somatosensory cortex. This somatosensory area in turn will send recurring impulses to stimulate the corresponding area in the motor cortex, triggering plasticity and increased connectivity in that part of the motor cortex.

Mechanisms through which sensory stimulation causes motor plasticity:

There are evidences that shows that sensory stimulations causing modulation of motor cortical excitability. Animal studies have shown that stimulation of somatosensory cortex by electrical stimulation of trigeminal nerve activated the primary motor cortex (154). Studies have shown that stimulation of ulnar nerve by electrical stimulus can increase the excitability of the cortical motor neurons (155). Electrical stimulation of the hand via whole-hand-mesh-glove has been reported to induce increased motor

cortical excitability (156). Other studies demonstrated the beneficial effect of a single session of peripheral sensory nerve stimulation by surface electrode applied over wrist which stimulated the Median nerve, and improved the motor function of hand in subacute stroke patients (157). Changes in sensory input may alter the excitability of motor cortex which is referred to as cross-system plasticity. A study has shown that short period of electrical stimulation of pharyngeal muscles produced increased cortical area of motor representation in healthy human volunteers that sustained for a long period of time (140).

Types of sensory stimulation: Different sensory stimulations can be applied to bring about cross system plasticity and to increase excitability of motor cortex. Use of electrical stimulation of nerve, whole hand electrical stimulation, functional electrical stimulation, proprioceptive stimulation in the form of vibration stimuli, vibrotactile stimulation and auditory stimulation have been described to produce increased motor cortical excitability or improvement of motor function (3,156,158).

Usefulness of vibration therapy: Vibration is a form of sensory stimulation which has been used to treat patients with various forms of motor impairment. Vibration therapy has been reported to produce improvement in patients with Stroke, Parkinsonism and Cerebral Palsy (3–7). Whole body vibration (WBV) therapy has been found to be useful in increasing hip bone mineral density (BMD) and increase muscle strength and no side effect was observed after 6 months of therapy (159). WBV in randomized controlled trial showed demonstrable improvement in muscle strength and balance in diplegic cerebral palsy patients (4). Another randomized controlled trial among cerebral palsy children using WBV found improvement in mobility (5). Vibrotactile stimulation can relieve spasticity by decreasing muscle tone and has been shown to

improve mobility in cerebral palsy patients (3). Adult patients with stroke also showed preliminary improvement in muscle strength following whole body vibration therapy. It was also found to be safe in them (6). WBV along with exercise has been found to be useful in raising the blood level of cortisol and IGF1 in geriatric population (160). Vibration alone is more effective in increasing skin blood flow and microcirculation in normal healthy individual than vibration with exercise or exercise alone (161). Vibration can also be useful in improving cognition and attention span in young individuals (162). However, there are also studies those failed to show any significant improvement in motor functions following vibration stimulation in stroke patients (163,164).

Local Vibration: Vibration therapy can be applied as whole body vibration or regional vibration. Site specific vibration therapy in diseased and healthy individuals has shown improvement of function of motor system. Regional vibration therapy over the trunk region in patients of spastic cerebral palsy has shown improvement of posture and gait of these children. But regional trunk vibration did not show any improvement in muscle power or reduction of spasticity. However, no side effect has been reported (124). Focal muscle vibration in the form of repetitive muscle vibration (rMV) therapy, over the upper limb of chronic stroke patients, improved the motor functions (8). TMS studies have shown that focal hand vibration can increase motor cortical excitability in healthy human subjects (165) while others have shown that focal vibration of lower limbs decreased the spasticity in cerebral palsy patients (9). Another TMS based study has shown that application of vibration stimulation over the immobilized arm can prevent the inter-hemispheric inhibition of the contralateral cortex by the ipsilateral normal cortex. The hemispheric balance is also maintained in case of limb immobilization if vibration is applied on the affected limb. These findings

also corroborate with the principle of constraint induced movement therapy for rehabilitation of adult stroke patients (139). But low amplitude vibration on one limb is capable of modulating excitability of both motor cortices. In patients with immobilized one limb, EMG output from the muscle is decreased following transcranial magnetic stimulation of contralateral motor cortex. This is probably mediated by transcallosal inter-hemispheric inhibition mechanism (166). Children with meningomyelocoele with damaged neuron, have movement restriction. Muscle vibration can improve the muscle strength and mobility (167).

Dosage of vibration:

Vibration for improving motor functions has been used in previous studies. The most commonly used effective vibration frequency is 12-100 Hz (3,9,125). Studies have administered vibration therapy for various durations ranging from single episode of application daily for 3 days, once weekly for 12 weeks, to 5 days a week for 6 months (3,125).

Mechanism of Vibration induced neuroplasticity:

The mechanism by which whole body vibration produces improvement of the motor function of CP children has not been clearly elucidated. WBV stimulates most of the structures of the body, including skin, bone, muscles and even endocrine glands (3,159–161). The exact mechanism by which WBV increases muscle power has not been clearly elucidated. Investigators have also attributed the effects to stimulation of muscle spindles and spinal motor neurons (168). Moreover it can stimulate the proprioceptive pathways and can stimulate the somatosensory cortex (139).

Comparison between Whole Body vibration and local vibration:

In the present study, we studied the effect of local area vibration applied bilaterally to the palms of CP children aged 6-15 years. The vibration is not aimed at any specific muscle but is intended to stimulate the tactile sensory receptors of the palm, and thereby provide sensory feedback to the sensory and motor cortices of the brain. The procedure is painless and without any deleterious effects (124). The equipment for producing localized vibration therapy is manufactured at a lower cost than the equipment required for whole body vibration and hence is available for purchase at a lower price. Many such products are currently available in the Indian market for purchase at low prices. The most commonly used effective vibration frequency is 12-100 Hz (3,159–161). In our study we used a frequency of 50 Hz which is known to stimulate Meissner's corpuscles (10,129).

The rationale of the present study:

In the present study, local site-specific vibration was given to the palms of both hands of CP children in the intervention group. The rationale for choosing vibration is that it can be easily quantified in terms of frequency and duration of application of stimulus, when compared to other forms of mechanical, tactile, thermal and noxious stimuli. We postulate that site specific vibration given to the palms would stimulate the ascending sensory pathways (dorsal column pathways) carrying vibration sense to the primary somatosensory cortex (S1) which project to the secondary somatosensory cortex and to the sensory association areas (10,11,129). It is known that there are extensive to and fro connections between these sensory cortices and the motor cortices (10).We postulated that repeated stimulation of the sensory cortices by the vibration therapy would strengthen its projections to the motor cortices and thus enhance the central

motor output to ultimately increase muscle power. Further, it is established that 40% of the descending motor pathways originating from the cortex (corticospinal tracts) is formed by the axons of cortical neurons of sensory cortices (Primary and association sensory areas (11). Thus sensory cortex stimulation by local area vibration therapy may serve to enhance the motor cortical output to the spinal cord. The motor cortices which includes the primary motor cortex (Brodmann's area 4) and the Supplementary and Pre-motor cortices (Brodmann's area 6) plan and program the motor events and initiates the skeletal muscle contraction by sending command signals via the descending motor pathways to the lower motor neurons supplying the skeletal muscles (10,11). Moreover, the normal development of motor functions seen in the normal growing child is restricted in the CP child. A contributing factor for this could be the reduced sensory feedback the child gets, as the interactions of the CP child with the surrounding environment is limited, when compared to the normal child. The CP child is not motivated to take part in various activities and to explore the world as much as the normal child, due to various degrees of cognitive impairment in addition to motor impairment. Thus the normal sensory feedback from tactile and proprioceptive receptors, which would aid the development of motor function, is often critically reduced in the CP child. The cortex mainly functions through maps. The cortical sensory mapping shows that the Palm has got greater area of sensory representation in the S1 (10,11,129). So, if the palm is stimulated, greater area of S1 will be stimulated. This can produce increased cortical motor excitability by the short term and long term neuroplasticity leading to improved transmission of impulses through corticospinal tracts, resulting in improved motor functioning of the hand. This argues for the role of sensory stimulation as a mode of therapy to enhance the motor function of hand in CP children. Thus the therapeutic potential of motor enhancement through peripheral

sensory stimulation warrants further investigations. However, to date, there are no studies in CP patients which report modulation of cortical motor excitability solely by vibratory palmar stimulation, which is a simple, painless, low cost feasible form of therapy in the Indian scenario.

The present study hypothesizes that vibration stimulation of the palmar region of the hands of cerebral palsy patients will stimulate a large segment of their sensory cortex which in turn will stimulate their motor cortex representing hand, to induce cortical plasticity, which will result in improvement of hand motor function of these patients.

AIMS
AND
OBJECTIVES

AIM:

Aim of the study was to investigate the effect and the usefulness of local area vibration therapy in improving motor hand function in cerebral palsy children.

OBJECTIVES:

Towards this, the study was designed as a randomized controlled trial where local vibration therapy was given only to the intervention group and standard conventional therapy was given to both the intervention and control group of cerebral palsy patients. Both groups were followed up for a period of 4 weeks during period the intervention was given.

The objectives were:

a) To compare the change in hand function, assessed by the Box and Block test, in the group receiving local vibration therapy in addition to conventional therapy, with the group receiving conventional therapy alone.

b) To compare the change in hand function, assessed by the Box and Block test, in each group individually before and after therapy.

c) To compare the change in the Activities of Daily Living (ADL) measured by Modified Barthel Index, in the group receiving local vibration therapy in addition to conventional therapy, with the group receiving conventional therapy alone.

d) To compare the change in the Activities of Daily Living (ADL) measured by Modified Barthel Index, in each group individually before and after therapy.

MATERIALS AND METHODS

MATERIALS AND METHODS:

To investigate whether sensory stimulation of the hands would produce motor improvement in hand function in cerebral palsy patients, a single blinded randomized controlled trial was designed. The sensory stimulation was given by applying local vibration therapy to the hands. The trial was to study whether local vibration therapy had an effect over and above routine standardised therapy, on the motor hand function of cerebral palsy children.

The study was approved by the Institutional Review Board and Ethics Committee.

TYPE OF STUDY:

Randomized Controlled Trial, Single blinded.

The study is registered under Clinical Trial Registry – India (Registry number CTRI/2013/05/003700)

SUBJECTS:

Cerebral Palsy children who were admitted for therapy in the department of Physical medicine and Rehabilitation of the Institute have been recruited. The diagnosis of cerebral palsy was made by history, clinical examination of the child and relevant investigations as per the protocol of the hospital. The patients who were diagnosed as cerebral palsy only had been recruited for the study.

Cerebral palsy patients with Hemiplegia or Diplegia or Triplegia or Quadriplegia were recruited in the study. All the patients were in the age group between 6 – 15 years and of either gender.

Patients with associated sensory impairment were excluded, as intact sensory pathways are crucial to the study to ensure that the sensory impulses reach the cortex. Similarly those CP patients who were unable to follow simple 2 step commands were not recruited as then, these children would not be able to perform the Box and Block test. CP patients with bleeding disorders were also excluded from the study, considering the possibility of the vibratory stimuli precipitating bleeding episodes in these individuals. So also, those CP children with infective, inflammatory or other painful lesions of the hands were excluded.

PRIMARY OUTCOME: Hand dexterity as assessed using the Box and Block test administered immediately before and after the trial.

SECONDARY OUTCOME: The ability to perform the Activities of Daily Living as measured by the Modified Barthel Index computed pre and post intervention.

SAMPLE SIZE:

Sample size had been calculated based on the following principle and method:

The primary outcome of our study was the Box and Block test which measures hand dexterity. Investigators have studied the Box and Block test in 6-19 year old normal children to establish normative data in this age group. As per their published findings, the normal result of the Box and Block test in 6-19 year olds is 65±6.3 (mean±SD) blocks (132)

A sample size of 25 subjects in each arm of the study was calculated using these published results.

ASSESSMENT OF PATIENTS (SUBJECTS):

CP patients admitted in the ward under the PMR department were screened to see if they had all the inclusion criteria and to ensure that they did not have any exclusion criteria.

PRE-INTERVENTION ASSESSMENT:

Pre-test assessment for manual dexterity was done by using a standardized tool called the **Box and Block test (BBT)**. The ability of the patients to perform various activities of daily living was qualitatively measured by computing the **Modified Barthel Index (MBI)** through a questionnaire for **Activity of Daily Living**

1. **BOX AND BLOCK TEST:**

INSTRUMENTATION:

To carry out the test, the Box and Block apparatus and a stop watch are required.

The Box and Block apparatus consists of three parts, a wooden box, a wooden partition and wooden blocks. (Figure 2 and Figure 3)

Wooden box: A wooden box separated in two equal halves and joined at one edge with metal hinge joint. The dimension of the box is 53.7 cm in length, 25.4 cm in breadth and 8.5 cm in depth. The two halves of the boxes can be put one upon another so that it can be stored like a briefcase when not used. Usually, blocks formed of wooden cubes are stored inside the 'briefcase'. For administering the test, the two halves of the boxes are kept open side by side and the separation plate is placed at the junction of the two.

Wooden partition: A thin wooden partition with dimensions of 25.4 cm x 15.2 cm x 1cm is placed in between the two equal halves of the box to separate them completely when administering the test. The partition can be detached and stored flat inside the box when not in use.

Wooden blocks: These are kept inside the box. Each block is a cube with the dimensions of 2.5 cm x 2.5 cm x 2.5 cm. The cubes are of different colours like red, green, yellow, blue. A total of 150 cubes are present in one box.

Stop watch: A standard battery operated stop watch to record time is necessary to carry out the test.

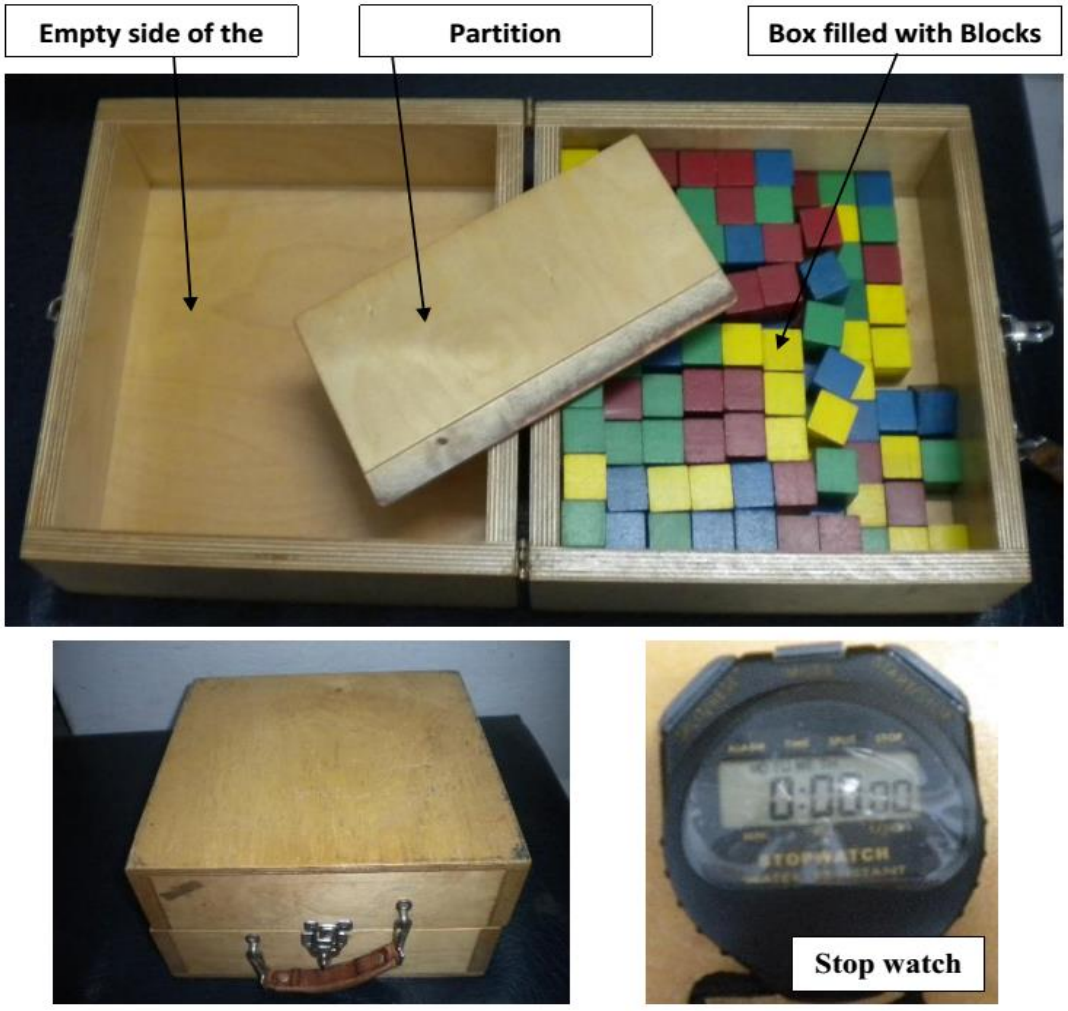

Figure 2: Box and Block Test instrument different parts

Figure 3: Box and Block test assembly

EXPERIMENTAL PROTOCOL

The handedness of the patients recruited into the study was determined by questioning the parents or legal guardians and was confirmed by examining the patients as well.

Administering the Box and Block test: The place where the test was performed was kept free from noise and was secluded from other people and patients to avoid distractions for the patient while doing the test.

The patent is made to sit comfortably on a stool or chair of standard height. Patients who can't sit unsupported, are given support at the back to ensure proper positioning.

The box and blocks are assembled and the partition plate is kept in the middle of the two halves of the box.

All the blocks are kept on one side of the box.

The box is placed on a standard height table, in front of the patient such that the chin of the patient is at least 10.5 cm above the mid portion of the partition of the boxes in the sitting erect position.

The Box is initially placed such that the half containing blocks is on the same side as the patient's dominant hand.

Once the test on dominant hand is over, the box is repositioned such that now the half of the box containing blocks, is on the same side as the non-dominant hand.

The examiner sits on a stool or chair in front of the patient facing the child so that he can watch the whole procedure comfortably.

At the start of the test, all the wooden cubes would be placed on one side of the partition. In response to a verbal command the patient has to transfer the cubes from one side to the other side as fast as possible, using first his dominant hand, for a period of one minute. The test is then repeated after an interval with the patient using his non-dominant hand to transfer the wooded cubes. The interval time can be variable depending on the time taken by individual patient to become ready for the next test. The number of cubes transferred over the period of one minute is noted in both cases.

The patient is allowed to have a trial test for a period of 1 minute.

The patient is explained about the whole procedure and reassured. The patient was instructed to place the hands on either sides of the box, just before the test was started.

The patient was instructed to start the test as soon as the verbal command to do so was given.

Initially the patient would transfer the blocks with dominant hand and then with the non-dominant hand. An interval was given between tests using dominant and non-dominant hand. It was given for the patients to get some rest. Once the patient was comfortable and confirmed that he or she is ready, the test is carried out for the other arm.

The patient is instructed to transfer the blocks as fast as possible for a fixed period of time of one minute.

During transfer of cube the patient is instructed to move the hand across the wooden partition to the opposite side. The block should be released to fall in to the opposite side of box. Only one block is to be transported at a time. If more than one block is accidentally picked up by the patient, only one would be counted. Or the extra number of blocks would be subtracted from the total count at the end of one minute.

While transferring, if any block is misplaced out of the second box but if the hand had crossed the midline before releasing the block, then credit would be given and the block would be counted as transferred.

The examiner monitors the time with the stop watch held in his. The patient should continue transferring the blocks for full one minute without any interruption.

At the end of the test the number of cubes transported correctly was noted. (Figure 4)

Precautions to be taken by the patient while performing the Box and Block test:

Patient should sit erect and comfortably and in a quiet room to avoid any distraction.

The patient should start transferring blocks from one side to the other as soon as the oral command to 'START' is given.

The patient should continue transferring the blocks for one full minute till the STOP command is given.

The transferring should be done as fast as possible without any interruption or distraction.

Only one block must be transferred at a time and the block must be released only when the hand crosses above the partition to the other side.

The patient is advised not to pick up more than one block at a time. However, if more than one block is picked up by chance, the patient is advised not to waste time trying to keep one back. Instead, the patient is instructed to continue performing the test with whatever number of blocks picked up by the hand and as fast as possible.

Further, the patient is also informed that if accidently, the transferred block falls out from the other side onto the table or the floor, to ignore it completely and not to make any effort to try to put it back into the box.

All the above precautions are explained to the patient before administering the test.

Figure 4: Box and Block Test in action

Box and Block test has got some limitations. Since this is a time bound test, any minor distraction can reduce the speed of transfer of block and hence can affect the results. So in children with less attention span, it may not give accurate results. But doing randomization of subjects in our study, we minimized this error. The results also depends not only on the motor functions of the patients but on mental status of patient as well. All subjects were encouraged to speed up the transfer of blocks during the test.

2. ASSESSMENT OF ACTIVITIES OF DAILY LIVING:

Activities of daily living are assessed from the Modified Barthel Index. The patient or parents of the patient is to answer the questions given in a pre-set, standard questionnaire. The patient or the caregiver was asked about the patient's ability or

efficiency in doing activities of daily living such as eating, bathing, brushing teeth. The examiner scores the responses based on established guidelines for the answers of the questionnaire.

MODIFIED BARTHEL INDEX:

The Modified Barthel Index is used to assess the Activities of Daily Living in patients with disability. A set of standardized parameters are assessed using a standard questionnaire and the responses are scored using the Modified Barthel Index scoring system. Dependency needs of individual patient is also evaluated using the same scoring table (127).

The following activities are assessed and scored as per the Modified Barthel Index assessment:

- Personal hygiene
- Bathing self
- Feeding
- Toilet use
- Stair climbing
- Dressing
- Bowel control ability
- Bladder control ability
- Ambulation
- Wheel chair
- Chair or bed transfer

DEPENDENCY NEEDS ASSESSMENT:

Dependency needs assessment is done through the scoring table of Modified Barthel Index (127) and the following dependency levels are computed or assigned or obtained.

- Total dependency – if the total score is 0 - 24
- Severe dependency – if the total score is 25 - 49
- Moderate dependency – if the total score is 50 – 74
- Mild dependency – if the total score is 75 – 90
- Minimal dependency – if the total score is 90 – 99

ALLOCATION OF PATIENTS INTO GROUPS

Randomization: Computer generated block randomization code was created using the statistical software package SAS.9.2. The so created randomly generated numbers were assigned to the intervention group and the control group, as the case may be, printed on separate papers and placed in a serially numbered sealed, opaque envelope and filed.

The sealed envelopes are kept with the occupational therapy staff. Randomization is done only after the pre-intervention box and block test and MBI scoring have been done after the informed consent is obtained. Randomization of the recruited patients into the control and intervention group was done by the occupational therapy staff.

The investigator who recruited the patients and did the pre and post assessment by the Box and Block rest and the Modified Barthel Index scoring scoring, was not aware of the randomization.

Intervention Group and Control Group:

Thus all the recruited patients were allocated into either the Intervention group or the Control group.

All the recruited patients of both groups were given the standard therapy that all CP patients admitted in the ward were given. In addition, the patients in the Intervention group received vibration therapy of the palms.

Vibration therapy

Commercially available hand held portable vibrator has been used in this study to administer the vibration therapy. The vibrator is operated electrically with normal AC power. It can be regulated at two separate speeds (frequencies) with the help of a switch cum regulator, having 0, 1, 2 level of speed. The front adapter of the instrument can be connected to fourteen different sets of attachments which actually transmits the vibrations to the body surface. In the present study, the attachment with the smooth surface was used in all the trials, since smooth surface would ensure least stimulation of the touch receptors, while transmitting the vibrations. (Figure 5)

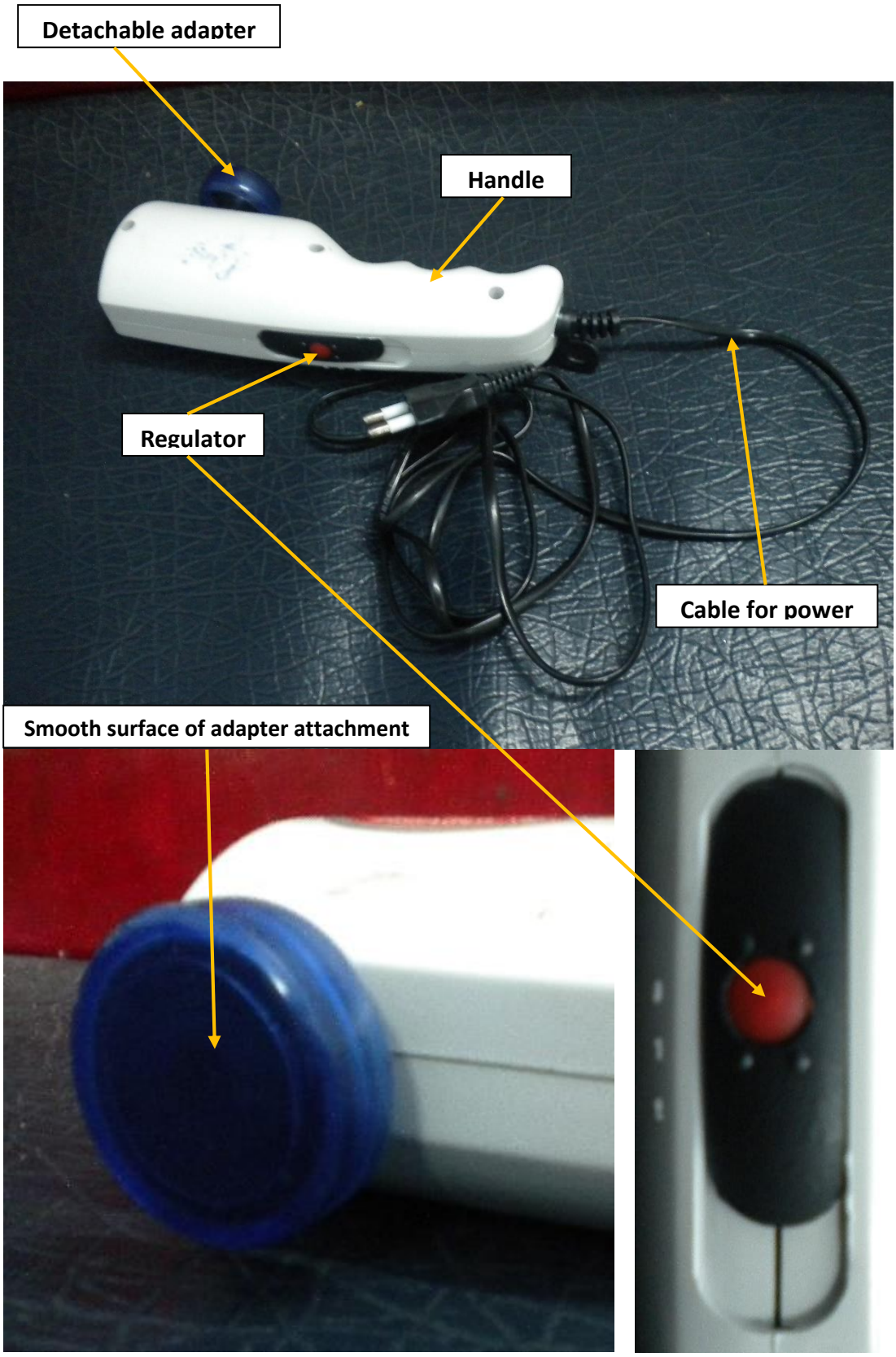

Figure 5: Hand held commercial vibrator

Calibration of frequency of vibrator:

The commercially available vibrator was calibrated using a force transducer and a data acquisition system (CMCdaq).

The force transducer was secured with multiple clamps with a table, fixed to the ground to prevent displacement during the procedure. Then the force transducer was connected to the CMCdaq and real time recording was obtained by the CMCdaq software in the computer. Then vibrator was connected to power and put at the regulator 1 frequency. The vibrating instrument is then placed over the force transducer. Vibrator was hold lightly over the force transducer to prevent displacement of transducer and also to prevent error in the recording due to manual force applied on the transducer. The recording of the force transducer was saved in the CMCdaq software for analysis. The same procedure was followed when the vibrator was put at regulator 2 frequency.

The analysis of the frequency was done by CMCdaq data analysis software. The vibrator caused periodic change of force on the transducer. This periodic change was actually at the frequency of the vibrator at which it was vibrating. The frequency of the instrument was then calculated by spectral analysis through CMCdaq software. The frequency of the low speed of vibration of the instrument was found to be 50 Hz (Figure 6) and the frequency of the high speed of vibration was 100 Hz (Figure 7).

The lower speed of vibration of 50 Hz frequency (low speed, at regulator point 1) of the portable vibrator was used to apply vibration therapy in the present study.

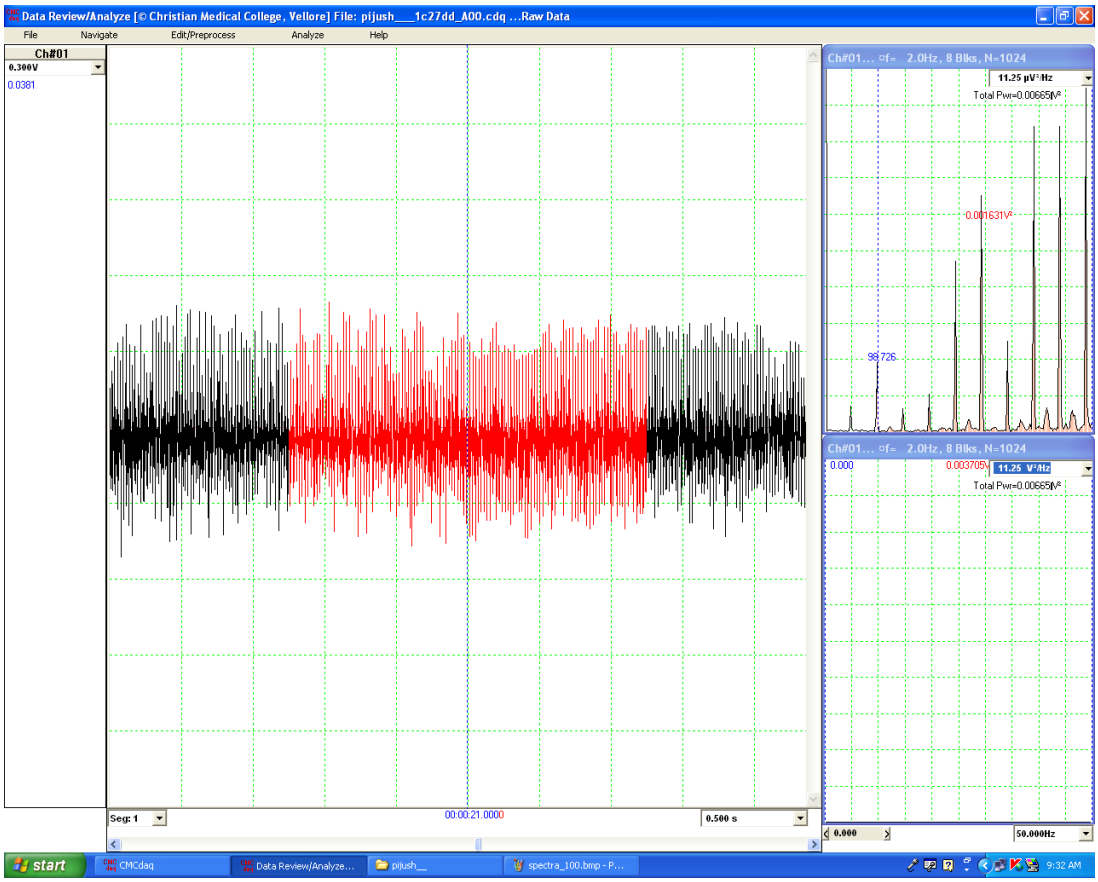

Figure 6: Spectral analysis of Vibrator frequency through CMCdaq software. Recorded using a force transducer. Showing 50 Hz frequency for the low speed (Regulator 1).

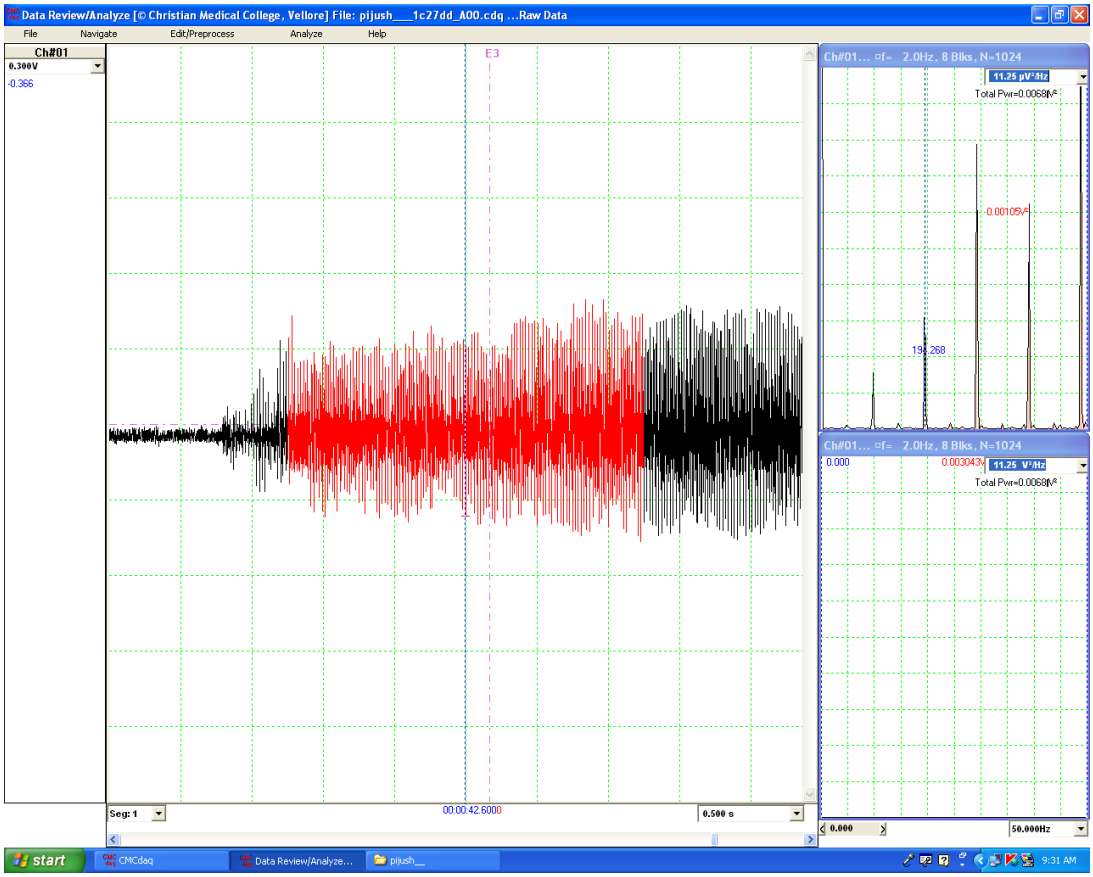

Figure 7: Spectral analysis of Vibrator frequency through CMCdaq software. Recorded using a force transducer. Showing 100 Hz frequency for the high speed (Regulator 2).

Protocol for vibration therapy:

Palmar vibration was given at 50 Hz, with the portable vibrator set at the lower frequency and with the smooth surface attachment connected to it. The vibration was applied on the palmar surface of both hands of the CP patients such that vibrations of 30 sec duration was interspersed with rest periods of 30 sec on each palm, alternately. Thus when one palm was getting 30 sec rest, the other palm was getting 30 sec of vibration. This was repeated till each palm got a total of 5 minutes of vibration per day. Vibration therapy was given in this manner daily, for 5 days a week, for 4 weeks

to the CP patients of the intervention group. The vibration therapy was administered by the occupational therapist along with other routine therapy and in the same therapy room as all the patients.

Procedure for administering the vibration therapy:

The patient was made to sit comfortably on a stool or chair. (Figure 8) Those patients who could not sit properly, were given suitable support to aid them to sit properly. The portable vibrator is then fitted with the detachable adapter. The attachment with the smooth surface was fitted to the adapter of the instrument. The vibrator is shown to the patient and the patient is allowed to hold it to become familiarised with it and to relieve any apprehension. Once the patient was comfortable with the instrument, the vibrator was taken back by the occupational therapist. The vibrator was then connected to the power source and switched on to the low speed (regulator 1). The patent was asked to stretch out one hand opening the fist to expose the palmar surface of hand. The dorsum of hand was supported either by the hand of the therapist or was kept on the soft pillow. With the vibrator vibrating, the adapter was then placed on the patient's palm. At the onset of touching the palm with the vibrator, the stop watch was simultaneously switched on to time the duration of vibration therapy. The patient is encouraged to close the fist over the vibrating adapter so as to hold it in the hand. If the patient does not close the fist over the vibrator, then the vibrating head was slowly moved in a circular manner all over the palm including the fingers. This was continued for 30 seconds. After 30 seconds the vibrator is placed on the other palm of the patient, following the same procedure. In this way, each of palm is given 30 seconds of vibration and 30 seconds of rest alternately till each palm gets a total 5 minutes of vibration therapy.

The vibrator was then disconnected from the power source.

This cycle of therapy was given for 5 days a week and for a total of four weeks.

The Intervention group also received the standard therapy, in addition to the vibration therapy.

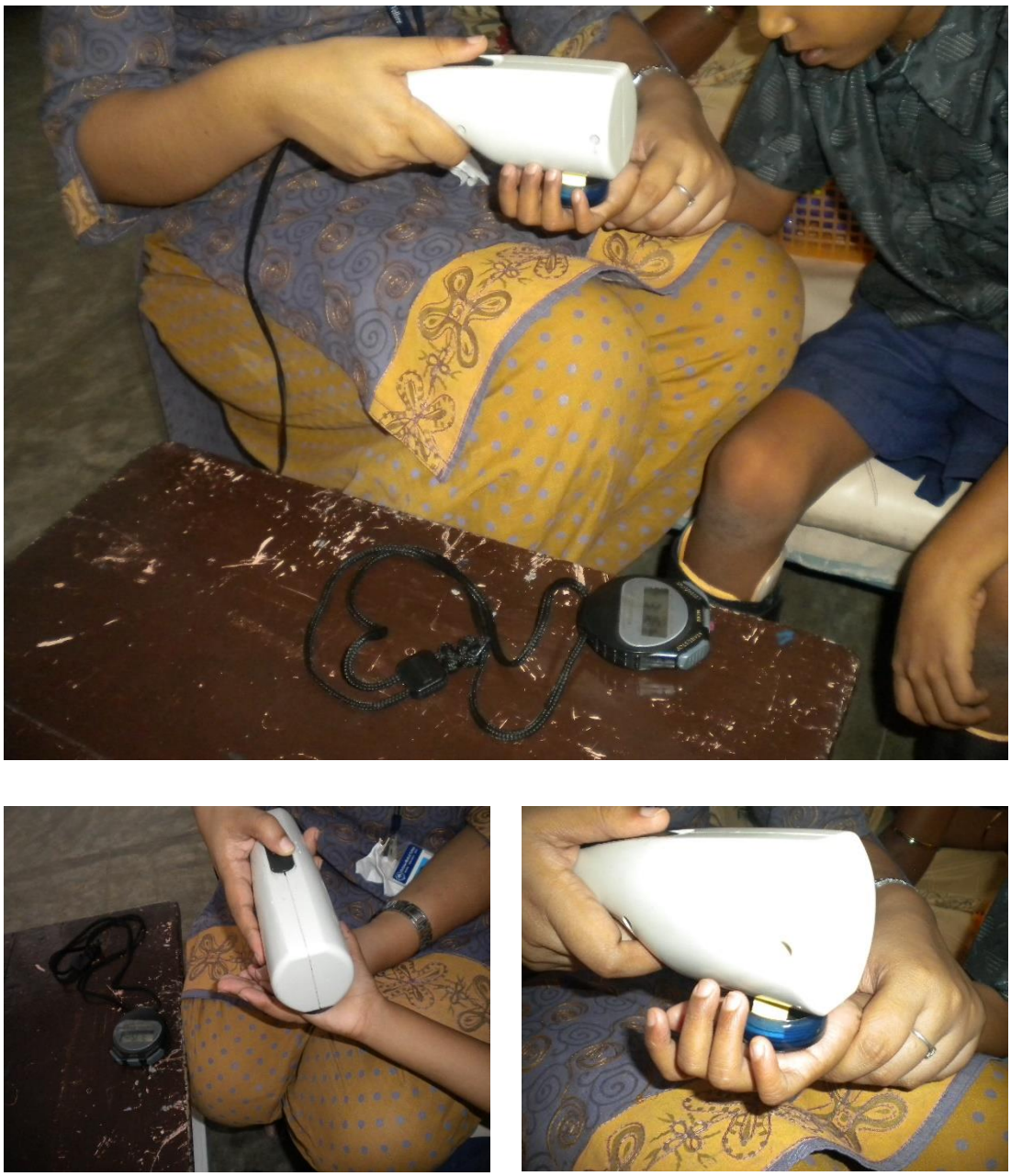

Figure 8: Intervention procedure

Control group:

The patients in the control group were allowed to hold the vibrator in their hand as a toy without applying the vibration and without connecting the vibrator to the electrical supply. This was done to ensure that there was no bias due to the novelty effect of the patients in the intervention group being given therapy with a new instrument.

In addition to vibration therapy, the intervention group also received the standard therapy which was routinely given to all in-patients with CP.

The control group, however, received standard therapy alone.

Standard Therapy:

This consisted of the combined therapy standardised for CP patients and instituted by the department of Physical Medicine and Rehabilitation for the treatment of in-patients with CP. It consists of a combination of occupational therapy, physiotherapy, speech therapy and drug therapy if needed.

Occupational therapy: It involves 14.5 hours of therapy per week, where the patient is trained in the following aspects.

Training in Balance is given in the sitting, standing and kneeling postures.

Training is also given to improve the gross motor skills. These are rolling, sitting, standing, transferring from one place to another.

To improve Hand function like reach, grasp, pinch, hand manipulation of objects and hand writing, appropriate training is given.

ADL training is a form of occupational therapy where the patients are trained for activities needed for normal day to day activities. Some of the activities of daily living are eating, use of toilet, dressing, maintaining personal hygiene and walking.

Behaviour and cognitive therapy for patients having behavioural disorders and cognitive problems in addition to motor disorders.

Age appropriate games are played by the children improve all the movements together and to improve motor functions.

Sensory integration therapy is also given to children with cerebral palsy.

Physiotherapy: It involves 16.5 hours of therapy per week, where the patient is subjected to the following exercise regimes and activities.

Stretching exercises are carried out to improve spasticity. Stretching reduces the tone of the muscles and aids in facilitation of movements of joints. Strengthening exercises are done with weight/ resistance ± gravity for better outcome.

Active exercises for both upper and lower limb are done by the patients as a part of physiotherapy. This helps in reducing tone and gaining power of the muscle.

Trunk control exercise are given as physiotherapy for those who have difficulty in attaining an erect posture due to poor power of axial muscles.

Gait training is also done by parallel bar, walker and crutch. This also video recorded and periodically evaluated for improvement.

Speech therapy: Patients those have difficulty in articulation, speech therapy is applied on them for improving speech.

Drug therapy: Some patients need administration of drugs, mostly centrally acting muscle relaxants to reduce hypertonia and to facilitate movement.

POST-INTERVENTION ASSESSMENT:

Post intervention assessment was done on the day of completion of the four weeks of therapy or on the day after the therapy ended. The Box and Block test and Activities of Daily Living as assessed by Modified Barthel Index were repeated.

DEFAULTERS:

One patient in the control arm did not complete the therapy. The patient took voluntary discharge from the ward and left in the middle of therapy. Post intervention assessment could not be carried out on this patient. Therefore the data of this patient was not included in the analysis.

In 3 patients of the intervention group, the vibration therapy was extended to over 4 days as the patients had been ill.

STATISTICAL ANALYSIS:

Comparison of Pre- and post-intervention Box and block test scores [Median (inter-quartile ranges)] and Modified Barthel Index scores [Median (inter-quartile ranges)] were analysed using Wilcoxon signed rank test. Inter group analysis of Box and Block Test score Median [(inter-quartile ranges)] and Modified Barthel Index score [Median (inter-quartile ranges)] were calculated using Mann Whitney U test. P value of < 0.05 was considered as statistically significant.

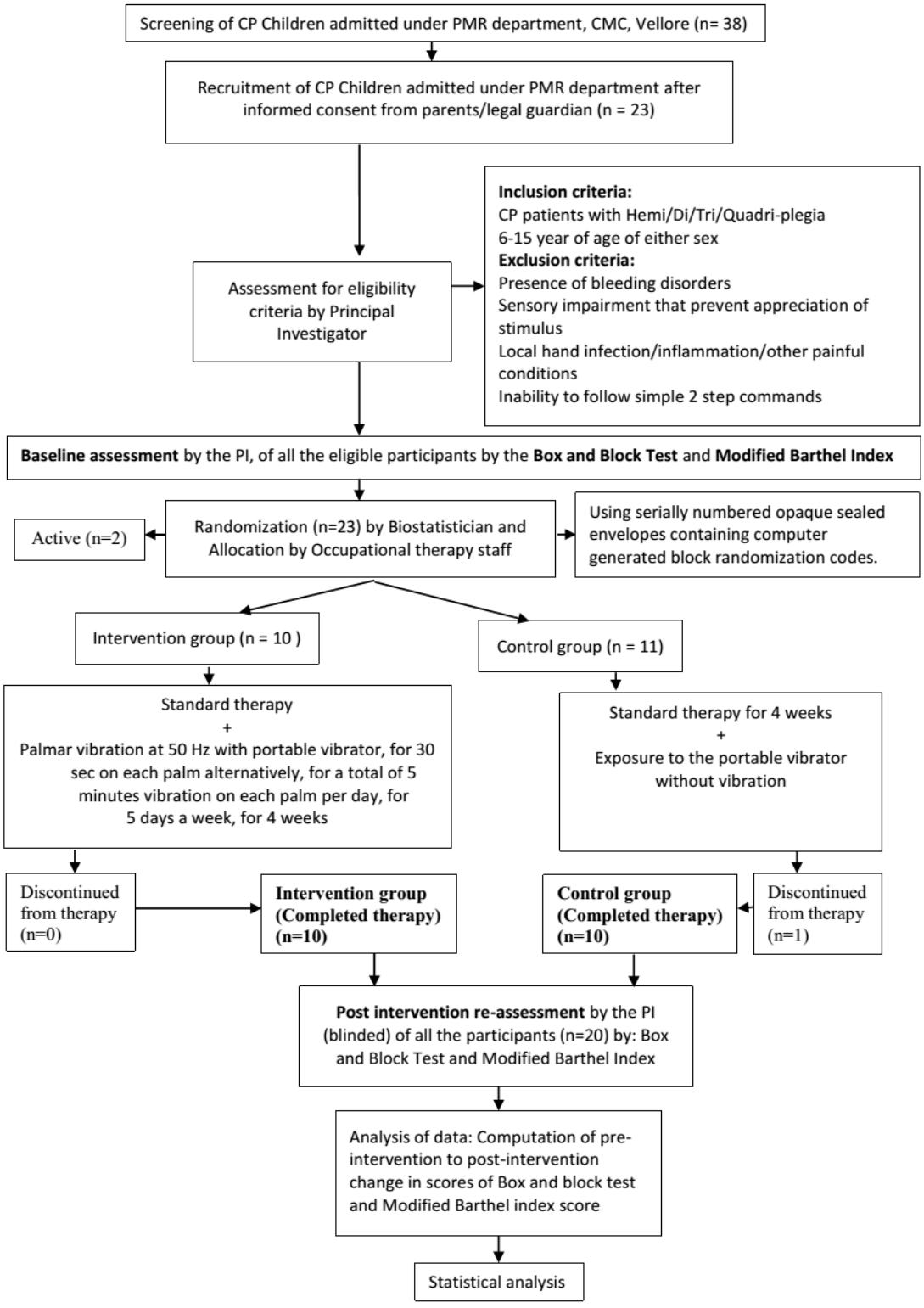

Figure 9: Detailed diagrammatic algorithm of study method

RESULTS

RESULTS:

An interim analysis of the ongoing randomised controlled trial was done, the results of which are given below. The interim analysis was done after obtaining permission from the Institutional review board.

Subjects:

A total of 38 CP patients admitted in the department of Physical medicine and rehabilitation were screened as of date. Of these, 23 patients were found to be eligible for recruitment as per the stated inclusion and exclusion criteria, and were invited to participate in the study. All the 23 patients enrolled into the study after giving written informed consent. The consent was given either by the patients or the parents. The enrolled patients were randomized and allocated into either the control group or the treatment group. Of the 23 patients enrolled till now, 20 completed the study, one patient discontinued from study and 2 patients are yet to complete the study (Figure 10). The interim analysis of the data collected from the twenty patients who have completed the study is reported here. The interim analysis was done after obtaining permission from Institutional review board. Figure 10 gives the flow chart of the study to date, according to the Consolidated Standards of Reporting Trials (CONSORT).

Dropouts:

Of the 21 patients randomised, one patient discontinued from the study. Thus the dropout rate is about 4.8%. The patient who dropped out was recruited and randomized, but requested early discharge for some personal reason and left before completion of therapy.

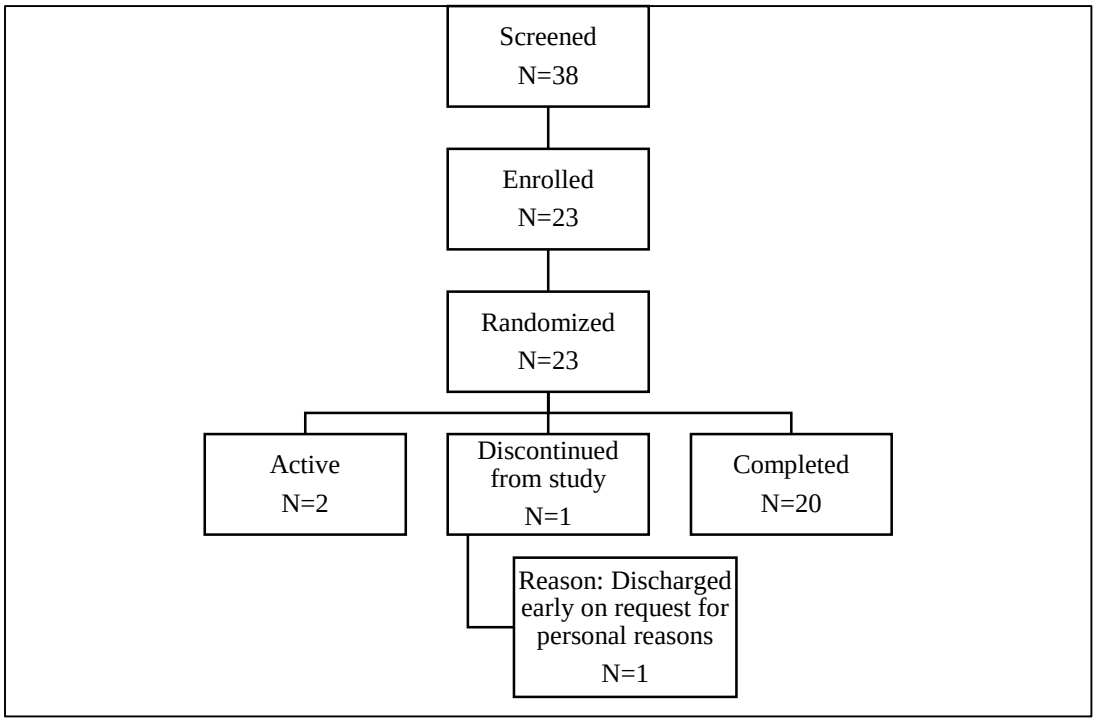

Figure 10: Flow chart of study till date, as per the CONSORT statement

Demography of participants:

Of the 20 patients who completed the study, 10 were in the control group and 10 were in the intervention group (Table 2). The age of the participants in the control group was 10.6±2.99 years (mean±SD) and that of the test group was 10±3.42 years (mean±SD). (Table 2; Figure 11) In both groups, there were 6 male (60%) and 4 female (40%) participants. (Table 2; Figure 12)

Of the 10 patients in the intervention group 8 had right hand dominance (80%) and 2 had left hand dominance (20%). In the intervention group 7 had right hand dominance (70%) and 3 had left hand dominance (30%). (Table 2; Figure 13)

In the intervention group there were 4 Spastic diplegic CP (40%), 2 Spastic triplegic CP (20%) and 4 Spastic quadriplegic CP (40%). There were also one Ataxic subtype (10%) in the intervention group. In the control group there were 1 spastic hemiplegic CP (10%), 4 Spastic diplegic CP (20%), 2 Spastic triplegic CP (30%) and 4 Spastic

quadriplegic CP (40%). (Table 2; Figure 14) There were also 2 patients who had dystonia in addition (20%) (Table 2; Figure 15). In the intervention group there were 2 patients who had seizure disorder (20%) and one patient had obesity (10%) as comorbidities. In the control group there were 2 seizure disorder (20%), one mental retardation (10%), one behavioural problem (10%), and one strabismus (10%) patients. (Table 2)

Table 1: Demographic and clinical data of individual subjects at the time of recruitment (N=20)

Sl No.	Age (Years)	Sex(M/F)	Dominant Hand (R/L)	Diagnosis-classification	Co-morbidities
1	6.5	M	R	Spastic Triplegic CP	Obesity, Seizure disorder
2	15	M	R	Spastic Quadriplegic CP	Seizure disorder
3	14	M	R	Spastic Quadriplegic CP	Strabismus
4	9	M	R	Spastic Quadriplegic CP	Post encephalitic
5	7	F	R	Spastic Quadriplegic CP	Ataxia, Seizure disorder
6	10	F	R	Spastic Diplegic CP	Nil
7	7	M	R	Spastic Diplegic CP	Nil
8	10	F	L	Spastic Hemiplegic CP	Dystonia with MR
9	12	M	R	Spastic Triplegic CP	Dystonia
10	9	F	R	Spastic Diplegic CP	Nil
11	8	F	L	Spastic Quadriplegic CP	Nil
12	14	F	R	Spastic Triplegic CP	Nil
13	11	F	R	Spastic Triplegic CP	Nil
14	12	M	R	Spastic Triplegic CP	Nil
15	6.5	M	R	Spastic Quadriplegic CP	Nil
16	15	F	L	Spastic Diplegic CP	Nil
17	14	M	L	Spastic Triplegic CP	Nil
18	7	M	R	Spastic Quadriplegic CP	Seizure disorder, Behavioural problem
19	13	M	L	Spastic Triplegic CP	Nil
20	6	M	R	Spastic Diplegic CP	Nil

Table 2: Demography and functional classification of study participants in the two groups (N=20)

Variables	Intervention Group (N=10)	Control Group (N=10)
Age(Years) Mean±SD	10±3.42	10.6±2.99
Sex	Male - 6 (60%) Female - 4 (40%)	Male - 6 (60%) Female - 4 (40%)
Diagnosis		
Spastic Hemiplegic CP	0 (0%)	1 (10%)
Spastic Diplegic CP	4 (30%)	2 (20%)
Spastic Triplegic CP	2 (40%)	3 (30%)
Spastic Quadriplegic CP	4 (30%)	4 (40%)
Other Subtypes of CP		
Ataxia	1 (10%)	0 (0%)
Dystonia	0 (0%)	2 (20%)
Co morbidities		
Seizure disorder	2 (20%)	2 (20%)
Mental Retardation	0 (0%)	1 (10%)
Behavioural problems	0 (0%)	1 (10%)
Strabismus	0 (0%)	1 (10%)
Obesity	1 (10%)	0 (0%)
Dominant Hand		
Right	8 (80%)	7 (70%)
Left	2 (20%)	3 (30%)

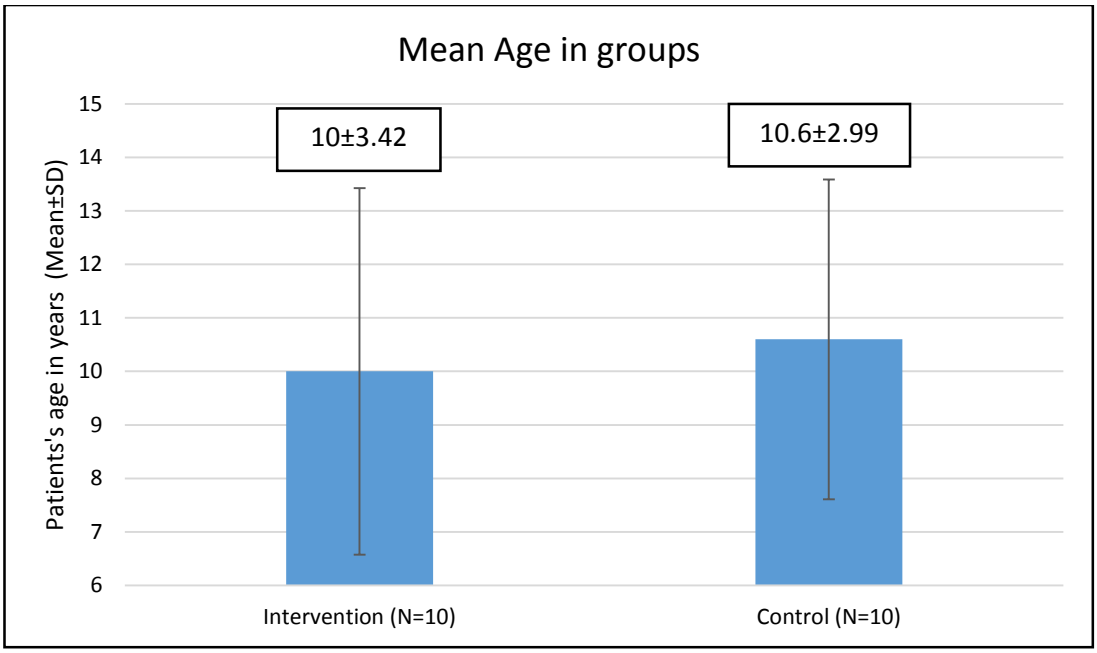

Figure 11: Age of patients in Intervention and Control group

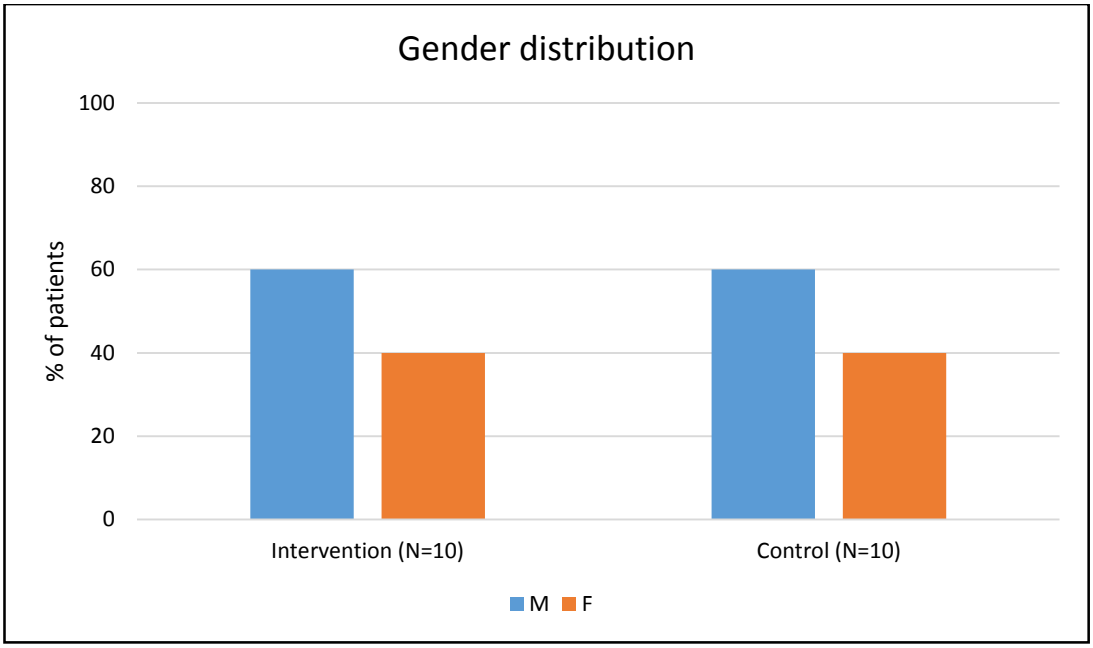

Figure 12: Gender distribution of Intervention and Control group (M=Male; F= Female)

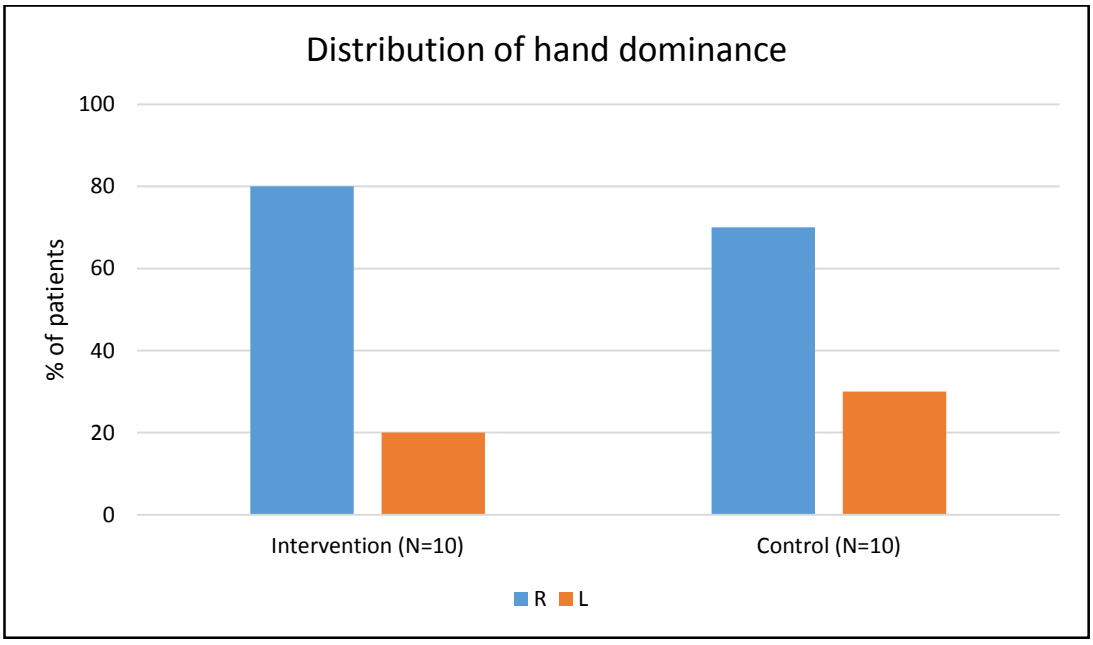

Figure 13: Distribution of hand dominance in Intervention and Control group

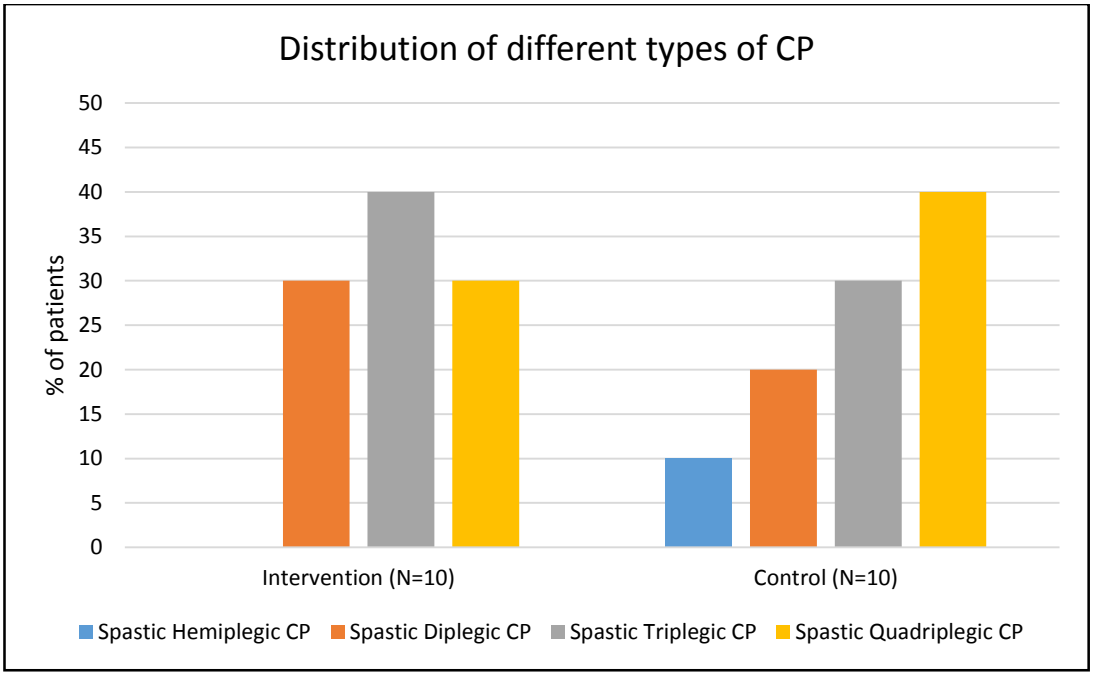

Figure 14: Distribution of different types of CP in Intervention group and Control group

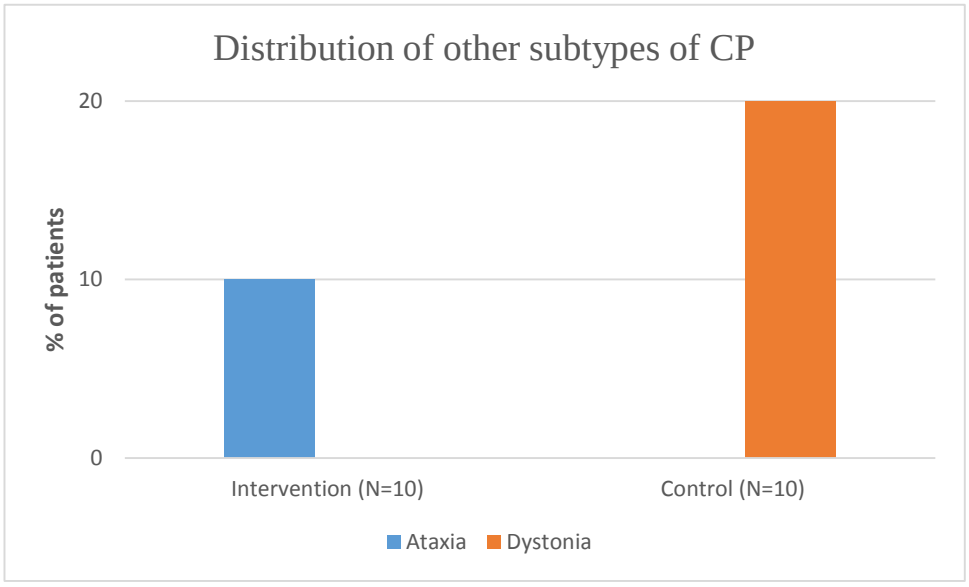

Figure 15: Distribution of other subtypes of Cerebral palsy (CP) in Intervention and Control group

The severity of the disease of the recruited patients were assessed by the Modified Barthel Index score by assessing the activities of daily living. The pre intervention assessment showed that 20% and 50% of the patients in the intervention and control group respectively had Total dependency. Thirty percent of the patients in the intervention group were severely dependent, while 40% in the control group had the same level of dependency. There were 40% of patients who were moderately dependent, in the intervention group only. Ten percent of patients each in intervention and control group had mild dependency. No patient with minimal dependency was there in either of the group. (Figure 16)

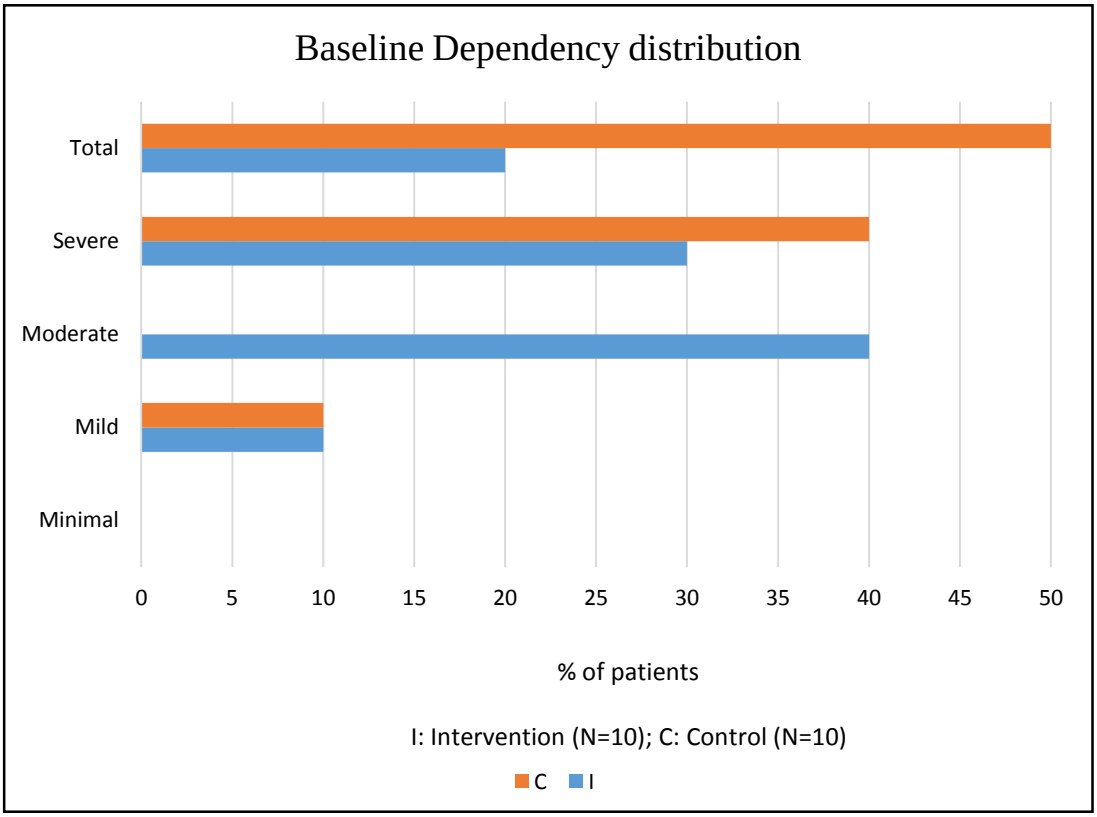

Figure 16: Distribution of baseline dependency needs in Intervention and Control Group.

Table 3: Pre-intervention and Post-intervention outcome measures of Intervention group (N=10)

Sl No.	BOX AND BLOCK TEST SCORE						Modified Barthel Index Score			Dependency needs classification	
	Dominant Hand			Non-Dominant Hand							
	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff	Pre	Post
1	10	16	6	8	14	6	31	31	0	Severe	Severe
4	17	24	7	10	9	-1	42	53	11	Severe	Moderate
5	17	25	8	6	16	10	62	70	8	Moderate	Moderate
7	17	24	7	12	20	8	38	38	0	Severe	Severe
10	14	22	8	12	19	7	60	60	0	Moderate	Moderate
12	25	27	2	15	18	3	56	56	0	Moderate	Moderate
14	28	31	3	24	30	6	54	57	3	Moderate	Moderate
15	0	0	0	0	0	0	10	10	0	Total	Total
16	32	44	12	32	39	7	83	91	8	Mild	Minimal
17	20	26	6	3	6	3	4	4	0	Total	Total

Table 4: Pre-intervention and Post-intervention outcome measures of Control group (N=10)

Sl No.	BOX AND BLOCK TEST SCORE						Modified Barthel Index Score			Dependency needs classification	
	Dominant Hand			Non-Dominant Hand							
	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff	Pre	Post
2	10	12	2	0	0	0	20	20	0	Total	Severe
3	19	31	12	4	12	8	32	34	2	Severe	Total
6	28	36	8	20	28	8	81	81	0	Mild	Severe
8	15	17	2	12	13	1	20	20	0	Total	Mild
9	25	24	-1	0	1	1	18	18	0	Total	Total
11	9	11	2	7	8	1	22	22	0	Total	Total
13	33	34	1	9	11	2	34	34	0	Severe	Total
19	11	12	1	5	5	0	18	18	0	Total	Severe
20	37	37	0	6	3	-3	39	39	0	Severe	Total
21	26	27	1	25	25	0	40	40	0	Severe	Severe

Pre intervention Box and Block test score [median (inter-quartile ranges)] of the dominant and non-dominant hands in the intervention group were 17 (13, 25.75) and 11 (5.25, 17.25) respectively. Post intervention, the same scores were 24.5 (20.5, 28) and 17 (8.25, 22.5) for dominant and non-dominant hands respectively in the intervention group. (Table 5; Figure 17; Figure 18)

Pre intervention Modified Barthel Index score [median (inter-quartile ranges)] in the intervention group was 48 (25.75, 60.5). Post intervention, the same scores was 54.5 (25.75, 62.5) in the intervention group. (Table 5; Figure 19)

Comparison of pre- and post-intervention Box and Block test score in the intervention group had shown significant difference both in dominant hand (p=0.008) (Table 5; Figure 17) and non-dominant hand (p=0.011) (Table 5; Figure 18). But comparison of pre- and post-intervention Modified Barthel Index score in the intervention group did not show any significant difference (p=0.066) (Table 5; Figure 19)

Table 5: Comparison of pre-intervention and post-intervention parameters in the Intervention group (N=10)

Variable	Pre-intervention	Post-intervention	P value
BBT Score in DH	17 (13, 25.75)	24.5 (20.5, 28)	0.008*****
BBT Score in NDH	11 (5.25, 17.25)	17 (8.25, 22.5)	0.011$^{\#}$
MBI Score	48 (25.75, 60.5)	54.5 (25.75, 62.5)	0.066

Values are Median, (IQR); BBT - Box and Block Test; DH - Dominant hand; NDH - Non-dominant hand; MBI- Modified Barthel Index.

*** P < 0.01, $^{\#}$ P< 0.05 (Wilcoxon signed rank test)**

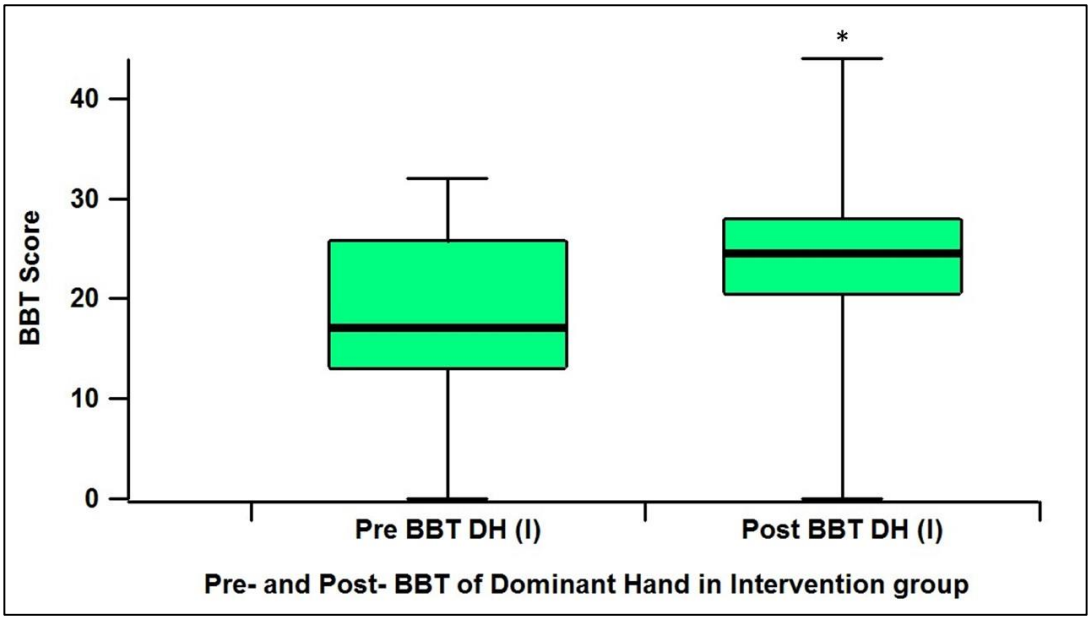

Figure 17: Box Plot showing the comparison of Pre and Post Box and Block Test (BBT) scores in the Intervention group in DH (Dominant Hand); (N=10)
*** Significantly different from the pre-intervention score, P=0.011, Wilcoxon Signed rank Test**

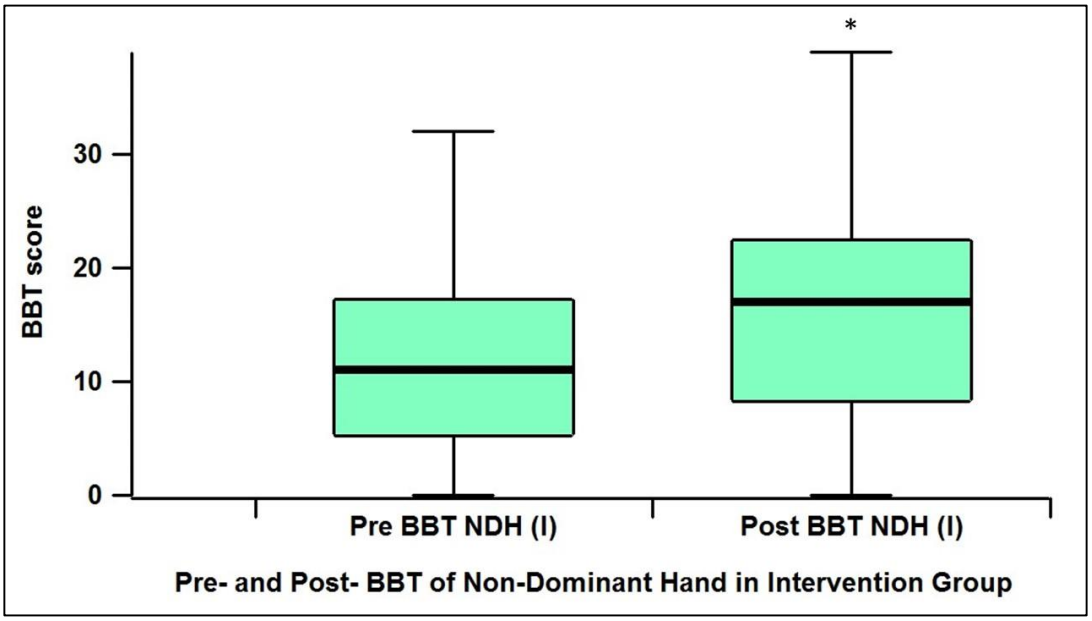

Figure 18: Comparison of Pre and Post Box and Block Test (BBT) scores in the Intervention group in NDH (Non-Dominant Hand); (N=10)
*** Significantly different from the pre-intervention score, P=0.008, Wilcoxon Signed rank Test**

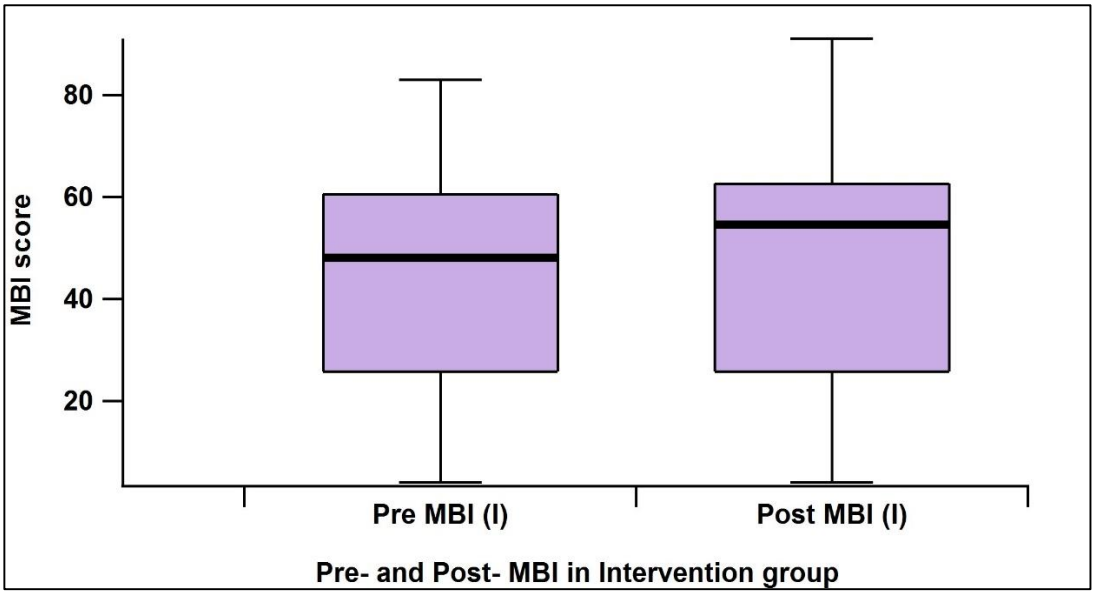

Figure 19: Comparison of Pre and Post-intervention Modified Barthel Index (MBI) Scores in the Intervention (I) group; (N=10). No significant difference with Wilcoxon Signed rank Test

Pre intervention Box and Block test score [median (inter-quartile ranges)] of the dominant and non-dominant hands in the control group were 22 (10.75, 29.25) and 6.5 (3, 14) respectively. Post intervention, the same scores were 25.5 (12, 34.5) and 9.5 (2.5, 16) for dominant and non-dominant hands respectively in the control group. (Table 6; Figure 20; Figure 21)

Pre intervention Modified Barthel Index score [median (inter-quartile ranges)] in the control group was 27 (19.5, 39.25). Post intervention, the same scores was 28 (19.5, 39.25) in the control group. (Table 6; Figure 22)

Comparison of pre- and post-intervention Box and Block test score in the control group had shown significant difference in the dominant hand (p=0.016) (Table 6; Fig 20) but there were no significance in the non-dominant hand (p=0.125) (Table 6; Figure 21). Comparison of pre- and post-intervention Modified Barthel Index score in the control group did not show any significant difference (p=0.317) (Table 6; Figure 22)

Table 6: Comparison of pre-intervention and post-intervention parameters in the Control group (N=10)

Variable	Pre	Post	P value
BBT Score in DH	22 (10.75, 29.25)	25.5 (12, 34.5)	0.016*
BBT Score in NDH	6.5 (3, 14)	9.5 (2.5, 16)	0.125
MBI Score	27 (19.5, 39.25)	28 (19.5, 39.25)	0.317

Values are Median, (IQR); BBT - Box and Block Test; DH - Dominant hand and NDH - Non-dominant hand; MBI- Modified Barthel Index scores.
*** P < 0.05 (Wilcoxon signed rank test)**

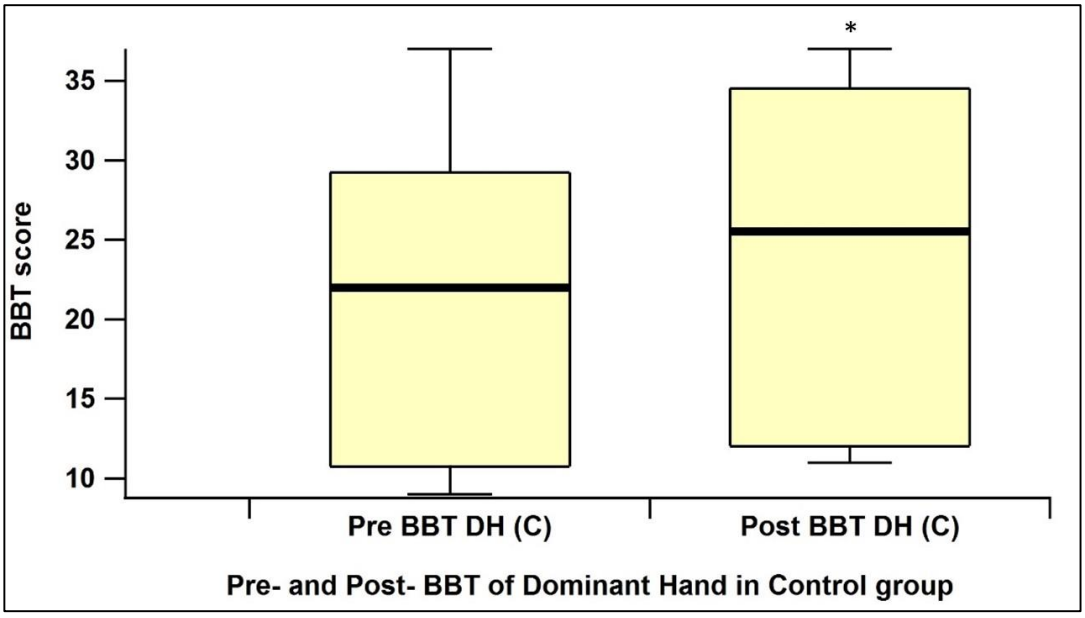

Figure 20: Box Plot showing the comparison of Pre and Post Box and Block Test (BBT) scores in the Control group in DH (Dominant Hand); (N=10)
*** Significantly different from the pre-intervention score, p=0.016, Wilcoxon Signed rank Test**

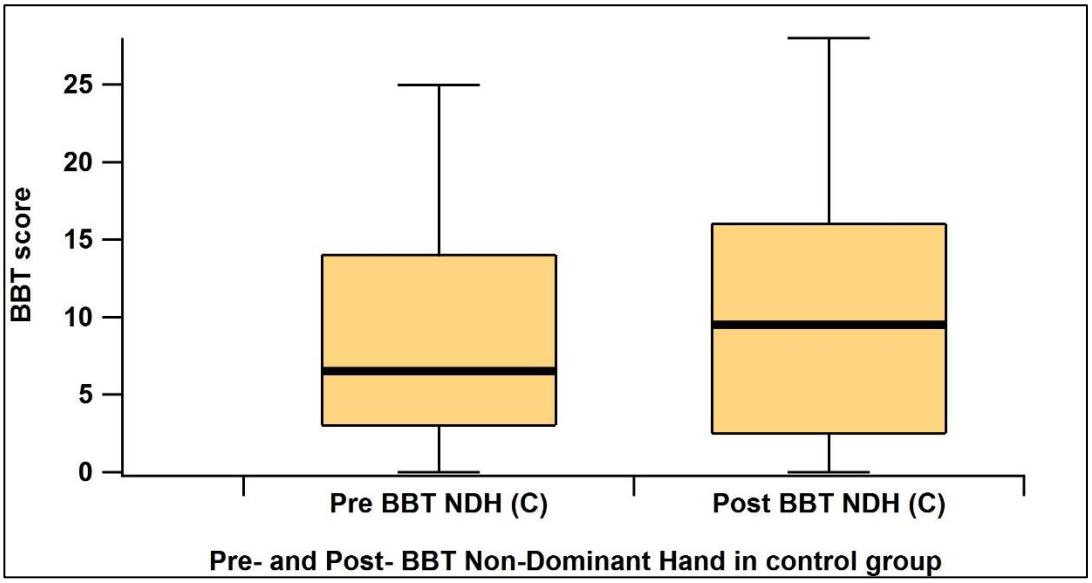

Figure 21: Box Plot showing the comparison of Pre and Post Box and Block Test (BBT) scores in the Control group in NDH (Non-Dominant Hand); (N=10). No significant difference with Wilcoxon Signed rank Test

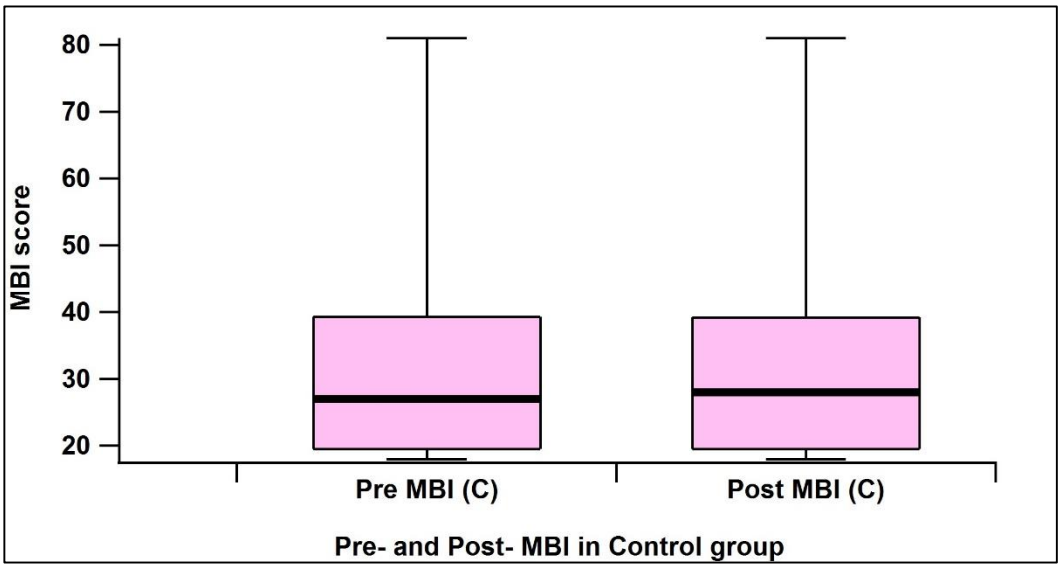

Figure 22: Comparison of Pre and Post-intervention Modified Barthel Index (MBI) Scores in the Control (C) group; (N=10). No significant difference with Wilcoxon Signed rank Test

Inter group comparison of Box and block test score had shown no significant difference between intervention and control in both dominant (p=0.062) (Table 7; Fig 123 and non-dominant hands (p=0.118) (Table 7; Figure 24). Inter group comparison of Modified Barthel Index also did not show any significant difference (p=0.091) (Table 7; Figure 25).

The Box and plot graph of the Pre- and Post-intervention difference of Box and Block scoring [median (inter-quartile ranges)] showed a definite higher median both in dominant hand and non-dominant hand (Figure 23 & Figure 24).

Table 7: Comparison of the change in parameters between Intervention group and control group

Variables	**Intervention Group (N=10)**	**Control Group (N=10)**	**P value**
Pre-Post difference in BBT Score (DH)	6.5 (2.75, 8)	1.5 (0.75, 3.5)	0.062
Pre-Post difference in BBT Score (NDH)	6 (2.25, 7.25)	1 (0.00, 3.5)	0.118
Pre-Post difference in MBI score	0 (0.00, 8)	0 (0.00, 0.00)	0.091

Values are Median, (IQR); BBT - Box and Block Test; DH – Dominant Hand; NDH - Non-dominant hand; MBI- Modified Barthel Index. No significant difference with Mann Whitney U test.

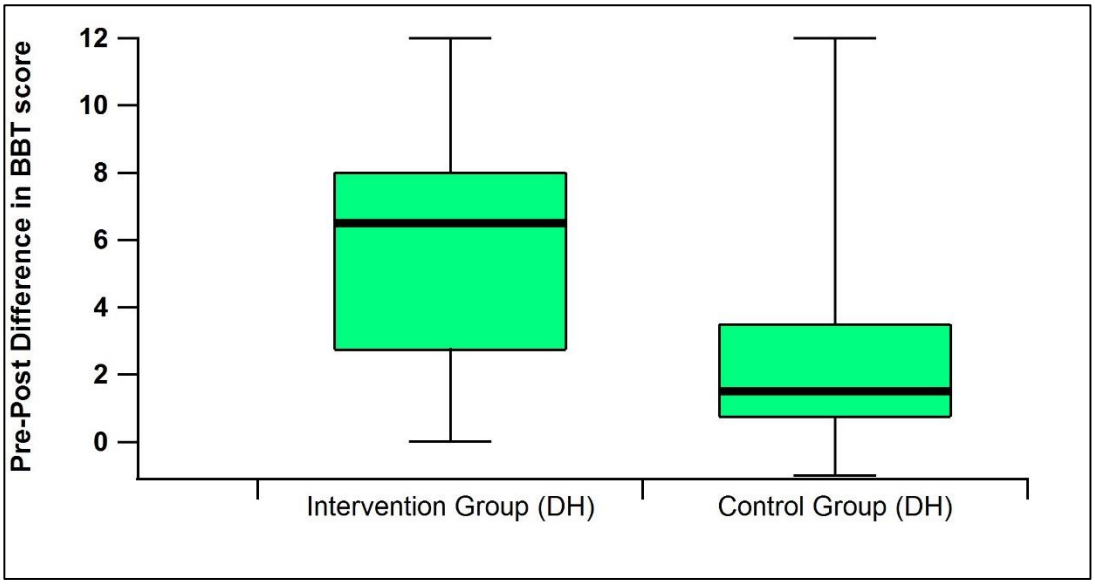

Figure 23: Box Plot showing comparison of the change (Pre and Post difference) of the Box and Block test (BBT) scores between Intervention (I) and Control (C) group in dominant hand (DH). No significant difference with Mann Whitney U test

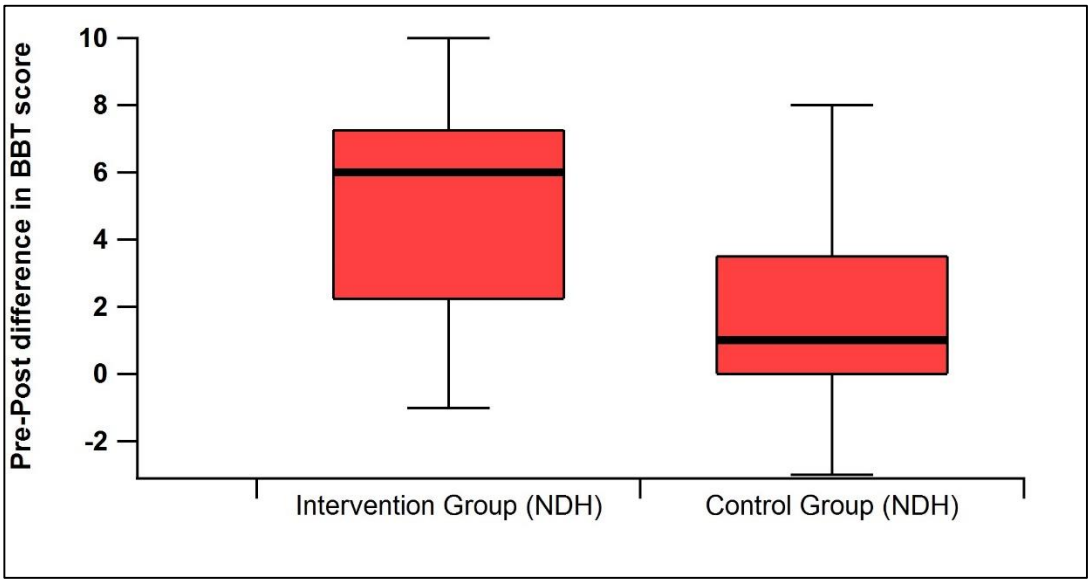

Figure 24: Box Plot showing comparison of the change (Pre and Post difference) of the Box and Block test (BBT) scores between Intervention (I) and Control (C) group in Non-dominant hand (NDH). No significant difference with Mann Whitney U test

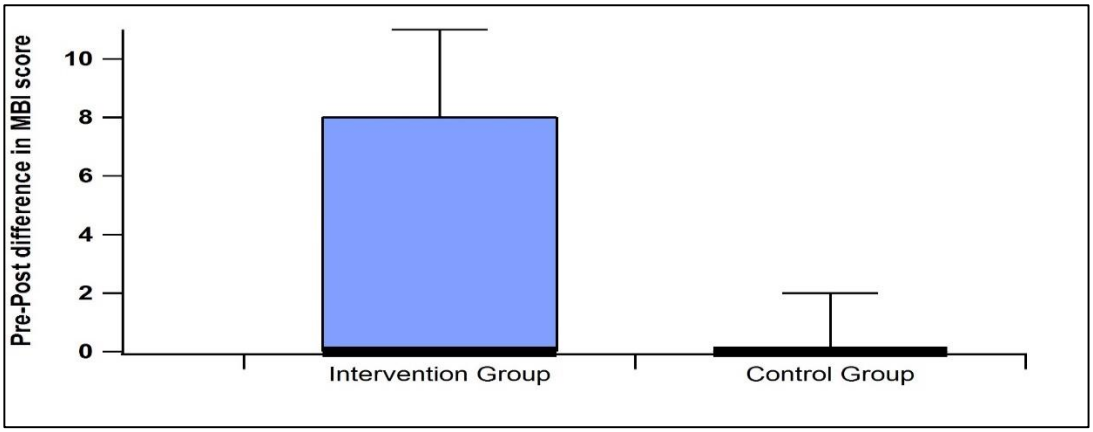

Figure 25: Box Plot showing comparison of the change (Pre and Post difference) in Modified Barthel Index (MBI) scores between Intervention and Control group. No significant difference with Mann Whitney U test

Post-intervention dependency needs classification based on MBI scoring reveals that 2 patients (20%) were reclassified to one higher stage. There were, however, no patient who could have been reclassified in the control group. (Figure 26)

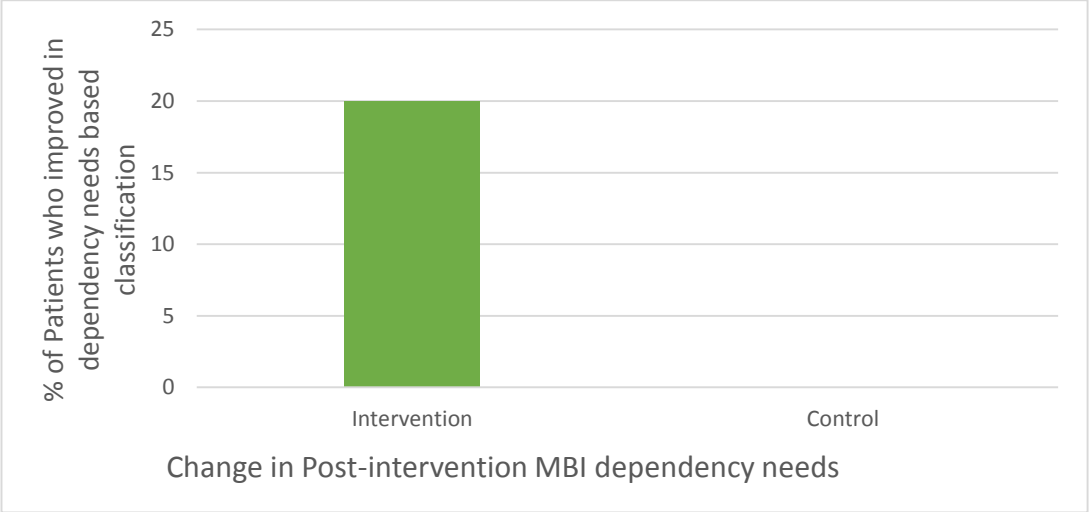

Figure 26: Distribution of patients based on improvement in dependency needs based classification in Intervention and control group

DISCUSSION

DISCUSSION:

There is currently no cure for CP and treatment is mainly supportive to improve quality of life by improving functional ability either by improving motor function or by the use of assistive devices or techniques (109). Management of cerebral palsy is multidisciplinary (110). None of the single therapy alone is sufficient to manage these patients. Aim of management is to give a near normal status to patient as far as possible. That is why different approaches are sought to improve different parameters of the disease condition. Improving motor function is one of the most important aims in management since this is essential for becoming self-efficient to carry out work for earning a living. To improve quality of life and activities of daily living, ensuring a good hand function is one of the essential elements that needs to be addressed.

Improving motor cortical excitability by exploiting the property of neuroplasticity, motor hand function can be improved (3,165,166). Motor cortical excitability can be modulated by modulating the sensory cortex since there are multiple to and fro connections between them. Sensory stimulation has been shown to modulate the motor cortical excitability (155,165,166,169).

With this background, the present study was done administering local vibration therapy, a form of sensory stimulation, to both palms of CP children and the improvement in motor hand function was studied. The study was designed as a single-blinded randomized controlled trial where local vibration therapy was given only to the intervention group and standard conventional therapy was given to both the intervention and control group of cerebral palsy patients. Both groups were followed up for a period of 4 weeks, during which period the intervention was given.

The target sample size was 50 with 25 patients in each arm. The study is ongoing with active recruitment of patients. With the approval of the Institutional review board, an interim analysis of the study was done, to see the effectiveness of vibration therapy in patients in the intervention group. At the time of interim analysis, a total of 38 patients were screened, 23 patients were recruited into the study and 20 patients had completed the study. Details of trial at the time of interim analysis are given in Figure 10.

It was found that of the 20 CP patients who completed the study, 10 had been allocated to the Control group and 10 to the Intervention group. The primary outcome of the study was dexterity of the hand as measured by the Box and Block test. The secondary outcome was Activities of Daily Living as assessed by the Modified Barthel Index score. Both these were measured before and after 4 weeks of the study.

The findings of the interim analysis showed no statistically significant difference in the quantum of change of the primary or secondary outcomes between the intervention and control groups. Thus, the change in the Box and Block test score after intervention was not statistically different between the intervention and control group [Intervention group, Dominant hand 6.5 (2.75, 8); Control group, Dominant hand = 1.5 (0.75, 3.5), median (IQR); P = 0.062 and Intervention group, Non-dominant hand 6 (2.25, 7.25); Control group, Non-dominant hand = 1 (0.00, 3.5), median (IQR); P = 0.118] (Table 7; Figure 23; Figure 24). Similarly, the change in the ADL as gauged by the Modified Barthel Index score was not statistically significant across the 2 groups [Intervention group = 0 (0.00, 8); Control group = 0 (0.00, 0.00), median (IQR); P = 0.091]. (Table 7; Figure 25)

However, intra-group analysis revealed statistically significant improvement in the Box and Block test score of both the dominant and non-dominant hands of the

intervention group, when comparing the post-intervention test score with the pre-intervention test score [Dominant hand pre-intervention score = 17 (13, 25.75), post-intervention score = 24.5 (20.5, 28), median (IQR), P = 0.008; Non-dominant hand pre-intervention score = 11 (5.25, 17.25), post-intervention score = 17 (8.25, 22.5), median (IQR), P = 0.011] (Table 5; Figure 17; Figure 18). Conversely, in the Control group, intra-group analysis revealed statistically significant improvement in the Box and Block test score of only the dominant hand [Pre-intervention score = 22 (10.75, 29.25), Post-intervention score = 25.5 (12, 34.5), median (IQR); P = 0.016] (Table 6; Figure 20) and not in the non-dominant hand [Pre-intervention score = 6.5 (3, 14), Post-intervention score = 9.5 (2.5, 16), median (IQR); P = 0.125]. (Table 6; Figure 21).

The findings of the intra-group analysis of the Box and Block test scores point towards an effect of the intervention on improving motor function. As motor function of the non-dominant hand of the Intervention group improved but that of the Control group did not improve, it would be reasonable to postulate that the difference is contributed to by the Vibration therapy.

As both control and intervention groups were receiving conventional standard therapy in the form of various physiotherapy, occupational therapy and behavioural therapy, both groups are expected to show an improvement in hand function by the end of 4 weeks of the study period. So the finding of an improvement of hand dexterity of the dominant hand in both the groups is not a surprise, but is an expected finding and validates the efficacy of the conventional therapy. However, the improvement in the hand function of the dominant hand of the Intervention group was not significantly more than that of the dominant hand of the Control group. The same finding was

revealed when comparing the change in hand dexterity of the non-dominant hand between the groups.

Nonetheless, the finding of within group analysis, showing a significant improvement in dexterity of non-dominant hand in Intervention group, but not in the Control group is note-worthy. This result of current interim analysis hints that local palmar vibration therapy may be effective in improving motor hand function. This points towards the effectiveness of vibration therapy in improving motor functions in cerebral palsy children. This revealed that the function of the weaker hand (non-dominant) improved in those CP patients who received vibration therapy in addition to standard therapy, but not in those who received only standard therapy. Bilateral vibration therapy along with standard therapy may be a better way of management than standard therapy alone in improving motor function of weaker limb.

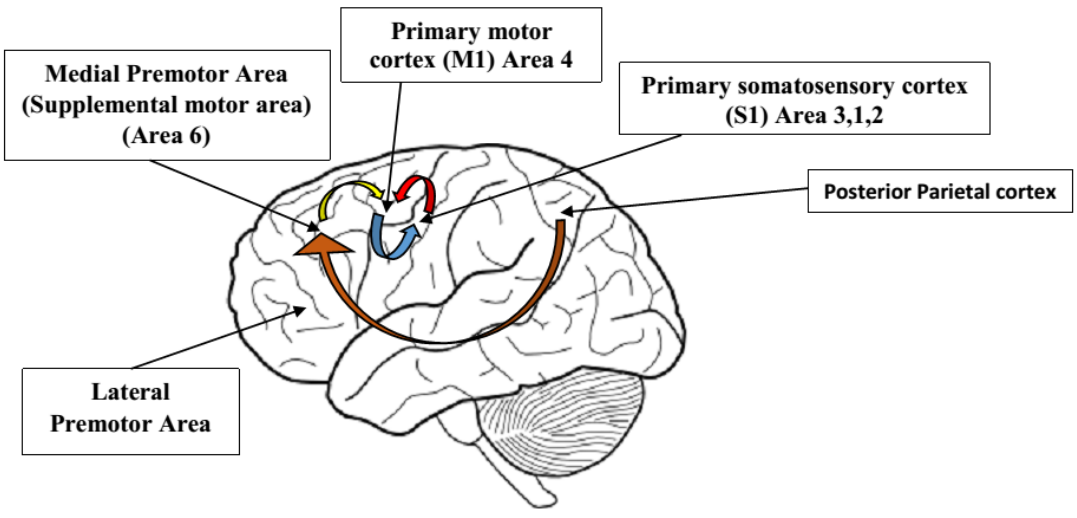

Figure 27: Sensory and motor cortical areas and their connections

The effectiveness of vibration therapy may be explained by the extensive to and fro connections between the sensory cortices and motor cortices (10). The primary motor cortex (M1) receives somatosensory afferents. The somatosensory input is relayed in such a fashion that it comes from an area which is homologous to the motor cortex (10). Since both the sensory and motor cortex are somatotopically organized, the sensory outputs from one area of sensory cortex transmits tactile and proprioceptive information which projects to the same functional area of representation of that region in the motor cortex (10,11,129). So the somatosensory area for hand representation sends tactile, vibration sense and proprioceptive inputs to the motor hand area which when excited causes movements of muscles of hands. All the inputs do not directly project to the motor cortex from the somatosensory area. Some sensory inputs are relayed through the thalamic relay nucleus to the motor cortex (10). The ventral posterolateral nucleus of thalamus is also somatotopically mapped like the somatosensory and motor cortices. So the relay is also organized somatotopically from somatosensory area of hand representation to the area of hand representation in the thalamus to the corresponding hand area of primary motor cortex (10).

The palmar vibration applied locally to both hands of CP patients of the Intervention group would have definitely served as a sensory input to the motor cortex of these patients. It may be postulated that this sensory input applied for 5 minutes daily, for 5 days a week, for 4 weeks initiated neuroplasticity in the motor cortex to aid in the motor improvement of hand function of the CP patients of the Intervention group. However, as both Intervention and Control group were receiving standard therapy, the contribution of vibration therapy may be submerged in the effect of the standard therapy. Further conclusions can be drawn only after the trial is completed and final analysis is done.

Nevertheless this interim analysis has given some useful information. From the results of the interim analysis it may be confidently stated that vibration therapy did not negatively impact the conventional therapy given to CP patients. Further the interim analysis gave an opportunity to validate the methods employed in the study against previously published reports.

The Box and Block test was used for assessing motor function in the CP patients of the present study. The Box and Block test is a simple, easy to administer, inexpensive test to assess manual dexterity in CP patients. Box and Block test results positively correlate with the MACS (Manual Ability Classification System) results in cerebral palsy patients (136). The Box and Block test has been validated in children in the age group of 6 – 19 years (128,132). The mean age of all the patients recruited into the study at the time of interim analysis was 10.5 ± 3.23 years (mean±SD). The oldest CP patient was 15 years old and the youngest was 6 years old. In the intervention group the mean age of the patients was 10 ± 3.423 years and in the control group it was 10.6 ± 2.98 years. There are also reports of studies which have used the Box and Block test to accurately assess hand function in CP children (128,136,138) of 6-19 years. The age group of patients of present study matched with these studies. The Box and Block test scores obtained by the interim analysis ranged from 0 to 44 (17±11.04, mean±SD) which is comparable to previous study done on patients of cerebral palsy, aged between 6 to 15 years (138).

Of the patients who completed the study at the time of interim analysis, 60% were male and 40% were female patients in both the intervention and control groups. A recent study conducted by the Centre for Disease Control and Prevention (CDC) in 2008, report in addition to other important epidemiological facts about cerebral palsy,

that the disease is more common in males than females (17). The gender distribution of the recruited CP patients, as observed in the interim analysis of the present study, is in line with this report (17). This is an indication that the study population of present study is representative of CP patients of the world.

All the patients in both intervention and control groups had spastic type of paralysis. This is in line with other studies which have reported that spastic type CP is more common and accounts for 77.4% of the cases (17). The distribution of different types of CP in the 2 groups was found to be in the similar range. Associated co-morbidities like Seizure disorders were present in both the groups to almost the same extent. Twenty percent of the patients in both intervention and the control group had seizure disorders.

The vibration protocol of the present study consisted of the application of local bilateral palmar vibration of 50 Hz vibration frequency. Previous studies have shown that vibration in the range of 25 to 80 Hz can improve the motor cortical excitability or motor function in subjects (3,139,165). Prior studies have administered vibration therapy for various durations ranging from single episode of application daily for 3 days, once weekly for 12 weeks, to 5 days a week for 6 months (3,125). In the present study protocol vibration therapy was applied for 5 days a week for 4 weeks.

The damage that occurs in the cortices of CP children are not always equal in extent on both sides. The damage to the 2 hemispheres may be asymmetric, such that one is more damaged than the other (170,171). Previous studies have shown that the better functioning motor cortex of one hemisphere can inhibit the excitability of the opposite worse hemisphere, through the phenomenon of inter-hemispheric inhibition (139,166,172). The preferential use of the dominant hand, sub served by the better

functioning motor cortex, for daily activities, can further increase the motor cortical excitability of the hemisphere dominant for motor function (139). The superior motor cortex in turn can inhibit the excitability of the weaker cortex through the phenomenon of inter-hemispheric inhibition through transcallosal connections (139). It has been reported that sensory inputs in the form of vibration stimuli, applied to the less mobile hand can negate the effect of inter-hemispheric inhibition and reduce the negative impact that the superior cortex has on the weaker hemisphere (139). The results of the current study corroborate this finding. Unilateral transcranial magnetic stimulation of the suppressed cerebral motor cortex or the disadvantaged motor cortex has been shown to improve the motor function of the contralateral relatively immobile limb. On the other hand, transcranial magnetic stimulation of the normal healthy motor cortex further attenuated the function of the immobile limb, through inter-hemispheric inhibition (139,166,172,173). In the present study, vibration was applied on both the palms of the patients. This would have stimulated both the motor cortices (154,166). The better functioning motor cortex could have depressed the function of the worse side and thereby reduced the motor functioning of the more paretic limb. However, this did not happen in the CP patients who received the intervention, rather the motor functioning of the weaker hand also improved in them. The bilateral improvement of motor hand function in the intervention group may be accounted for by the bilateral application of palmar vibration, adopted in the study protocol for the intervention. Thus, interim analysis of the study reveals that the protocol used in the study for the application of vibration therapy, has overcome the effects of inter-hemispheric cortical inhibition, and was useful in producing bilateral improvement in hand function in the intervention group.

The finding that non-dominant hand function did not improve with Conventional therapy alone, raises questions about the efficacy of the standard therapy in strengthening the weaker hand. Is it that the techniques of conventional therapy are not addressing the needs of the weaker non-dominant hand? The vibration therapy was applied equally to both dominant and non-dominant hands of CP patients to produce sensory modulation of both motor cortices. This would have mitigated the effects of inter-hemispheric inhibition, as improved hand dexterity was observed in both dominant and non-dominant hands of the Intervention group. In the Control group, there was no improvement of motor hand function of the non-dominant hand. The Control group received only standard conventional therapy. It may be argued that the different modes of therapy that made up the conventional therapy, failed to alleviate the inter-hemispheric inhibition. Noticeably, standard therapy failed to improve dexterity of the non-dominant hand. The finding that vibration therapy succeeded in improving motor hand function of non-dominant hand while conventional therapy did not, implies that the latter may not be addressing the increased sensory input needs of the more damaged or the less functioning cortex.

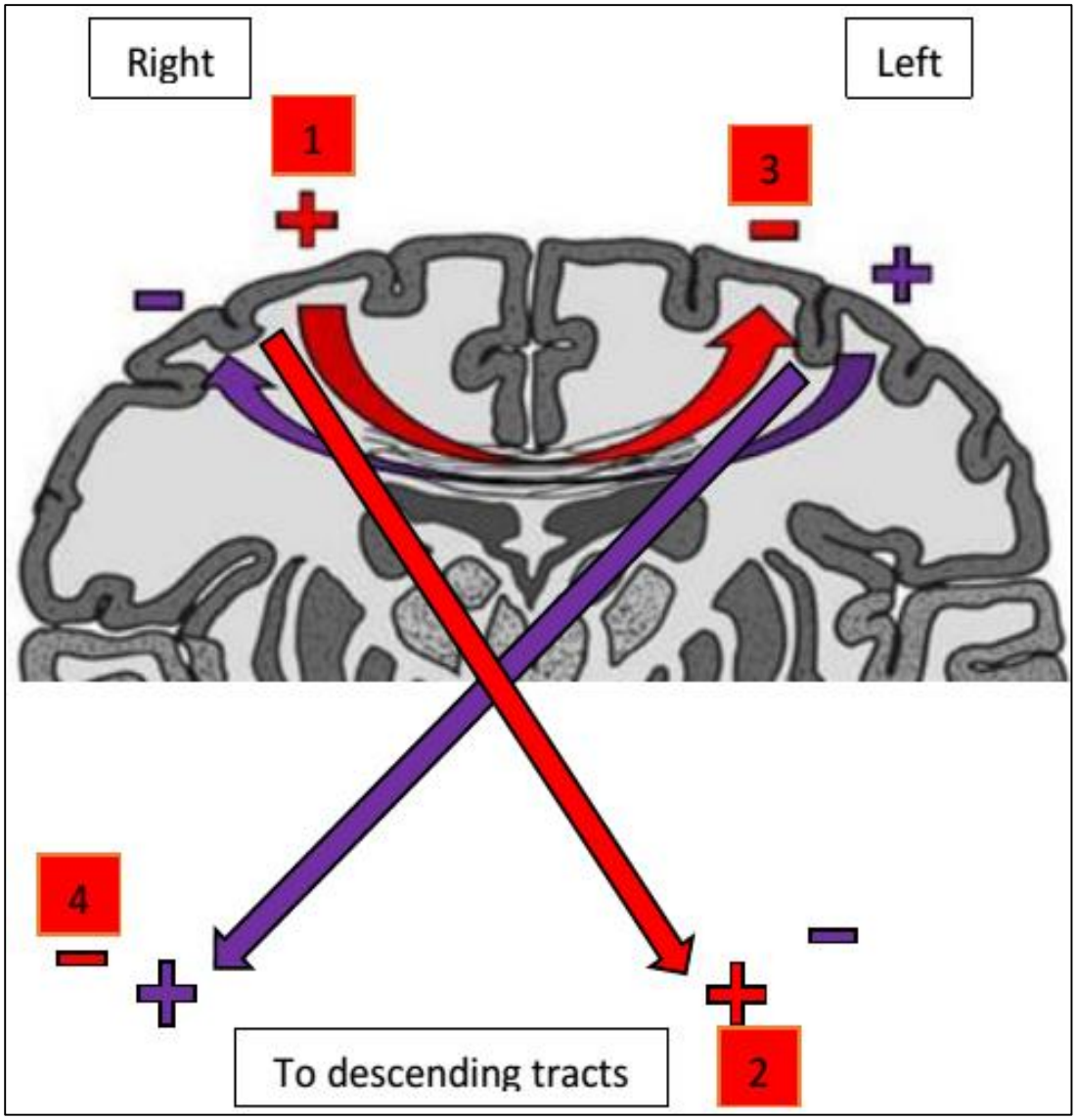

Figure 28: Inter-hemispheric inhibition: showing stimulation of right motor cortex stimulates the left limbs and inhibition of left motor cortex through inter-hemispheric inhibition and inhibition of right limbs. Similar events are mirrored on the opposite side if left motor cortex is stimulated (1-Stimulation of right motor cortex; 2-stimulation of left limbs; 3- inhibition of left motor cortex through inter-hemispheric inhibition; 4- inhibition of right limbs)

Comparison of the post and pre intervention difference in the Box and Block test score, between the Intervention & Control groups showed no statistically significant difference in both dominant (p=0.062) and non-dominant hand (p=0.118) at this juncture of interim analysis. However, the comparison is between the intervention group and an active control group, and not a passive control group. Only if vibration therapy produced an effect over and above that of conventional therapy, would there be a significantly more improvement in the Intervention group compared to the Control group. From the findings of the interim analysis it appears that vibration therapy has not produced such a marked effect to bring out a difference in the 20 CP patients who completed the study at the time of interim analysis. Nonetheless, interim analysis also reveals that vibration therapy did not produce any negative impact on the motor function or treatment of the in-patient CP children who completed the study.

The interim analysis also brings out indirect evidences that speaks for a favourable effect of vibration therapy on the hand motor functions. The Median value of the Post and Pre intervention difference of Box and Block Test (BBT) scores showed a higher absolute value in the Intervention group for both dominant and non-dominant hands, compared to the Control group, which seems promising (Figure 23; Figure 24).

Post intervention Modified Barthel Index score compared to pre intervention, both in the intervention (p=0.066) (Table 5; Figure 19) and control (p=0.091) (Table 6; Figure 22) groups had not shown any significant difference. However, 4 patients (40%) in the intervention group showed an absolute improvement in Modified Barthel Index score compared to just one patient (10%) in the control group. Thus more number of patients in the Intervention group showed an absolute improvement in the Modified Barthel Index score compared to the control group (Figure 23, Figure 24). Thus, descriptive

statistics of the primary and secondary outcomes in this interim analysis, favours effectiveness of vibration therapy in improving hand motor function in children with CP.

Studies have shown that vibration can modulate the motor cortical excitability (139). It can also reduce the negative effect that prolonged immobilization of hand has on the contralateral motor cortex, if applied on the affected hand (139).

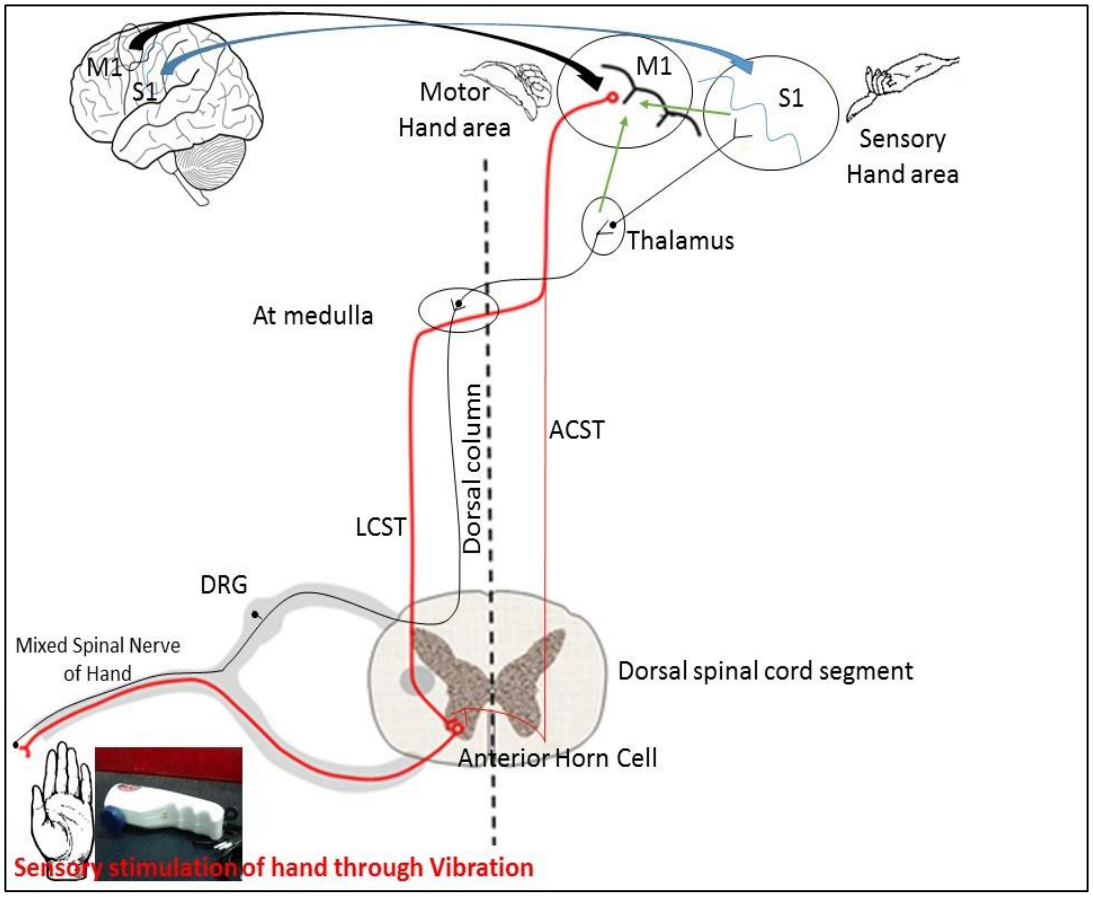

Figure 29: Showing modulation of sensory-motor cortical excitability through sensory stimulation in the form of vibration (S1- Sensory cortex; M1- Primary motor cortex; ACST- Anterior corticospinal tract; LCST- Lateral corticospinal tract)

The findings of the interim analysis of this study, that vibration therapy could be of help in improving motor functions in cerebral palsy children is in line with the findings of previous studies that showed that vibration therapy had improved the motor cortical excitability (4,5,124,125).

Interim analysis showed improvement of motor function of dominant hand in both the intervention and control group but the motor improvement of non-dominant hand was only observed in intervention group but not in the control group. The study showed vibration therapy could be beneficial in improving motor function in cerebral palsy children. The therapy failed to produce any statistically significant improvement in motor hand function over and above the standard therapy. Since both the intervention and control groups received standard therapy and intervention group received vibration therapy in addition, the potential effect of vibration therapy alone, against a group which received no therapy at all could not be assessed. In spite of this, the significant improvement of motor function in the non-dominant hand of the intervention group, in the absence of motor improvement in the control group, gives a definite clue that vibration therapy as a sensory stimulus, has a role in improving motor function and in attenuating the effect of inter-hemispheric inhibition in cerebral palsy children.

LIMITATIONS

LIMITATIONS:

Direct real time assessment of motor cortical excitability by fMRI or PET scan, following sensory stimulation, was not done in the study. Transcranial magnetic stimulation would also have been a good tool to evaluate real time motor cortical excitability, which was also not done in this study. Present study considered clinical outcome data as an indirect evidence of cortical neuroplasticity. Hand dexterity and Activities of Daily Living were evaluated as outcome measures, which might require large changes in cortical excitability to produce significant changes in its values.

Lastly, the study design applied to this trial did not have an arm with CP children receiving only vibration therapy. Such a design would have enabled comparison of the effect of vibration therapy versus no therapy at all, on hand motor function. It would have been unethical to design such a study in a hospital setting where CP children admitted for therapy were being recruited in to the study. Hence, results of current study showed only the effect of vibration therapy over and above the effect of standard therapy.

CONCLUSION

CONCLUSION:

A single-blinded, randomised controlled trial was designed to evaluate the efficacy of sensory stimulation in improving hand dexterity, over and above standard conventional therapy, in children with cerebral palsy. Sensory stimulation was applied in the form of local bilateral palmar vibration therapy. Interim analysis of the trial was done when 20 recruited CP patients had completed the study. The results of this analysis, while giving no conclusive proof for a positive effect of the vibration therapy over and above standard therapy, gave other evidences indicating a probable favourable role of vibration therapy in improving hand motor function in children with cerebral palsy. Further, the findings of the interim analysis revealed that the protocol followed in the application of vibration therapy in the study, minimised the negative effect of inter-hemispheric inhibition. Inter-hemispheric inhibition is the phenomenon whereby the better functioning motor cortex depresses the functioning of the weaker motor cortex, especially when more sensory stimuli is received by the dominant cortex. In the protocol of the current study, vibration was given equally to both hands, which seems to have produced beneficial effects not only in terms of negating the effects of inter-hemispheric inhibition, but also in producing an improvement in the hand dexterity of the non-dominant hand. Children in the Control group, while demonstrating improved hand dexterity of dominant hand did not show any improvement in the non-dominant hand. On the other hand, children in the intervention group revealed improvement in function of both hands. From this finding it may be postulated that bilateral vibration therapy, along with standard therapy may be a better way of management than standard therapy alone, in improving motor function of the weaker limb. A definite recommendation can be made only after completion of the study.

FUTURE COURSE

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Studies may be designed to explore the effect of vibration therapy applied over other parts of the body on the motor function of that part of the body.

Transcranial Magnetic Stimulation studies can be carried out to correlate the degree of modulation of motor cortical excitability with the clinical outcomes of motor function.

SUMMARY

SUMMARY:

Cerebral palsy is one of the most common causes of physical disability of childhood (2). It is a static encephalopathy produced by injury to the developing brain in the perinatal period. Clinically it is mainly a disease of posture and movement, although there are other co-morbidities. CP is topographically classified-into Hemiplegia, Diplegia, Triplegia and Quadriplegia (2). To improve the functional ability of these patients, motor improvement is crucial. Hence treatment of CP is aimed at improving motor functions through a multidisciplinary approach involving physiotherapy, occupational therapy, pharmacotherapy and surgery (13). The normal development of motor functions seen in the normal growing child is restricted in the CP child. A contributing factor for this is the reduced sensory feedback the child gets, as the interactions of the CP child with the surrounding environment is limited.

Vibration is a form of sensory stimulus which has been investigated as a modality of therapy in many conditions like CP, Stroke and Parkinsonism (7,125,163). Whole Body Vibration has been reported to produce motor improvement in CP patients (3–5,125), and local site specific vibration has been found to reduce spasticity in CP children (9). The exact mechanism by which the beneficial effect of vibration is produced is still not elucidated.

Extensive to and fro connections exist between the sensory and motor areas of the brain cortex (10). The motor cortex receives input from the adjacent sensory cortices, namely the primary sensory cortex and the sensory association areas of the parietal lobe. Further 40% of the Corticospinal tract fibres (Motor descending pathways) originate from the somatosensory cortices, and only the rest arise from motor cortices (10,11). The presence of the extensive sensory input to the motor cortices and to the

motor descending pathways raised the potential of using sensory stimulation of the extremities to produce neuroplasticity and to improve motor function. Would regular application of painless sensory stimuli to the palms of cerebral palsy patients enhance the excitability of the motor cortex and produce reorganization of the sensory and motor cortices through the phenomenon of neural plasticity, leading to improved motor functions in these patients? Published literature reports studies, where localized electrical or vibratory stimulation increased excitability and reorganization of the motor cortex (139,156). This suggests that localized site-specific vibration of the hands alone may contribute to improved motor function of the hands.

The present study addressed this question by designing a single-blinded randomised controlled trial, where cerebral palsy patients of age group 6 - 15 years were recruited, randomised and allocated into control and intervention groups. Standard treatment was given to both groups. In addition, vibratory stimuli were applied to both palms of intervention group. The extent of improvement of hand function, as assessed by the Box and Block Test in the two groups, was compared. Further, the change in Activities of daily Living, measured using Modified Barthel Index, was also compared between the 2 groups.

An interim analysis of the trial was done with the approval of the Institutional review board. A total of 38 CP patients admitted in the department of Physical medicine and rehabilitation were screened as of date. Of these, 23 patients were found to be eligible for recruitment as per the stated inclusion and exclusion criteria, and were invited to participate in the study. Of the 23 patients enrolled till now, 20 completed the study, one patient discontinued from study and 2 patients are yet to complete the study. The intra-group analysis of box and block test score and Modified Barthel Index score were

done using Wilcoxon Signed Tank test. The inter-group comparison of BBT score and MBI score were done using Mann Whitney U test. The data was expressed in terms of [median (inter-quartile ranges)]. $P< 0.05$ was considered as significant. The intergroup analysis of the change in the box and block test score in both the dominant ($p=0.062$) and non-dominant hand ($p=0.118$) showed no significant difference between Control and Intervention groups. The findings of the intra-group analysis of the Box and Block test scores point towards an effect of the intervention on improving motor function. Motor function of the non-dominant hand of the Intervention group was improved ($p=0.011$), but that of the Control group did not improve ($p=0.125$). Both inter-group ($p=0.091$) and intra-group [control: $p=0.317$; Intervention: $p=0.066$] comparison of Modified Barthel Index score did not show any statistically significant difference. However, 4 patients (40%) in the intervention group showed an absolute improvement in Modified Barthel Index score compared to just one patient (10%) in the control group. Thus more number of patients in the Intervention group showed an absolute improvement in the Modified Barthel Index score compared to the control group. All these findings point towards the effectiveness of vibration therapy in improving motor functions in cerebral palsy children. Moreover the findings of the study demonstrate that bilateral vibration therapy can overcome the effect of inter-hemispheric inhibition to the damaged cortex. Bilateral vibration therapy along with standard therapy may be a better way of management than standard therapy alone in improving motor function of the weaker limb.

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ANNEXURE

ANNEXURE I:

Patient's information sheet and informed consent form in ENGLISH:

Christian Medical College, Vellore

Patient Information sheet

Study Title: *Effect of local vibration therapy on hand function of cerebral palsy children: a randomized controlled trial*

You are being requested to allow your son/daughter to participate in a study which aims to compare the active voluntary function of the hand before and after application of vibration stimulation over palm. This study attempts to answer the question whether sensory stimulus over palm by vibration therapy can improve the voluntary functioning of hand in cerebral palsy patients. This will be achieved by comparing the hand function in cerebral palsy children who receive local palmar vibration therapy with the group of cerebral palsy children who do not receive this vibration therapy.

What happens to the voluntary function of body and hand in Cerebral palsy and what will the vibration do?

Cerebral palsy is a disease of movement and posture due to defects in the brain. Vibration therapy applied over the palm will stimulate the brain areas involved in control of movement, which has the potential to improve the performance of the hand function.

Does local vibration therapy have any side effects?

There are no known side effects for local vibration therapy.

If your son/daughter takes part in the study what will he/she have to do and what will happen to him/her?

If you agree to allow your son/daughter to participate in this study, first he/she will be assessed for hand function ability and will be randomly allocated into either the intervention group which will receive the local palmar vibration therapy or into the control group which will receive no vibration therapy. Neither you nor your doctor will know which group your ward has been allocated to. Both the groups will receive the usual standard therapy for rehabilitation, administered by the department of PMR, and will be followed up for 4 weeks, at the end of which the hand function of all participants of the study will be reassessed. The local vibration therapy will be administered by applying a portable hand held instrument to the palms of both hands alternately for a period of 30sec each application, such that each palm receives vibration for a total of 5 minutes. The vibration therapy will be given for 5 days a week, for 4 weeks. All other treatments that your son/daughter is already on will be continued and your regular treatment will not be changed during this study.

Can you withdraw from this study after it starts?

The participation of your child in this study is entirely voluntary and you are free to decide to withdraw your child from this study at any time. If you do so, this will not affect your

(P.T.O.)

son's/daughter's usual treatment at this hospital in any way. In addition, if he/she experiences any side effect or if his/her condition worsens, the study will be stopped for him/her and he/she may be given additional treatment.

What will happen if your son/daughter develops any study related injury?

We do not expect any injury to happen to your child, but if your son/daughter does develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will you have to pay for the intervention?

No. This is free.

What happens after the study is over?

Your son/daughter may or may not benefit from the study intervention that is given. Once the study is over, if your son/daughter was given vibration therapy and if it has helped his/her hand function to improve and you wish to continue, then your doctor may think of further applying it for your son/daughter. If your son/daughter was not given the vibration and vibration therapy has helped the children who took it, then your doctor may think to give you the choice of allowing your child to undergo vibration stimulation.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but your child will not be identified by name in any publication or presentation of results. However, the data collected from your son/daughter may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please contact:

1) **Dr.Pijush Kanti Bagchi(Tel: CMC extn: 4268/Cell: 9940713438) or email: drpkbagchi@cmcvellore.ac.in**

2) **Dr. Judy A David (CMC extn:2158)**

3) **Mr. Samuel Kamalesh Kumar (cell: / CMC extn:5274)**

4) **Dr. Elizabeth Tharion (CMC extn: 4268)**

Christian Medical College, Vellore

CONSENT FORM

Study Title: *Effect of local vibration therapy on hand function of cerebral palsy children: a randomized controlled trial*

Study Number:
Participant's Father's/Mother's/ legal guardian's name:
Date of Birth / Age (in years):

I_____
_____, son/daughter of _____
(Please tick boxes)
Declare that I have/been read to the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]
I also understand that my child's participation in this study is entirely voluntary and that I am free to withdraw permission for my child to continue to participate at any time without affecting my son's/daughter's usual treatment or my legal rights [ ]
I also understand that neither I, nor my doctors, will have any choice or knowledge of whether my child will get vibration or not [ ]
I also understand that during the 4 weeks of the study, if my child/ward is in the intervention group, the intervention will be provided free, but after this, if vibration is prescribed/given, I may have to pay for it. [ ]
I understand that my son/daughter will receive free treatment for any study related injury or adverse event but I will not receive any other financial compensation [ ]
I understand that the study staff and institutional ethics committee members will not need my permission to look at my child's health records even if I withdraw from the study. I agree to this access [ ]
I understand that my child's identity will not be revealed in any information released to third parties or published [ ]
I voluntarily agree to allow my child to take part in this study [ ]

Signature (or Thumb impression) of the Legally Acceptable Representative:_____

Date: _____/_____/_____
Signatory's Name: _____

Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____

Signature of the Witness: _____
Date:_____/_____/_____
Name of the Witness: _____

Patient's information sheet and informed consent form in TAMIL:

Christian Medical College, Vellore

நோயாளிகள் / பங்கேற்போருக்கான தகவல்கள்

ஆய்வுத்தலைப்பு:
பெருமூளைவாதம் நோயால் பாதிக்கப்பட்ட குழந்தைகளின் கை செயல்பாட்டில் உள்ளூர் அதிர்வு சிகிச்சையின் விளைவு: ஒரு சமவாய்ப்பீட்டு கட்டுப்படுத்தப்பட்ட சோதனை

பெருமூளைவாதம் நோயால் பாதிக்கப்பட்டகுழந்தைகளின் மறுவாழ்வு சிகிச்சையில் கைகளில் அதிர்வு தூண்டுதல் சிகிச்சை அளிப்பதன் விளைவு பற்றிய ஒரு ஆய்வில் நீங்கள் உங்கள் மகன் / மகள் பங்கேற்க அனுமதிக்க வேண்டும்
இந்த ஆய்வு பெருமூளை வாதம் நோயாளிகளுக்கு கைகளில் அதிர்வு சிகிச்சை மூலம் உணர்ச்சிகளை ஊக்கப்படுத்துவதன் மூலம் கைகளில் தன்னார்வ செயல்பாட்டை மேம்படுத்த முடியும் என்பதை மதிப்பீடு செய்ய முயற்சிக்கிறது.

பெருமூளை வாதம் என்றால் என்ன அர்த்தம் மற்றும் அதிர்வு சிகிச்சை என்ன செய்ய முடியும்?
பெருமூளை வாதம் மூளையில் சில குறைபாடுகள் காரணமாக வருகிறது. இந்த நோய் உடல்இயக்கம் மற்றும் உடல்நிலையைப் பாதிக்கிறது.
கைகளி ன் உள்ளங்கை பகுதியில் அதிர்வுசிகிச்சை மூலம் உணர்ச்சிகளை ஊக்கப்படுத்துவதன் மூலம் இயக்கத்தை கட்டுப்படுத்தும் மூளையின் பகுதிகளைத் தூண்ட இயலும் . இதன் மூலம் கைகளி ன் தன்னிச்சையான செயல்திறனை அதிகரிக்கும் சாத்தியம் உள்ளது.

உள்ளூர் அதிர்வு சிகிச்சைக்கு ஏதேனும் பக்க விளைவுகள் உள்ளதா?
இதுவரை எந்த பக்க விளைவுகளும் அறியப்படவில்லை .

உங்கள் மகன் / மகள் ஆய்வில் பங்கேற்க அவன் / அவள் என்ன செய்ய வேண்டும் ?

Christian Medical College, Vellore

நீங்கள் உங்கள் மகன் / மகள் இந்த ஆய்வில் பங்கேற்க அனுமதிக்க ஏற்றுக்கொண்டால், முதலில் அவன் / அவள் கைகளின் செயல்பாட்டு திறன் மதிப்பீடு செய்ய வேண்டும்.

இந்த ஆய்வில் பங்குபெரும் அனைவரும் இரண்டு குழுக்களாகப் பிரிக்கப்படுவார்கள் ,ஒரு குழுவானது அதிர்வுசிகிச்சை பெறும் ,மற்றொரு குழு எந்தசிகிச்சையும் பெறாது.

அதன் பின் இரண்டு குழுக்களும் பி.எம்.ஆர் துறையால் நிர்வகிக்கப்படும் வழக்கமான தரமான புனர்வாழ்வு சிகிச்சை 4 வாரங்கள் வரை பெறுவர் . பின்பு இரண்டு குழுவினரின் செயல்பாடுகளும் மதிப்பிடப் படும் .

உங்களுக்கோ அல்லது மருத்துவர்களுக்கோ நீங்கள் எந்த குழுவில் இருப்பீர்கள் என்பது தெரியாது .உங்கள் வழக்கமான சிகிச்சை தொடரும் .

நான் இந்த ஆய்வில் இருந்து எப்போது வேண்டுமானாலும் விலக இயலுமா ?

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்பு முற்றிலும் தன்னார்வமானது .மற்றும் நீங்கள் எந்த நேரத்திலும் இந்த ஆய்வில் இருந்து உங்கள் குழந்தை பங்கேற்பதற்கான அனுமதியை திரும்ப பெற முடிவு செய்யலாம். நீங்கள் இவ்வாறு செய்தால், அது உங்களைப் பாதிக்காது.

எனது மகன் / மகளுக்கு ஏதேனும் ஆய்வு தொடர்பான பாதிப்பு உருவாகிறது என்றால் என்ன நடக்கும்?

உங்கள் குழந்தைக்கு எந்த பாதிப்பும் வர வாய்ப்பில்லை , எனினும் உங்கள் மகன் / மகளுக்கு ஆய்வு காரணமாக எந்த பக்க விளைவுகள் அல்லது பிரச்சனைகள் உருவாகிறது என்றால், அதற்கு அவர்கள் கட்டணம் இன்றி சிகிச்சை பெறுவர். எந்த பண இழப்பீடும் வழங்க இயலாது .

நீங்கள் பணம் ஏதும் கொடுக்க வேண்டுமா?

இல்லை, இது இலவசம்.

உங்கள் தனிப்பட்ட விவரங்கள் ரகசியமாக வைக்கப்படுமா ?

இந்த ஆய்வு முடிவு மருத்துவ இதழ்களில் வெளியிடப்படும் .ஆனால் உங்கள் குழந்தையின் அடையாளம் , பெயர் மற்றும் இதர விவரங்கள்

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இரகசியமாக வைக்கப்படும். எனினும், உங்கள் மகன் / மகளிடம் இருந்து சேகரிக்கப்பட்ட தகவல்களை உங்கள் கூடுதல் அனுமதி இல்லாமல், ஆய்வு தொடர்புடைய நபர்கள் மதிப்பாய்வு செய்ய வாய்ப்பு உள்ளது .

மேலும் கேள்விகள் இருந்தால், தொடர்பு கொள்ளவும்:

1) டாக்டர் **பிஜு ஷ் காந்த்தி பக்சி**
(தொலைபேசி: CMC Extn: 4268/Cell: 9940713438) அல்லது
மின்னஞ்சல்: drpkbagchi@cmcvellore.ac.in

2) டாக்டர் ஜூடி A டேவிட் (CMC Extn: 2158)

3) திரு சாமுவேல் கமலேஷ் குமார் (செல்: / CMC Extn: 5274)

4) டாக்டர் எலிசபெத் தரியன் (CMC Extn: 4268)

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ஒப்புகைப் படிவம்

ஆய்வுத்தலைப்பு:
பெருமூளைவாதம் நோயால் பாதிக்கப்பட்ட குழந்தைகளின் கை செயல்பாட்டில் உள்ளூர் அதிர்வு சிகிச்சையின் விளைவு: ஒரு சமவாய்ப்பீட்டு கட்டுப்படுத்தப்பட்ட சோதனை

ஆய்வு எண்:
பங்கேற்பாளரின் தந்தையின் / தாயின் / பாதுகாவலர் பெயர்:
குழந்தை பிறப்பு / வயது தேதி (ஆண்டுகளில்):

_____ என்கிற நான்
_____ என்பவரின் மகன் / மகள்
(தயவு செய்து பெட்டிகளை டிக் செய்யவும்)

நோயாளிகள் /பங்கேற்போருக்கான தகவல் தாளில் உள்ள இந்த ஆய்வு

குறித்த தகவல்களை வாசித்தேன் /வாசித்துக்காட்ட ப்பட்டது .
இந்த ஆய்வு குறித்து எனக்கு இருந்த எல்லா சந்தேகங்களும் தெளிவுபடுத்தப்பட்டன. எனக்கு எந்த சந்தேகமும் இல்லை என்று உறுதி அளிக்கிறேன் . [ ]

இந்த ஆய்வில் என் குழந்தையின் பங்கேற்பு முற்றிலும் தன்னார்வ மானது மற்றும் என் மகனின் / மகளின் வழக்கமான சிகிச்சை அல்லது என் சட்ட உரிமைகள் பாதிக்காமல் பங்கேற்கவும் அப்படி நேரிடுமாயின் அனுமதியை எந்த நேரத்திலும் திரும்பப் பெறவும் எனக்கு உரிமை உள்ளது என்பதையும் நான் புரிந்து கொண்டுள்ளேன். [ ]

என் குழந்தை அதிர்வு சிகிச்சை பெறுவது / பெறாமல் இருப்பது என்பதை நானோ அல்லது மருத்துவர்களோ முடிவு செய்ய முடியாது என்பதை நான் அறிந்துள்ளேன். [ ]
ஆய்வுக் காலமான 4 வாரங்களின் போது, உங்கள் குழந்தை அதிர்வு சிகிச்சை குழுவில் இருந்தால், அதிர்வு சிகிச்சை பெறுவது இலவசம். ஆனால் ஆய்வுக்காலதிற்குப் பின்பு பரிந்துரைக்கப்படும் / வழங்கப்படும்

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அதிர்வு சிகிச்சைக்கு நான் பணம் செலுத்த வேண்டும் என்பதை நான் அறிந்துள்ளேன். [ ]

என் மகன் / மகளுக்கு ஏதேனும் ஆய்வு தொடர்பான காயம் அல்லது எதிர்விளைவுகள் ஏற்பட்டால் இலவச சிகிச்சை வழங்கப்படும். ஆனால் எந்த நிதி இழப்பீடும் வழங்கப்படமாட்டது என்பதை அறிந்துள்ளேன். [ ]

ஒருவேளை இந்த ஆய்வில் இருந்து விலகினாலும், ஆய்வுக் குழு/ நிறுவன நன்னடத்தை குழு உறுப்பினர்கள் என் குழந்தையின் சுகாதாரப் பதிவேடுகளை பார்வையிட எனது அனுமதி தேவை இல்லை என்பதை நான் அறிந்துள்ளேன். [ ]

என் குழந்தையின் அடையாளம் , பெயர் மற்றும் இதர விவரங்கள் வெளியிடப்படாது என்பதை நான் அறிந்துள்ளேன் [ ]

நான் தன்னிச்சையாக முன்வந்து என் குழந்தை இந்த ஆய்வில் கலந்து கொள்ள அனுமதிக்க ஒப்புக்கொள்கிறேன் .[ ]

சட்டப் பூர்வமாக ஏற்கப்படக்கூடிய பிரதிநிதியின் கையொப்பம் (அல்லது கைநாட்டு): _____
தேதி: _____ / _____ / _____
கையொப்பமிட்டவரின் பெயர்: _____

ஆராய்ச்சியாளரின் கையொப்பம்: _____
தேதி: _____ / _____ / _____
ஆய்வு ஆராய்ச்சியாளரின் பெயர்: _____

சாட்சி கையொப்பம்: _____
தேதி: _____ / _____ / _____
சாட்சி பெயர்: _____

Patient's information sheet and informed consent form in HINDI:

क्रिश्चियन मेडिकल कॉलेज, वेल्लूर

रोगी सूचना पत्र

अध्ययन शीर्षक : सेरेब्रल पालसी से पीड़ित बच्चों के हाथ के कामकाज में स्थानीय कंपन का प्रभाव : एक क्रमरहित नियंत्रित परीक्षण।

आपसे अनुरोध है कि आप अपने पुत्र/पुत्री को इस अध्ययन में भाग लेने की अनुमति दें, जो हथेली के सक्रिय स्वैच्छिक कामकाज की तुलना कंपन उत्तेजना के पहले और बाद में करना चाहता है। यह अध्ययन इस प्रश्न का उत्तर देने की कोशिश कर रहा है कि क्या कंपन चिकित्सा द्वारा हथेली पर हुई संवेदी उत्तेजना, सेरेब्रल पालसी के रोगियों में सुधार कर सकती है ? इसे प्राप्त करने के लिए, सेरेब्रल पालसी से पीड़ित बच्चों, जिन्हें हथेली पर कंपन चिकित्सा देकर हाथ के स्वैच्छिक कामकाज की तुलना उन बच्चो से की जाएगी जिन्हें कंपन चिकित्सा प्राप्त नहीं होगी।

सेरेब्रल पालसी से शरीर और हाथ के स्वैच्छिक कामकाज पर क्या प्रभाव पड़ता है और कंपन से क्या होगा ?
सेरेब्रल पालसी, मस्तिष्क में दोष के कारण मुद्रा और चलने-फिरने में होने वाली परेशानी दरशाती हुई एक बिमारी है। हथेली पर की गई कंपन चिकित्सा, मस्तिष्क के उन भागों को प्रोत्साहित करेगी जो चलने फिरने से संबंधित हैं; इस प्रकार हाथ के काम-काज में सुधार आ सकता है।

क्या स्थानीय कंपन चिकित्सा के कोई बुरे प्रभाव हैं ?
स्थानीय कंपन चिकित्सा के कोई सात बुरे प्रभाव नहीं हैं।

यदि आपका पुत्र/पुत्री इस अध्ययन में भाग लेता/लेती है, तो उन्हें क्या करना होगा; उनके साथ होने वाली अध्ययन प्रक्रिया क्या होगी ?
यदि आप अपने पुत्र/पुत्री को अध्ययन में भाग लेने की अनुमति देते हैं, तो पहले उनके हाथ के कामकाज की क्षमता का मूल्यांकन किया जाएगा और फिर बेतरकीब ढंग से उन्हे या तो 'हस्तक्षेप' समूह में डाला जाएगा जिन्हे स्थानीय कंपन प्राप्त होगी या फिर 'नियंत्रन' समूह में डाला जाएगा, जिन्हे यह कंपन चिकित्सा प्राप्त नहीं होगी। दोनो समूहों का पूनर्वास, PMR विभाग द्वारा प्रशासित किया जाएगा जिसमे सामान्य चिकित्सा और 4 सप्ताह देख-रेख की जाएगी, जिसके अंत में

सभी सहभागी : हाथ के कामकाज करने की क्षमता फिरसे जांची जाएगी। कंपन चिकित्सा एक हाथ में पकड़े जाने वाले साधन द्वारा दोनो हथेलियों को एकांतर 30 क्षणों की अवधि के लिए दी जाएगी ताकि प्रत्येक हथेली पर 5 मिनट कुल कंपन प्राप्त हो। कंपन चिकित्सा सप्ताह में 5 दिन और इस प्रकार 4 सप्ताह दी जाएगी।

न तो आपको, न ही आपके डॉक्टर को ज्ञात होगा कि आप पुत्र/पुत्री किस समूह में है। पहले से जारी अन्य सभी उपचार जिसपर आपका पुत्र/पुत्री है, वह चलते रहेंगे और इस अध्ययन के दौरान नियमित चलती चिकित्सा में कोई बदलाव नहीं आएगा।

क्या आप यह अध्ययन शुरू होने के बाद छोड़ सकते है?
इस अध्ययन में आपके बच्चे की भागीदारी पूरी तरह से स्वैच्छिक है और आप किसी भी समय अपने बच्चे को अध्ययन से बाहर निकालने का निश्चय करने के लिए स्वतंत्र हैं। आपके ऐसा करने पर आपके बच्चे की नियमित चिकित्सा में कोई बदलाव नहीं आएगा. इससे अतिरिक्त, अगर आपके बच्चे को इस बीच बुरा प्रभाव हो या उसकी हालत बिगड़ जाए तो अध्ययन बंद किया जाएगा और उपचार दिया जाएगा।

क्या होगा अगर आपके पुत्र/पुत्री को कोई अध्ययन संबंधी चोट विकसित हो?
किसी प्रकार की चोट आने की संभावना नहीं है परंतु आपके पुत्र/पुत्री को अगर अध्ययन संबंधी बुरे प्रभाव द्वारा को समस्या हो तो उसका पूरा इलाज निःशुल्क किया जाएगा। लेकिन हम किसी प्रकार का मौद्रिक मुआवज़ा प्रदान करने में असमर्थ है।

क्या 'हस्तक्षेप' करने के लिए भुगतान करना होगा?
नही यह मुफ्त है।

अध्ययन समाप्त होने के बाद क्या होगा?
दिए जाने वाले हस्तक्षेप से आपके पुत्र/पुत्री को लाभ हो सकता है या नहीं भी। अध्ययन समाप्त होने पर यदि आपके पुत्र/पुत्री को कंपन चिकित्सा प्राप्त हुई थी और उसके कामकाज में सुधार हुआ और आप यह उपचार जारी रखना चाहते है,

तो आपके डॉक्टर इसके बारे में आगे सोच सकते हैं। अगर आपके बच्चे को यह चिकित्सा प्राप्त नहीं हुई थी और इससे अन्य बच्चों को लाभ हुआ हो तो आपके डॉक्टर आपके बच्चे को यह उपचार देने की अनुमति का विकल्प कर सकते हैं।

क्या आपकी व्यक्तिगत जानकारी को गोपनीय रखा जाएगा?
इस अध्ययन के परिणाम एक मेडिकल जर्नल में प्रकाशित किए जाएँगे, लेकिन आपके बच्चे का नाम किसी भी प्रकाशन में या परिणामों की प्रस्तुति में नहीं पहचाना जाएगा। परंतु यदि आप इस अध्ययन में अपने बच्चे की भागीदारी की अनुमति देते हैं तो उनके आंकड़े अध्ययन से जुड़े लोगों द्वारा समीक्षित होंगे।

यदि आपके पास अन्य को भी प्रश्न हैं, कृपया संपर्क करें:

1) डॉ. पीजूश कांति बागची (दूरभाष: CMC extn./cell: 9940713138 4268 या email: drpkbagchi@cmcvellore.ac.in)

2) डॉ. जूडी ए. डेविड (CMC extn: 2158)

3) श्री. सामुयल कमलेश कुमार (CMC extn: 5274)

4) डॉ. एलिज़ाबैथ थरियन (CMC extn: 4268)

क्रिस्टियन मेडिकल कालेज

सहमति फार्म

अध्ययन शीर्षक: सेरेब्रल पालसी से पीड़ित बच्चों के हाथ के कामकाज में स्थानीय कंपन का प्रभाव : एक क्रमरहित नियंत्रित परीक्षण।

. अध्ययन संख्या:
. भागीदार के पिता / माता / कानूनी अभिभावक का नाम:
. जन्म की तारीख (वर्षों में)

मैं _____,
का पुत्र/पुत्री (कृपया बक्से को टिक करें)

घोषणा करता हूँ कि मैंने इस अध्ययन से संबंधित जानकारी पत्र पढ़ा है और मुझे सब स्पष्ट है। [ ]

मैं यह भी समझता हूँ कि मेरे पुत्र/पुत्री की भागीदारी पूरी तरह से स्वैच्छिक है और किसी भी समय में इस अध्ययन से मेरे बच्चे की भागीदारी वापिस लेने का निर्णय ले सकता हूँ। इससे मेरे बच्चे की चलती हुई चिकित्सा पर कोई प्रभाव नहीं पड़ेगा। [ ]

मैं यह भी समझता हूँ कि न मैं और न ही मेरे डॉक्टर, यह जानकारी रखते हैं यदि मेरे बच्चे को कंपन चिकित्सा प्राप्त होगी या नहीं। [ ]

मैं यह भी समझता हूँ कि ~~इस~~ 4 सप्ताहों में किया गया हस्तक्षेप, अगर मेरा बच्चा हस्तक्षेप समूह में आता है तो, निःशुल्क है, परंतु इसके बाद, अगर यह चिकित्सा जारी होती हो या दी जाती है तो मुझे उसका भुगतान करना होगा। [ ]

मैं समझता हूँ कि मेरे पुत्र/पुत्री का इलाज निःशुल्क होगा अगर अध्ययन से संबंधित किसी भी प्रकार की समस्या होती है। परंतु मुझे किसी प्रकार का मौद्रिक मुआफ़ज़ा नहीं मिलेगा। [ ]

मैं समझता हूँ कि अध्ययन कर्मचारियों और संस्थागत नैतिकता समिति के सदस्यों को, मेरे पुत्र/पुत्री के स्वास्थ्य रिकार्ड देखने के लिए मेरी अनुमति नहीं चाहिए, तब भी यदि मैं अपने पुत्र/पुत्री का नाम अध्ययन से वापिस ले लूँ।

मैं इस उपयोग के लिए सहमति देता हूँ। [ ]

मैं समझता हूँ कि मेरे बच्चे की पहचान किसी तीसरे पक्ष को या फिर किसी प्रकाशन में जारी नहीं किया जाएगा। [ ]

मैं स्वेच्छा से मेरे बच्चे को इस अध्ययनमेंभाग लेने की अनुमति देता हूँ। [ ]

कानूनी तौर पर स्वीकार्य प्रतिनिधि के हस्ताक्षर (या अंगूठे का निशान)

तिथि ____/____/____

हस्ताक्षरकर्ता का नाम _____

अन्वेषक के हस्ताक्षर _____

तिथि ____/____/____

अन्वेषक का नाम _____

गवाह के हस्ताक्षर _____

तिथि ____/____/____

गवाह का नाम _____

ANNEXURE II

MODIFIED BARTHEL INDEX SCORING

The following Table sets out the way in which the Modified Barthel Index is scored

Item	Unable to perform task	Substantial help required	Moderate help provided	Minimal help required	Fully independent
Personal hygiene	0	1	3	4	5
Bathing self	0	1	3	4	5
Feeding	0	2	5	8	10
Toilet	0	2	5	8	10
Stair climbing	0	2	5	8	10
Dressing	0	2	5	8	10
Bowel control	0	2	5	8	10
Bladder control	0	2	5	8	10
Ambulation	0	3	8	12	15
or Wheelchair*	0	1	3	4	5
Chair/Bed transfer	0	3	8	12	15

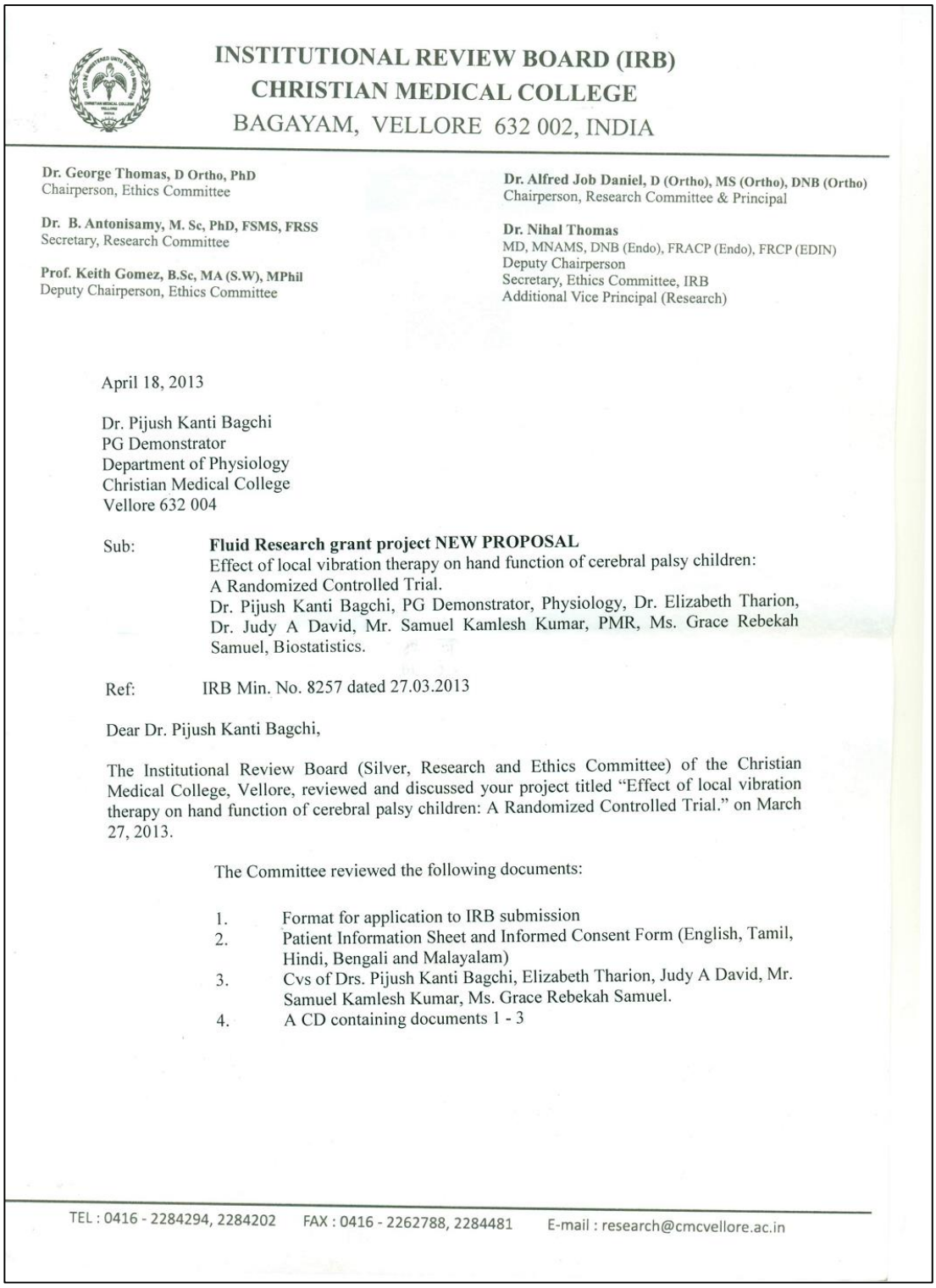
*Score only if patient is unable to ambulate and is trained in wheelchair management

The following Table sets out the dependency needs

Categories	MBI Total Scores	Dependency Level	Hours of Help Required per Week (maximum)
1	0 - 24	Total	27.0
2	25 - 49	Severe	23.5
3	50-74	Moderate	20.0
4	75 – 90	Mild	13.0
5	91 - 99	Minimal	< 10.0

ANNEXURE III

INSTITUTIONAL REVIEW BOARD (IRB) CERTIFICATE



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April 18, 2013

Dr. Pijush Kanti Bagchi
PG Demonstrator
Department of Physiology
Christian Medical College
Vellore 632 004

Sub: **Fluid Research grant project NEW PROPOSAL**
Effect of local vibration therapy on hand function of cerebral palsy children: A Randomized Controlled Trial.
Dr. Pijush Kanti Bagchi, PG Demonstrator, Physiology, Dr. Elizabeth Tharion, Dr. Judy A David, Mr. Samuel Kamlesh Kumar, PMR, Ms. Grace Rebekah Samuel, Biostatistics.

Ref: IRB Min. No. 8257 dated 27.03.2013

Dear Dr. Pijush Kanti Bagchi,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Effect of local vibration therapy on hand function of cerebral palsy children: A Randomized Controlled Trial." on March 27, 2013.

The Committee reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Informed Consent Form (English, Tamil, Hindi, Bengali and Malayalam)
3. Cvs of Drs. Pijush Kanti Bagchi, Elizabeth Tharion, Judy A David, Mr. Samuel Kamlesh Kumar, Ms. Grace Rebekah Samuel.
4. A CD containing documents 1 - 3

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on March 27, 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. George Thomas	MBBS, D Ortho, PhD	Chairperson (IRB) & Orthopaedic Surgeon, St.Isabel Hospital, Chennai & Former Editor, Indian Journal of Medical Ethics	External, Clinician
Dr. Poonkuzhali	MSC, PhD	Professor, Haematology,CMC	Internal, Basic Medical Scientist
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, CMC	Internal, Clinician
Dr. Anuradha Bose	MBBS, DCH, MD, MRCP, FRCPCH	Professor, Pediatrics, CMC	Internal, Clinician
Dr. Binu Susan Mathew	MBBS, MD	Associate Professor, Dept. of Clinical Pharmacology	Internal, Pharmacologist
Dr. Suresh Devasahayam	BE, MS, PhD	Professor, Bioengineering, CMC	
Dr. Vinod Joseph Abraham	MBBS, MD, MPH	Professor, Community Medicine, CMC	Internal, Clinician
Dr. DJ Christopher	BSc, MBBS, DTCD, DNB, FCCP	Professor, Pulmonary Medicine, CMC	Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay person
Mr. Sampath	BSc, BL	Advocate	External, Legal Expert
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	Internal, Legal Expert
Mrs. Mary Johnson	M.Sc	Professor, Child Health Nursing, CMC.	Internal, Nurse

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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Asha Mary Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Retired Professor, Vellore	External
Dr. P. Zachariah	MBBS, PhD	Retired Professor	External
Mrs. Selva Titus Chacko	MSc	Professor, Medical Surgical Nursing, CMC	Internal, Nurse
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Deputy Chairperson (IRB) & Students' Counsellor, Loyola College, Chennai	External, Social Scientist
Dr. Thambu David	MBBS, MD, DNB	Professor, Medicine, CMC	Internal, Clinician
Dr. B.S. Ramakrishna	MBBS, MD, DM, PhD, FAMS, AGAF, FNA	Retired Professor	External, Clinician
Dr. B. Antonisamy	M.Sc PhD FSMS, FRSS, FRCS	Professor & Head Dept. of Biostatistics & Secretary IRB (EC), CMC	Internal, Statistician
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

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The trial need to be registered with Clinical Trial Registry India (CTRI) http://ctri.nic.in before commencing the study.

The study has to report to Internal Data Safety Monitoring Board (DSMB) http://172.16.11.136/Research/IRB_Policies.html

A sum of Rs. 34,000/- (Rupees Thirty Four Thousand only) will be granted for 1 year 3 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Elizabeth Tharion, Department of Physiology, CMC

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