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ORIGINAL ARTICLE

EFFECTIVENESS OF TIZANIDINE AND INTENSIVE REHABILITATION IN SPASTIC CEREBRAL PALSY

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Abstract:

Background: *The treatment of cerebral palsy is multifactorial. The aim of the study is to find out the efficacy of tizanidine and intensive rehabilitation in the treatment of spastic cerebral palsy.* ***Methods:*** *This observational study was conducted over 35 patients in Sir Salimullah Medical Mitford Hospital from January 2022 to December 2022.The patients satisfying the inclusion and exclusion criteria were enrolled: total 35 patients received tizanidine (2mg) orally at a dose of 1 mg given at bed time under 10 years and 2 mg given at bed time more than 10 years of age, then after 1 week maintenance dose was given at 0.3 mg/kg/day, three times daily in combination with intensive rehabilitation 1 hour daily five times a week. Total 24 weeks of intensive rehabilitation was given. All patients were followed up at 4 weeks interval and were evaluated for a total of 24 weeks.* ***Results:*** *The study shows high efficacy in reducing tone in spastic cerebral palsy measured by using Modified Ashworth scale ($p<0.001$).Also there is improvement in physician rating scale crouch ($p<0.0001$) and foot contact, ($p<0.0001$) and also improvement in gross motor function ($p<0.01$).* ***Conclusion:*** *Combination of tizanidine and intensive rehabilitation is effective for reduction of generalized spasticity regarding muscle tone, range of motion of the joint and improvement of gait in cerebral palsy patients.*

Key words: *Cerebral Palsy, Spasticity, Tizanidine, Intensive Rehabilitation*

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Introduction:

Cerebral palsy is the most common disability of childhood that affects motor function as a result of injury to the developing brain.[1] It is now well known that the prime risk factors for cerebral palsy are delivery before 37 weeks and birth weight of less than 2.5 kg; however, there are some other problems evident in the literature which are found to be some of the prominent reasons for brain damage, some of which includes malformation of the brain in the developmental period, genetic causes, in utero mother and fetus infections, and various other issues.[2]

The presenting signs and symptoms of CP are diverse and mainly consist of motor disorders, sensory deficits, and associated comorbidities which occur due to a static lesion to the developing brain. These signs and symptoms change as the child ages and new features are added to the list. Thus, with advanced age, there is a worsening of the neuromuscular system and functional capability of the child even though the damage in the brain is static.[3]The most common movement disorders seen in cerebral palsy are spastic muscles and dystonia

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with difficulties in coordination, strength, and selective motor control. Spasticity is the major challenge in the management of CP children. It causes spasticity-induced bone and joint deformity, pain, and functional loss[4].Commonly used medicines found in the literature to relieve spasticity are baclofen, diazepam, clonazepam, dantrolene, and tizanidine. Baclofen and diazepam help in relaxing the muscles but have many side effects.[5] Treatment of spastic cerebral palsy includes physiotherapy along with antispastic medication. Tizanidine is similar to diazepam and baclofen in the effectiveness of tone reduction.[6] Tizanidine is readily absorbed after oral administration and metabolized in the liver. Alpha 2 adrenergic agonists have an anti-nociceptive effect, which may assist in their tone-reducing abilities because pain is known to increase spasticity; it is possible that this effect is mediated through the release of substance P in the spinal cord[7]. Tizanidine is possibly effective, but there are insufficient data on its effect on improvement of motor function and its side-effect profile. The tizanidine and baclofen are currently most promising drugs treated for cerebral palsy. Intensive rehabilitation may be defined as 1 hourly intervention, 5 days a week, as opposed to a therapy session once a week or once every second week[8]. It consists of neurodevelopmental treatment (NDT), therapeutic exercises (TEs) and activities of daily living (ADL) training.[9] The aim of this study was to find out the efficacy of tizanidineand intensive rehabilitation in reducing spasticity in cerebral palsy.

Methods:

Subjects:

An observational study was done in Sir Salimullah Medical College Mitford Hospital from January 2022 to December 2022. All the spastic cerebral palsy patients seeking treatment in outpatient department of Physical Medicine & Rehabilitation and Pediatrics were the reference population. From reference population, patients enrolled in the study who met the inclusion and exclusion criteria. Sample size estimates suggested that 35 subjects would be sufficient to detect a 5% level of significance. Patients aged between 12 months to 12 years; with disorder in the development of movement and posture presumably of cerebral origin started before 2 years of age, presence of spasticity associated with or characterized by increased tone reflexes, clonus or extensor plantar response, and delayed milestones of development which is improving over time were included in this study. Those with mixed type of cerebral palsy; receiving systemic anti-spasticity medications or had received phenol and/or botulinum toxin type A injections; past surgical intervention that might interfere with ankle joint movement; neurodegenerative disorders, chromosomal abnormality such as Down syndrome, inborn errors of metabolism such as galactosemia and presence of comorbidity such as epilepsy were excluded.

Procedure:

A total number of 35 patients were primarily selected. Complete history and clinical examination were done for all enrolled patients.

After taking written informed consent from parents,they were finally selected for the study. All patients received intensive rehabilitation (1 hour daily for 5 days a week) and oral tizanidine (2mg) orally at a dose of 1 mg given at bed time under 10 years and 2 mg 10 years or more, then after 1 week maintenance dose was 0.3 mg/kg/day three times daily was given for 24 weeks. Patients were first assessed with Modified Asworth Scale (MAS)[10] based on muscle tone to determine the extent of spasticity. Then Physician Rating Scale[11]to measure joint angle (crouch) especially by standard goniometer,knee recurvatum, foot contact and overall functional status by Gross Motor Functional Classification System.[12] Then intervention was done by giving oral tizanidine with intensive rehabilitation to reduce spasticity in the group and uniform intensive rehabilitation protocol was applied. After 4 weeks (1st follow up) during the continuation of drugs, patients were again assessed using before mentioned 3 scales and adverseeffect of oral tizanidine was recorded in follow-up sheet. After 8 weeks (2nd follow up), patients were again assessed using before mentioned 3 scales and adverse effect of oral tizanidinewas recorded in follow up sheet. Then follow upassessment was done every 4 weekly at 12th week, 16thweek, 20th week and lastly 24th week for total with continuing the drugs using same scales. Patients were advised intensive rehabilitation by an experienced physiotherapist at the department of Physical Medicine & Rehabilitation, Sir Salimullah Medical College Mitford Hospital, Dhaka.

Drug administration and titration:

After selection, tizanidine was given according to following dose schedule. Oraltizanidine (2mg) at a dose of 1 mg given at bed time under 10 years and 2 mg given at bed time more than 10 years of age, then after 1 week maintenance dose was 0.3 mg/kg/day three times daily.

Intensive rehabilitation:

One-hour intensive physiotherapy was given daily for 5 days a week. Activities included in each session

were body alignment weight transfer in various positions, bimanual activities and facilitation sequences of movements.

Ethical issues:

Ethical clearance has been obtained from the ethical committee of Sir Salimullah Medical College to conduct the research work.

Data analysis:

Data were collected through a pretested structured questionnaire. Data were processed and analyzed using SPSS (statistical package for social science) version 17. Test statistics used to analysis the data were chi square Test and student T test. The level of significance was set 0.05 and p-value of less than 0.05 was considered significant.

Results:

A total of 35 patients were recruited for the study. The mean age of the patients was 31.97 months. Patients receiving tizanidine and intensive rehabilitation were 39% inASscore-3 before starting treatment. However, 46.0%of patients later on began to show alower Ashworth score which at 3rd month in 2nd follow up shifted to ASscore-2 because of improvement. This improvement in the 4th month compared to the3rd month was found to be highly significant (p < 0.0001) (Figure-1).

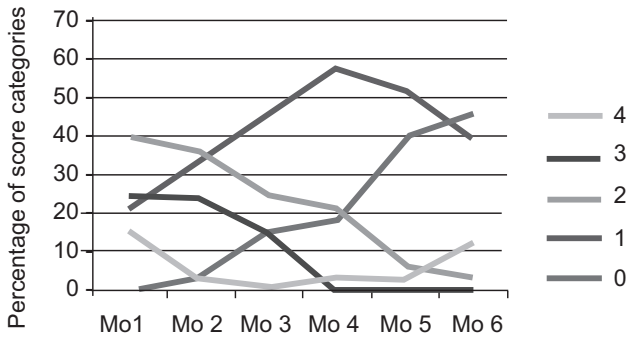

Fig.-1: *Monthly change of muscle tone by modified ash worth scores*

The patients showed variation in percentage of score of joint angle measured by crouch scores of physician rating scale. For example, 49% of the patients had severe spasticity in the first month. However, in the second month 61% patient had moderate angle, although the mean score improvement was not statistically significant (p = 0.21) from the 4th month another shift of improvement was observed among patients. 46% of the patients in the 4th month had mild variety, the condition lasting through the end of the follow up and significant change in mean scores at 5th month (p = 0.03) but nonsignificant from 5th to 6thmonth (p = 0.14). (Figure-2).

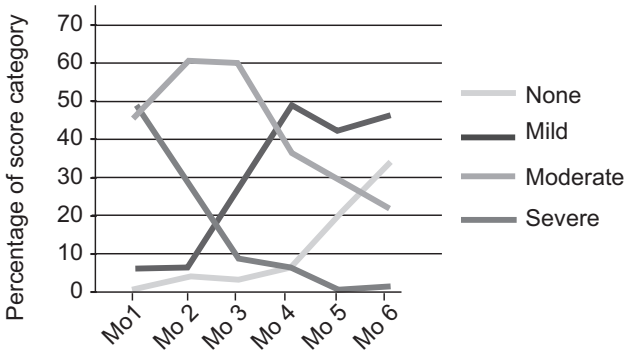

Fig.-2: *Monthly change of joint angle measured by crouch scores of physician rating scale*

Another component of physician rating scale of the patients had a score of 0 in month 1 and 2 (about 70% and 52% respectively), a change in score was seen in 3rd month (about 61% had score 1) of the follow-up, however, the change in mean score from 2nd to 3rd month was not statistically significant (p = 0.67). Statistically significant improvement (p < 0.0001in mean score began between 3rd to 4th month and the trend continued till the end of the follow-up (Figure-3).

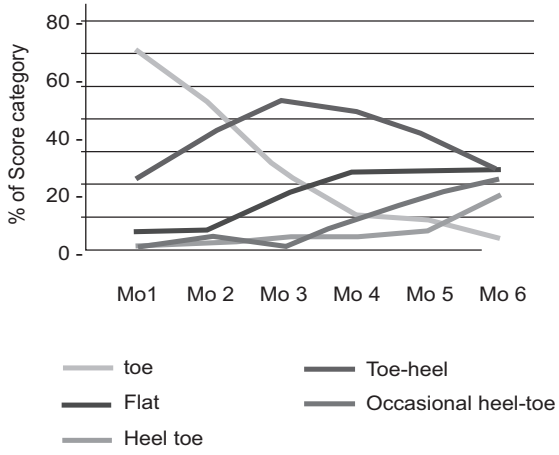

Fig.-3. Monthly change of gait measured by foot contact scores of physician rating scale.

Before starting treatment,52% patients were at level 5% and 32% patient were at level 4. In Month 4 follow-up it was found that over half the patients (56.0%) improved to Level 3. The difference in mean score was statistically highly significant (p = 0.001). Although a large proportion of these patients eventually improved towards level 2 (30.0%) or level 1 (9.0%), the majority of the sample remained in level 3 in the 4th (56.0%), 5th (56.0%) and 6th month (46.0%) of follow up time (Figure-4).

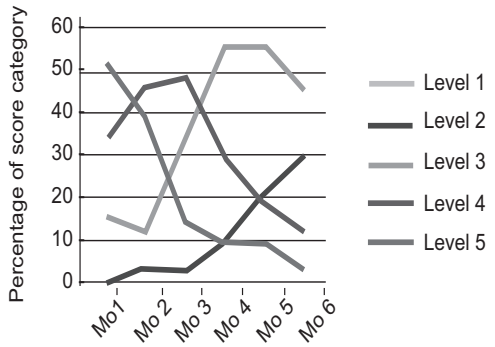

Figure 4.*Monthly change of gross motor function.*

Discussion:

The syndrome of spastic hypertonia develops when the supra segmental control over the spinal cord segmental reflexes is lost[13]. Spasticity can range from mild muscle stiffness to severe, painful, and uncontrollable muscle spasm. It is associated with some common neurological disorders: Multiple sclerosis, stroke, cerebral palsy, spinal cord and brain injuries, and neurodegenerative diseases affecting the upper motor neuron, pyramidal and extrapyramidal pathways[14]. Mean age of the patients was 31.97 months.

Nikkhahet al.[15] found mean age of 7.3 ± 3.4 years and Adam et al.[16] found mean age of 7.4 ± 2.3 years. The difference between this study and other study is that patients are not coming to physician after 5 years due to socioeconomic condition and false belief. Nikkhahet al.[15] found the mean Ashworth score decreased in 50% of the patients receiving tizanidine versus 6.7% of patients receiving the placebo ($p < 0.0001$). In a previous study by Vasqueset al.[17] found that in the group receiving tizanidine 78.8% reported having reduced spasticity compared with only 76% patients receiving the placebo ($p < 0.0001$). Alperet al.[18] found that the mean score of gross motor function measure is highly significant and modified Asworth is significant. This study suggests that adjuvant treatment with oral tizanidine is more effective than baclofen in combination with botulinum toxin for spastic equines foot deformity due to cerebral palsy. Significant improvement was demonstrated using gross motor and modified Asworth scale ($p < 0.05$). In present study in gross motor function score, it was found that the mean gross motor function score of the patients receiving tizanidine with Intensive Rehabilitation was lower. Physician ratings scales comprise crouch measure and foot contract score. A higher mean crouch score for patients receiving tizanidine with Intensive Rehabilitation was statistically highly significant ($p < 0.0001$).

Wagstaffet al.[19] found improvement in muscle tone occurred in 60% to 82% of tizanidine recipients compared with 60% to 65% of baclofen. Adam et al. [16] using Tardiew score found that score was 4.4 for baclofen and placebo. 49% of the patients had severe spasticity in the first month. However, in the second month 61% patient had moderate angle, although the mean score improvement

was not statistically significant ($p = 0.21$) from the 4th month another shift of improvement was observed among patients receiving tizanidine and Intensive Rehabilitation. 46% of the patients in the 4th month had mild variety, the condition lasting through the end of the follow up and significant change in mean scores at 5th month ($p = 0.03$) but non-significant from 5^{th} to 6^{th} month ($p = 0.14$).

During measuring crouch, patients receiving tizanidine with Intensive Rehabilitation showed remarkable variation in scores and accordingly change in severity of ankle compared to patients receiving intensive rehabilitation. For example majority of (about 49%) of the patients had severe spasticity in the first month. However in the second month majority of patient (about 61%) had moderate Ankle measure, although the mean score improvement was not statically significant ($p = 0.21$). Statically significant improvement of spasticity by change of mean score, using MAS score it is at 4th month. Using crouch score, there is statistically significant improvement in the patients getting tizanidine with Intensive rehabilitation in the 5th month. Nikkhah et al. [15] showed after 2weeks improvement of tizanidine group compared to placebo. Alper et al. [18] showed improvement after 3rd month comparing tizanidine with botulinum compared to baclofen with botulinum in GMFCS score & MAS score.

Conclusion:

Result of this study shows that basic motor abilities and self-care improved after intensive physiotherapy with tizanidine is effective for reducing generalized spasticity regarding muscle tone and joint angle stiffness and gait improvement in cerebral palsy patients. Further larger scale study is required to know the effectiveness of both tizanadine and intensive physiotherapy in the treatment of cerebral palsy patients.

Limitations:

Small sample size and this single hospital based study did not reflect exact scenario of the whole community. Patients from all socioeconomic status and all parts of the country did not come to seek medical attention in the study place.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

Funding:

This research received no external funding

Ethical consideration:

The study was conducted after approval from the ethical review committee. The study was approved by the Ethical Research Committee of Sir Salimullah Medical College The confidentiality and anonymity of the study participants were maintained.

Authors' Contributions:

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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