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ORIGINAL ARTICLE

INTENSIVE REHABILITATION IS BETTER WHEN IT IS COMBINED WITH TIZANIDINE IN SPASTIC CEREBRAL PALSY- A RANDOMIZED CLINICAL TRIAL

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Abstract:

Background: *To find out the combined efficacy of Tizanidine and intensive rehabilitation in the treatment of spastic cerebral palsy.* ***Methods:*** *This randomized clinical trial was conducted over 70 patients in Sir Salimullah Medical College Hospital from January 2022 to December 2022.The patient satisfying the inclusion and exclusion criteria was randomly enrolled into two groups; Group- A (Case) included 35 patients received only intensive rehabilitation and Group- B (Control). included 35 patients who received 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 in combination with intensive rehabilitation 1 hour daily five times a week for 24 weeks. All patients were followed up at 4 weeks interval and were evaluated for a total of 24 weeks. Combination of Tizanidine and intensive rehabilitation has superior efficacy in reducing tone in spastic cerebral palsy over only rehabilitation measured by using Modified ashworth scale ($p<0.001$).* ***Results:*** *Combination of Tizanidine and intensive rehabilitation is improved 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 group has superior efficacy than only rehabilitation group 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 CP are delivery before 37 weeks and birth weight of less than 2.5kg; 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

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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 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 sessions 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 Tizanidine in combination with intensive rehabilitation in reducing spasticity in cerebral palsy.

Methods:

Subjects:

A randomized controlled clinical trial was done in Sir Salimullah Medical College Hospital from January 2022 to December 2022. All the spastic cerebral palsy patients seeking treatment in outpatient department of Physical Medicine & Rehabilitation and Paediatrics 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 in each group would be sufficient to detect a 5% level of significance. Patients aged between 12 months to 12 years of both sexes; 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 miles stones 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 70 patients were primarily selected and were randomized into two groups (Group A and Group B), each of which included 35 patients. Complete history and clinical examination were done for all enrolled patients.

After taking written informed consent they were finally selected for the study and randomization was done by lottery. In group A only intensive rehabilitation (1 hour daily for 5 days a week for 24 weeks) was given. In group B 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 Group B and Uniform intensive rehabilitation protocol was applied. After 4 weeks (1st follow up) during the continuation of drugs, patients were again assessed by principal investigator using before mentioned 3 scales and adverse effect of oral tizanidine was recorded in follow-up sheet. After 8 weeks (2nd follow up) were again assessed by principal investigator using before mentioned 3 scales and

adverse effect of oral baclofen was recorded in follow up sheet. Then follow up assessment was done every 4 weekly at 12th week, 16th week, 20th week and lastly 24th week for total with continuing the drugs using same scales by principal investigator. Both groups were given intensive rehabilitation by an experienced physiotherapist at the department of Physical Medicine & Rehabilitation, Sir Salimullah Medical College Hospital, Dhaka.

Drug administration and titration:
After group allocation, tizanidine was given according to following dose schedule. Oral Tizanidine (2mg) was started 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.

Intensive rehabilitation:
One hour intensive physiotherapy was done 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.

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 number of 70 cerebral palsy children were recruited for this study of which 35 patients were in Tizanidine and Intensive Rehabilitation group and 35 patients were in Intensive Rehabilitation group. Data on patient's age was collected in months. Age range of patients was with a mean of 28.62. Thus the mean age in tizanidine group was 31.97 months with a standard error of 2.71. However, the mean age of Intensive Rehabilitation group was 25.27. Lower by about 7 months and relatively higher standard error (2.23) compared to tizanidine and Intensive Rehabilitation group (Table-1).

In this study about 46.0% of patients receiving Intensive Rehabilitation had AS score-3 before starting the treatment. In the 2nd and 3rd month the same trend was observed and the score remained within 40.0% to 50.0%. However, it was not until the 4th month that about 42.0% of the patients receiving Intensive Rehabilitation shifted to score 2 following improvement. This improving trend persisted till the final follow-up at 6 month after initiating treatment. It was noteworthy that 39.0% of patients receiving Tizanidine and Intensive Rehabilitation were also in AS score-3 before starting treatment. However, 46.0% of patients in this group later on began to show a lower Ashworth score which at 3rd month in 2nd follow up shifted to AS score-2 because of improvement. This improvement in the 4th month compared to the 3rd month within the Tizanidine and Intensive Rehabilitation group was also found to be highly significant ($p < 0.0001$) using paired sample t test. Moreover, by the end of the follow-up period (about 46.0%) of the Tizanidine and Intensive Rehabilitation group Ashworth score 1 step more putting them into the 1st category (Figure-1).

In Intensive Rehabilitation group, before starting treatment 58% patient was in moderate variety. At final follow-up, 6 months after treatment with Intensive Rehabilitation the measured angle for crouch gait did not improve (58% VS. 60%). Before starting treatment no patient was in mild variety but after 6 months follow up 28% patient was found in mild variety. But this improvement in month wise follow up is not statistically significant. Tizandine and Intensive Rehabilitation group showed remarkable variation in scores and accordingly change in severity of angle compared to patients receiving Intensive Rehabilitation. For example, 49% 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

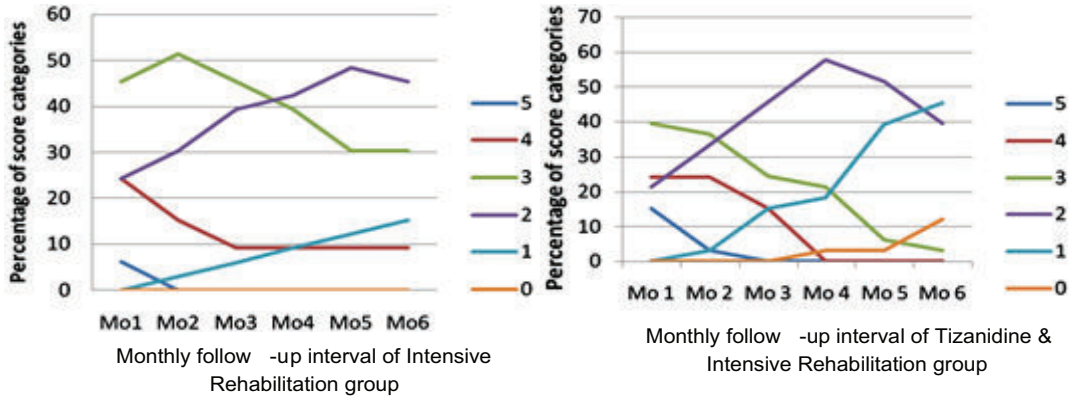

Figure-1. *Monthly change of muscle tone by modified ash worth scores between two treatment groups.*

Table-I

Age of patients (Mean ± SD).

Treatment Group	Age in Month	P value
Intensive Rehabilitation	25.27±12.81	0.048
Tizanidine & Intensive Rehabilitation	31.97±15.63	

among patients receiving Tizanidine and Intensive Rehabilitation and without any notable statistical significance (p = 0.33). 46% of the patients in the 4th month had mild variety, the condition lasting through the end of the follow up and with statisitcal signficant change in mean scores at 5th month (p = 0.03) but nonsignficant from 5th to 6th month (p = 0.14) (Figure-2).

Another component of physician rating scale of Intensive Rehabilitation group is foot contact score ranging from 0 grade (patient walk on toe) grade 4 (patient starts walking contact the ground first by heel and end by toe). It was found that patients receiving Intensive Rehabilitation showed detrimental trend in toe-walking on subsequent follow-up, which changed from base line (79%) to subsequent follow-up at 2nd and 3rd month, 64% and 52% respectively. It was not until the 4th month that 60% patients receiving Intensive Rehabilitation had a score of 1(starts walking with toe then heel). The change in mean scores from 3rd to 4th month was statistically significant (p = 0.04). The pattern of change continued till the last month of follow-up (p = 0.12). Patients receiving Tizanidine and Intensive Rehabilitation 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 < 0.0001) in mean score began between 3rd to 4th month and the trend continued till the end of the follow-up (Figure-3).

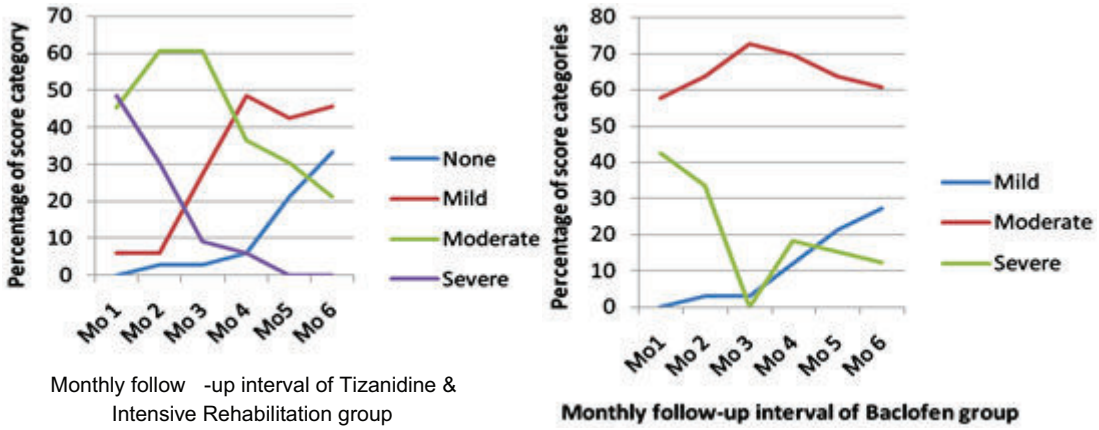

Figure-2. *Monthly change of joint angle measured by crouch scores of physician rating scale between two treatment groups.*

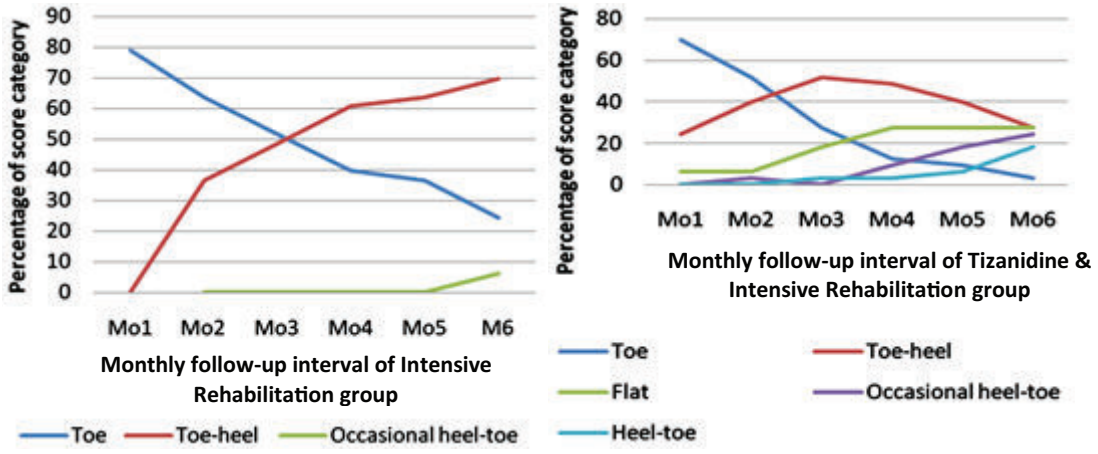

Figure-3. *Monthly change of gait measured by foot contact scores of physician rating scale between two treatment group.*

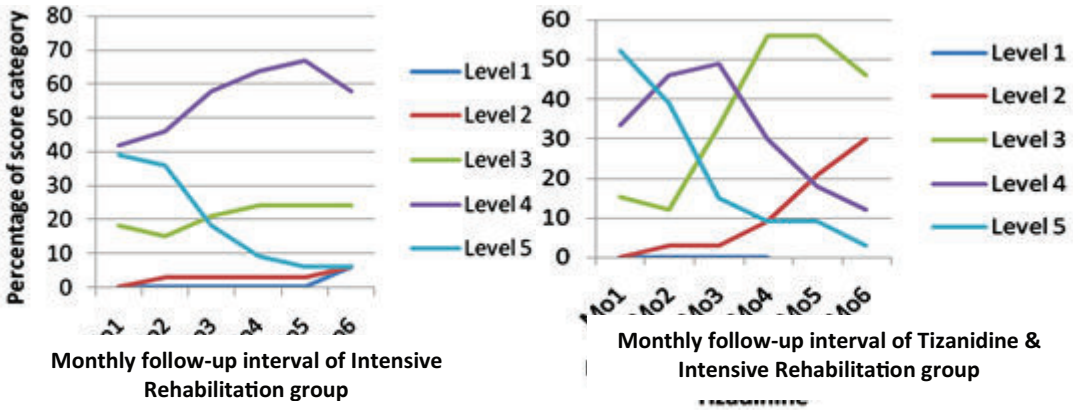

Figure-4. *Monthly change of gross motor function between two treatment groups.*

Before starting treatment, the majority of patients in the Intensive Rehabilitation group were in level-4 and level-5 (42% VS. 39% respectively). At 5th month (4th follow-up) the proportion of patients in level 4 increased to 67% whereas proportion of level-5 patients decreased to 8% but this improvement in gross motor function from level-5 to level-4 was not significant monthly follow-up was not statistically significant in any month. Tizanidine and Intensive Rehabilitation group: 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 receiving Tizanidine and Intensive Rehabilitation (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).

Discussion:

The syndrome of spastic hypertonia develops when the supra segmental control over the spinal cord segmental reflexes is lost[13]. Spasticity It 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] First we planned for a double blind comparative study between Intensive Rehabilitation and tizanidine with Intensive Rehabilitation for reducing spasticity in CP but due to unavailability of same dose formulation and non-convenience we compelled to do uniblind study. The minimum age for both the group was equal, although the maximum age differed by 6 months yielding a wider range of age among tizanidine with Intensive Rehabilitation group and therefore a larger mean compared to Intensive Rehabilitation. Mean age of tizanidine with Intensive Rehabilitation group was 31.97 months with SE 2.71. Mean age of Intensive Rehabilitation group was lower by about 7 months relating higher standard error (2.25). Independent t test showed that mean age of tizanidine with Intensive Rehabilitation was significantly higher (p = 0.048). This difference cannot be ruled out due to randomization process.

Nikkhah et 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 patient not coming to physician after 5 years due to socioeconomic condition & false belief. Nikkhah et 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 Vasques et 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). Alper et 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 among tizanidine with Intensive Rehabilitation receiving patients was lower compared to the gross motor function score of patients receiving Intensive Rehabilitation. But the difference by independent t test was non-significant (p > 0.05).

Physician ratings scales comprise crouch measure and foot contract score. Mean crouch score of patients receiving tizanidine with Intensive Rehabilitation and Intensive rehabilitation was tested for difference using independent t test. A higher mean crouch score for patients receiving tizanidine with Intensive Rehabilitation compared to Intensive Rehabilitation and the difference was statistically highly significant ($p < 0.0001$).

Wagstaff et 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. Data from this research shows that majority of the patients (abort 46%) receiving Intensive Rehabilitation were in a score of 3 of Asthwoth scale. It was not until the 4th month that the majority about 42% of the patient receiving intensive Rehabilitation improved to score 2. It is noteworthy that majority of the patients receiving tizanidine with Intensive Rehabilitation (about 39%). In the first month also were in Asthwoth some categories 3. However, majority of this later group began to show a lower Ashworth score in the 3rd month that is one month earlier than its Intensive Rehabilitation counterpart.

This improvement in the 3rd month to the 2nd month within the tizanidine with Intensive Rehabilitation group was also found to be statistically highly significant ($p < 0.0001$) using paired sample t test. During measuring crouch, majority (60% - 72%) of the patient in the Intensive Rehabilitation group had moderate angle based on crouch score. Also it is notable that no more than two patients improved from moderate to mild score in any given month time. Tizanidine with Intensive Rehabilitation group on the other hand 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 in Intensive Rehabilitation compared to tizanidine with Intensive Rehabilitation is at 3rd month. Using GFMS, there is no significant change in Intensive rehabilitation group but at 3rd month there is significant change in Intensive Rehabilitation group. Using foot contract Intensive Rehabilitation group has significant change at 4th month same as well tizanidine with Intensive Rehabilitation group. Using crouch score, there is no statistically significant improvement in Intensive Rehabilitation group whereas tizanidine with Intensive rehabilitation group has improvement in 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:

Analytical results 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 over intensive rehabilitation.

Limitation of the study:

Although sample size was calculated statistically, this was small in relation to the huge number of population of our country. It was a single-center study done in tertiary care hospital.

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:

No specific funding was received for this study.

Ethical consideration:

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

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