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Comparison of Baclofen and Tizanidine in Reducing Spasticity in Cerebral Palsy: A Randomized Control Trial

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Abstract

Background: Cerebral palsy is the most common chronic motor disability that begins in childhood with the predominant motor abnormality that is spasticity. **Objective:** The purpose of the present study was to compare the efficacy of oral baclofen and oral tizanidine in reducing spasticity in cerebral palsy patients. **Methodology:** This randomized controlled trial was conducted from January 2010 to December 2011 and it was carried out in the Out Patient Department (OPD) of Pediatrics at Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh and Center for Neurodevelopment and Autism in Children (CNAC) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. **Results**: A total number of 70 cerebral palsy children were recruited for this study of which 35 patients were in Tizanidine group and 35 patients were in baclofen group. Furthermore, 70 cerebral palsy children were taken as control who were treated with placebo. Tizanidine had superior efficacy in reducing tone in spastic cerebral palsy over baclofen measured by using Modified Ashworth scale in different time periods from AS score-3 to score-2 ($p < 0.05$). Tizanidine was also superior in joint angle improvement in spastic cerebral palsy measured by physician rating scale from AS score-3 to score-2 (crouch $p < 0.0001$) and foot contact from AS score-3 to score-2 ($p < 0.0001$); but no statistically significant improvement in gross motor function. Adverse effect was more in baclofen group. **Conclusion**: For reducing generalized spasticity with regards to muscle tone, joint angle and improvement in gait in cerebral palsy patients, tizanidine has superior efficacy and less adverse effects than baclofen.

Keywords

Cerebral Palsy, Spasticity, Baclofen, Tizanidine

1. Introduction

Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain [1]. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; by epilepsy, and by secondary musculoskeletal problems [1].

Once a decision is made to treat spasticity, a few drugs are available for consideration. These include benzodiazepines, baclofen, alpha-adrenergic agonists (tizanidine, clonidine), dantrolene sodium, and Gabapentine [2]. Baclofen is a GABA agonist that is used to reduce muscle tone. Baclofen crosses the blood-brain barrier and binds at the GABA ß receptors of the laminae I - IV of the spinal cord, where primary sensory fibers end [3].

Tizanidine is similar to diazepam and baclofen in the effectiveness of tone reduction [4]. 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 [5]. Tizanidine is possibly effective, but there are insufficient data on its effect on improvement of motor function and its side-effect profile. There are insufficient data to support or refute use of oral baclofen. But in clinical context baclofen is widely used to treat spasticity in children with cerebral palsy. The tizanidine and baclofen are currently most promising drugs treated for cerebral palsy. Therefore, these two drugs should be evaluated for their efficacy and safety. Thus, this present study was undertaken to compare the efficacy of oral baclofen and oral tizanidine in reducing spasticity in cerebral palsy patients.

2. Methodology

Study Population and Settings: This study was designed as parallel, single blinded randomized control trial. This study was conducted in the Department of Pediatrics at Dhaka Medical College, Dhaka, Bangladesh from January 2010 to December 2011 for a period of two (2) years. Patients who were attended in the Out Patient Department (OPD) of Pediatrics at Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh and Center for neurodevelopment and Autism in children (CNAC) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Necessary exclusion was done. This study was approved by Institutional review board (IRB) of the local institution.

Randomization and Blinding: All the spastic cerebral palsy patients seeking treatment at the above two OPD in all the working days were the reference population. From reference population patients fulfilling the selection criteria were enrolled as study population by systematic random sampling in which every second case was enrolled. Every second case was enrolled in the study who met the inclusion criteria and exclusion criteria, and their willingness to participate in this study. Age, sex, weight matching had been done at enrollment. Blinding was done by researcher.

Intervention and Allocation: After group allocation, drugs were given according to the dose schedule. Oral baclofen (10 g) was started with a very low dose (corresponding to approximately 0.3 mg/kg a day) in two divided doses. The dose was raised in 2 weeks interval. Doses for maintenance therapy was ranges between 1 to 2 mg/kg /day two divided doses for 6 months. Oral tizanidine (2 mg) was started at a dose of 1 mg given at bedtime for children under 10 years and 2 mg for children of 10 years or more; then after 1 week maintenance dose was 0.3 mg/kg/day divided three times daily for 6 months. After taking written inform consent and randomization, patient was first assessed with modified Asworth scale [6] (MAS) based on muscle tone. Then Physician rating scale [7] to measure joint angle specially by standard goniometer and overall functional status by gross motor functional classification system.

Follow up and Outcomes Measures: Drugs were given according to dose schedule after randomization and advice to follow up after 4 weeks. Mother or care giver was demonstrated how to give medicine to patient and total drugs for 4 weeks were given to ensure drug intake. Supervised physiotherapy given uniformly to both group by qualified physiotherapist of department of physical Medicine of Dhaka Medical College and BSMMU. After 4 weeks during the continuation of drugs patients was again assessed by author using before mentioned 3 scale again and recorded in follow up sheet. Follow up assessment was done every 4 monthly for total 6 month with continuing the drugs using same scales.

Statistical Analysis: Data was collected by a preformed questionnaire. Data analysis was done using computer software like SPSS 17.0. A p-value of <0.05 was considered significant. Qualitative data were expressed as frequency and percentage and quantitative data were expressed as mean and standard deviation. Comparison of qualitative data was performed by Chi-square test and student t test was done for quantitative data. All the test were 2 sided.

3. Results

A total number of 70 cerebral palsy children were recruited for this study of which 35 patients were in Tizanidine group and 35 patients were in baclofen group. Furthermore 70 cerebral palsy children were taken as control who were treated with placebo. 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 Baclofen

group was 25.27. Lower by about 7 months and relatively higher standard error (2.23) compared to tizanidine group (Table 1).

In this study about 46.0% of patients receiving Baclofen 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 reciving Baclofen 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 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 comapred to the 3rd month within the Tizanidine group was also found to be highly signficant ($p < 0.0001$) using paired sample t test. Moreover, by the end of the follow-up period (about 46.0%) of the Tizanidine group Ashworth score plumetted 1 step more putting them into the 1st category (Figure 1).

In Baclofen group, before starting treatment 58% patient was in moderate variety. At final follow-up, 6 months after treatment with baclofen 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 monthwise follow up is not statistically significant. Tizandine group on the other had showed remarkable variation in scores and accordingly change in severity of angle compared to patients recieving Baclofen. For example, 49% the patients had severe spacitcity 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 obsvered among patients

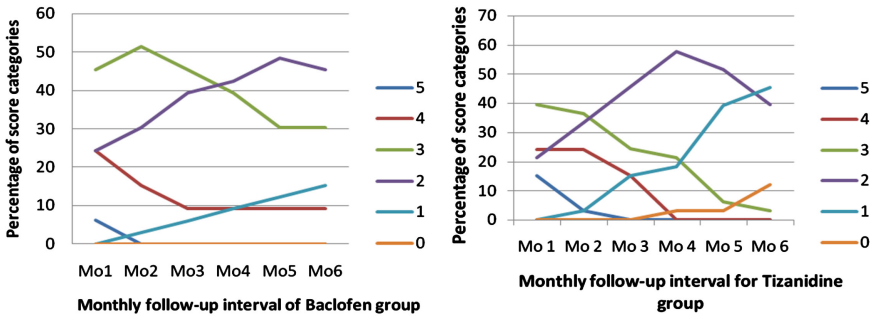

Figure 1. Monthly change of muscle tone by modified ash worth scores between two treatment groups.

Table 1. Demographic variables of patients (Mean ± SD).

Treatment Group	Age in Month	P value
Baclofen	25.27 ± 12.81	0.048
Tizanidine	31.97 ± 15.63	

recieving Tizanidine 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 Baclofen 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 recieving Baclofen showed deremental 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 untill the 4th month that 60% patients recieving Balofen had a score of 1(starts walking with toe then heel). The change in mean scores from 3rd to 4th month was statisitcally significant (p = 0.04). The pattern of change continued till the last month of follow-up (p = 0.12). Patients receiving Tizanidine 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 signficant (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).

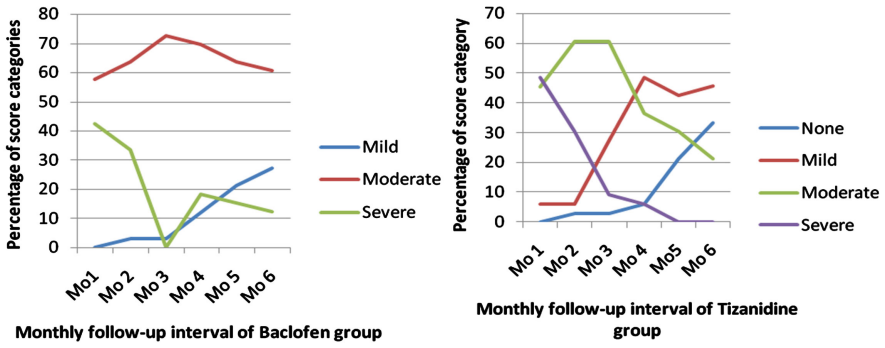

Figure 2. Monthly change of joint angle measured by crouch scores of physician rating scale between two treatment groups.

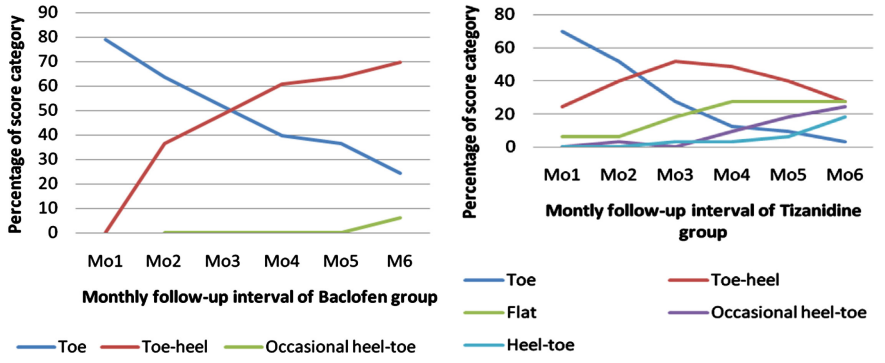

Figure 3. Monthly change of gait measured by foot contact scores of physician rating scale between two treatment group.

Before starting treatment, the majority of patients in the baclofen 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 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 (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).

4. Discussion

The syndrome of spastic hypertonia develops when the supra segmental control over the spinal cord segmental reflexes is lost [8]. Spasticity is defined as a motor disorder characterized by a velocity exaggerated increase in tonic stretch reflexes (muscle tone) with exaggerated reflex responses resulting from hyper activity of the stretch reflex [9]. First we planned for a double blind comparative study between baclofen and tizanidine 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 group and therefore a larger mean compared to baclofen. Mean age of tizanidine group was 31.97 months with SE 2.71. Mean age of baclofen group was lower by about 7 months relating higher standard error (2.25). Independent t test showed that mean age of tizanidine was significantly higher ($p = 0.048$). This difference cannot be ruled out due to randomization process.

Nikkhah *et al.* [10] found mean age of 7.3 ± 3.4 years and Adam *et al.* [11] 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.* [10] found the mean Ashworth score

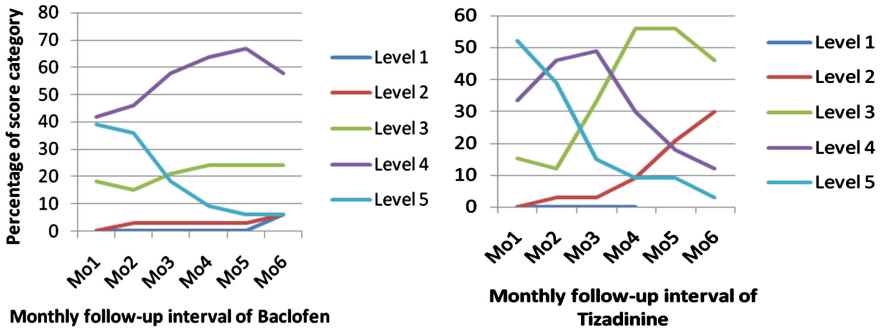

Figure 4. Monthly change of gross motor function between two treatment groups.

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.* [12] 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.* [13] 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 receiving patients was lower compared to the gross motor function score of patients receiving baclofen. 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 and baclofen was tested for difference using independent t test. A higher mean crouch score for patients receiving tizanidine compared to baclofen and the difference was statistically highly significant ($p < 0.0001$).

Wagstaff *et al.* [14] found improvement in muscle tone occurred in 60% to 82% of tizanidine recipients compared with 60% to 65% of baclofen. Adam *et al.* [11] 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 baclofen 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 baclofen improved to score 2. It is noteworthy that majority of the patients receiving tizanidine (about 39%). In the first month also were in Asthwoth some category 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 baclofen counterpart.

This improvement in the 3rd month to the 2nd month within the tizanidine 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 baclofen 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 group on the other hand showed remarkable variation in scores and accordingly change in severity of ankle compared to patients receiving baclofen. 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 baclofen compared to tizanidine is at 3rd month. Using GFMS, there is no significant change in baclofen group but at 3rd month there is significant change in baclofen group. Using foot contract baclofen group has significant change at 4th month same as well tizanidine group. Using crouch score, there is

no statistically significant improvement in baclofen group whereas tizanidine group has improvement in 5th month. Nikkhah *et al.* [10] showed after 2weeks improvement of tizanidine group compared to placebo. Alper *et al.* [13] showed improvement after 3rd month comparing tizanidine with botulinum compared to baclofen with botulinum in GMFCS score & MAS score.

5. Conclusion

In conclusion, tizanidine has superior efficacy and less adverse effect over baclofen for reducing generalized spasticity with regards to muscle tone and joint angle and gait improvement in cerebral palsy patients. Therefore, for reducing generalized spasticity with regards to muscle tone, joint angle and improvement in gait in cerebral palsy patients, tizanidine has superior efficacy and less adverse effects than baclofen.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Rosenbaum, P., Paneth, N., Leviton, A., *et al.* (2007) A Report: The Definition and Classification of Cerebral Palsy April 2006. *Developmental Medicine & Child Neurology*, **109**, 8-14.

[2] Thomas, M.O. (2008) Diagnosis, Treatment and Prevention of Cerebral Palsy. *Clinical Obstetrics and Gynecology*, **51**, 816-828. https://doi.org/10.1097/GRF.0b013e3181870ba7

[3] Surveillance of Cerebral Palsy in Europe (SCPE) (2000) Surveillance of Cerebral Palsy in Europe: A Collaboration of Cerebral Palsy Surveys and Registers. *Developmental Medicine & Child Neurology*, **42**, 816-824. https://doi.org/10.1017/S0012162200001511

[4] Reddihough, D.S. and Collins, K.J. (2003) The Epidemiology and Causes of Cerebral Palsy. *Aust Journal of Physiotherapy*, **49**, 456-462. https://doi.org/10.1016/S0004-9514(14)60183-5

[5] Paneth, N., Hong, T. and Korzeniewski, S. (2006) The Descriptive Epidemiology of Cerebral Palsy. *Clinics in Perinatology*, **33**, 251. https://doi.org/10.1016/j.clp.2006.03.011

[6] Aneja, S. (2004) Evaluation of a Child with Cerebral Palsy. *Indian Journal of Pediatrics*, **71**, 627-628. https://doi.org/10.1007/BF02724123

[7] Yam, W.K. and Leung, M.S. (2006) Inter Rater Reliability of Modified Ashworth Scale and Modified Tardieu Scale in Children with Spastic Cerebral Palsy. *Journal of Child Neurology*, **21**, 1031-1035. https://doi.org/10.1177/7010.2006.00222

[8] Mutlu, A., Livanelioglu, A. and Gunel, M.K. (2008) Reliability of Ashworth and Modified Ashworth Scales in Children with Spastic Cerebral Palsy. *BMC Musculoskeletal Disorders*, **9**, 44. https://doi.org/10.1186/1471-2474-9-44

[9] Katz, R.T. (1991) Management of Spastic Hypertonia after Stroke. *Journal of NeuroEngineering and Rehabilitation*, **5**, s5-s12. https://doi.org/10.1177/136140969100500502

[10] Nikkah, A., Mohammadi, M., Ashrafi, M.R. and Zamani, G.H. (2011) The Efficacy and Safety of Tizanidine in Treating Spasticity in Children with Cerebral Palsy. *Iranian Journal of Child Neurology*, **5**, 19-22.

[11] Adam, S., Kate, H., Lawrence, T.L. and Stephen, O.F. (2006) Oral Baclofen in Children with Cerebral Palsy: A Double Blind cross over Pilot Study. *Journal of Paediatrics and Child Health*, **42**, 715-720. https://doi.org/10.1111/j.1440-1754.2006.00957.x

[12] Vasques, B.A., Arellano, S.M.E., Leon, H.S.R. and Morales, O.M.G. (2006) The Usefulness of Tizanidine. A One Year Follow up of Treatment of Spasticity in Infantile Cerebral Palsy. *Revue Neurologique*, **43**, 132-136.

[13] Alper, I.D., Mohammad, W. and Safia, A. (2008) Botulinum Toxin Type A with Oral versus Oral Tizanidine: A Nonrandomized Pilot Comparison in Patients with Cerebral Palsy and Spastic Equinous Foot Deformity. *Journal of Child Neurology*, **23**, 1464. https://doi.org/10.1177/0883073808319074

[14] Wagstaff, A.J. and Bryson, H.M. (1997) Tizanidine a Review of Its Pharmacology, Clinical Efficacy and Tolerability in the Management of Associated with Cerebral and Spinal Disorders. *Drugs*, **53**, 435-452. https://doi.org/10.2165/00003495-199753030-00007