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Botulinum Toxin Type A With Oral Baclofen Versus Oral Tizanidine: A Nonrandomized Pilot Comparison in Patients With Cerebral Palsy and Spastic Equinus Foot Deformity

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The objective of this study was to compare the effectiveness of baclofen versus tizanidine as adjuvant treatment of botulinum toxin type A botulinum toxin type A in the management of children with spasticity. Thirty children with gastrocnemius spasticity were retrospectively reviewed at Gaziantep University Hospital, Gaziantep, Turkey. All patients were treated with localized botulinum toxin injections and baclofen or tizanidine for spasticity and were followed at 2- to 4-week intervals and evaluated for a total of 12 weeks; 17 children (57%) received baclofen and 13 (43%) received tizanidine. The mean score of Gross Motor Functional Measurement (76.63 ± 5.88 vs 68.17 ± 1.99; $P < .001$) and caregiver questionnaire scores (70.23 ± 4.76 vs 66.59 ± 3.53; $P = .03$) for the tizanidine group were significantly higher as compared with the baclofen group. This study suggests that combination of botulinum toxin type A with oral tizanidine is more effective with fewer side effects than combination of botulinum toxin type A and oral baclofen for spastic cerebral palsy.

Keywords: cerebral palsy; botulinum toxin; tizanidine; baclofen

Cerebral palsy is characterized by nonprogressive impairment of posture and motor function. Most oral medications used to treat the spasticity of cerebral palsy have been inadequately studied in children, and these drugs offer only a modest benefit because of undesirable side effects.

Abnormal motor function and spasticity are key features in children with cerebral palsy. Spasticity management requires the use of different treatment methods throughout the childhood.[1] For the walking child with spastic cerebral palsy, simple measures such as stretching, walking, and orthotic use can be supplemented by oral muscle relaxants and botulinum toxin.[2] Botulinum toxin type A improves the gait outcomes and the overall prognosis in children with cerebral palsy.[3] However, its duration of effect varies. The use of intramuscular botulinum toxin for focal spasticity may also increase the efficacy of orally administered drugs such as baclofen or tizanidine.[4]

Various oral medications have been used to diminish the sensitivity of local nerves and muscles to control their reactions to environmental stimuli that result in muscle overactivity or involuntary movements.[5] Baclofen, tizanidine, and diazepam are the most frequently prescribed oral agents. Tizanidine is a centrally acting α-2 adrenergic agonist. It has been shown to decrease polysynaptic reflex activity, probably by reducing release of excitatory neurotransmitters from presynaptic neurons. Baclofen acts centrally like most anti-spasticity medications. It binds to γ-aminobutyric acid (GABA) receptors and inhibits spinal reflexes. Both medications have been found to be effective in the treatment of spasticity of both cerebral and spinal origin among adult patients. The use of oral medications in children with cerebral palsy has not been thoroughly studied. Higher dosages are associated with systemic side effects such as sedation, weakness, and behavior change.[6] The purpose of this study was to compare the effectiveness of baclofen and tizanidine in

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children receiving intramuscular botulinum type A for spasticity.

Patients and Methods

We retrospectively reviewed 30 children with gastrocnemius spasticity who were evaluated at Gaziantep University Hospital, Turkey, between 2005 and 2007. All of these children had spastic equinus foot deformity associated with cerebral palsy or static encephalopathy confirmed by a pediatric neurologist.

All patients were enrolled in a rehabilitation program and given local injections of botulinum type A for spasticity. Selection criteria for intramuscular botulinum type A injections included dynamic deformity interfering with function, producing pain, or contributing to progressive deformity; painful spasticity with or without fixed muscle contracture.[7] We injected 20 to 24 U of botulinum type A (Botox, Allergan Pharma, Irvine, CA) per kilogram of body weight with a maximum of 300 U per child on 1 occasion with a maximum dose of 50 U per injection site.[8] Intranasal midazolam was used as an anesthetic agent during the procedure.[9]

A 1:1 dilution of botulinum toxin and normal saline was used. We palpated the gastrocnemius muscle, using the skin as a fulcrum to determine needle placement without electromyography guidance. The short 1-mL "diabetic" all-in-one syringe and needle were used for this purpose. Both gastrocnemius muscles were injected with botulinum type A at each injection session.

A total of 17 children were treated with adjuvant oral baclofen and 13 received oral tizanidine. The tizanidine dosage ranged from 0.3 mg/kg/day to 0.5 mg/kg/day in 4 divided doses.[10] The baclofen dosage ranged from 10 mg/kg/day to 15 mg/kg/day in 3 divided doses to a maximum of 40 mg/day if less than 8 years of age or to 60 mg/day if more than 8 years of age.[11] The patients were not randomized, and the decision to chose one medication or the other was entirely based on physician preference.

The treatment protocol was approved by the hospital's ethical committee, and an informed consent was obtained from the patients or guardians. All parents were asked to fill out "caregiver questionnaire" form (CHQ)[12] and to document the side effects from tizanidine or baclofen before and for 3 months after the botulinum type A injections.

All patients were followed at 2- to 4-week intervals and evaluated for a total of 12 weeks. The therapeutic response in both the groups was assessed by means of Gross Motor Functional Measurement (GMFM)[13] and the modified Ashworth scale (MAS)[14] for leg functional measurement and for leg spasticity assessment by the same pediatric neurologist. Laboratory tests (done monthly) included complete blood count and differential, liver function tests, thyroid function test, electrolytes, serum glucose, lipid, and albumin level.

Table 1. Baseline Clinical Characteristics of the Treatment Groups

	Baclofen Group	Tizanidine Group	*P* Value
Sex: male/female; n (%)	11/6 (64/36)	9/4 (69/31)	.55
Age: mean ± SD	5.71 ± 2.97	5.46 ± 2.63	.81
GMFM score: mean ± SD	46.04 ± 2.73	47.40 ± 1.51	.09
MAS score: mean ± SD	3.65 ± 0.60	3.69 ± 0.48	.82
CHQ score: mean ± SD	57.82 ± 3.76	58.08 ± 3.68	.85

GMFM, Gross Motor Function Measure; MAS, Modified Ashworth Scale; CHQ, Caregiver Questionnaire; SD, standard deviation.

Table 2. Clinical Outcome of the Treatment Groups After 3 Months

	Baclofen Group	Tizanidine Group	*P* Value
GMFM score: mean ± SD	68.17 ± 1.99	76.63 ± 5.88	< .001
MAS score: mean ± SD	2.24 ± 0.56	1.77 ± 0.59	.03
CHQ score: mean ± SD	66.59 ± 3.53	70.23 ± 4.76	.03

GMFM, Gross Motor Function Measure; MAS, Modified Ashworth Scale; CHQ, Caregiver Questionnaire; SD, standard deviation.

Statistical Analysis

Data were analyzed using a commercially available software package for social science SPSS (Release 14.0, standard version, copyright © SPSS; 1989-2002). Proportions were compared using the χ^2 test or Fisher exact test, where appropriate, and means were compared using Student *t* test. Probability values were two-tailed. Significance level was set at 5%.

Results

Thirty children were included in the study. Age ranged from 2 years to 14 years (mean; 5.6 years), and 20 (66%) participants were male. A total of 17 children (57%) were treated with oral baclofen and 13 (43%) received oral tizanidine. The 2 groups were similar in age, sex, and mean GMFM, MAS, and CHQ scores. Baseline characteristics of both groups are given in Table 1.

The mean scores of both the GMFM (76.63 ± 5.88 vs 68.17 ± 1.99; $P < .001$) and the CHQ (70.23 ± 4.76 vs 66.59 ± 3.53; $P = .03$) for the tizanidine group were significantly higher than those of the baclofen group (Table 2). Significant improvements in the CHQ score (2.24 ± 0.56) occurred in baclofen group ($P = .03$).

Side effect profile was also slightly better for the tizanidine treatment group. Patients treated with baclofen had more complains of anorexia and abdominal pain than the tizanidine-treated patients.

Discussion

This study compared the efficacy and safety of oral baclofen and tizanidine when used in conjunction with botulinum toxin type A for cerebral palsy. Our data suggest that adjuvant treatment with oral tizanidine is more effective than baclofen in combination with botulinum toxin for spastic equinus foot deformity due to cerebral palsy. Significant improvement was demonstrated using GMFM and the MAS ($P \leq .05$). The side-effect profile of tizanidine was superior to that of baclofen.

Botulinum toxin injections are currently a standard treatment for spastic cerebral palsy, but there is currently no consensus among clinicians about its optimal dose. There are no standard guidelines for dosing botulinum toxin type A in children. Reviews of previous publications indicate that the dose used for children with cerebral palsy has increased over time. Dosages of 16 U/kg to 24 U/kg body weight are now widely used. The current practice is to inject several muscles at each injection session, with smaller patients receiving higher doses than reported in the past.[8]

Another important confounding variable is the extensive use of physical and occupational therapy in the management of these children. As controversial as it may sound, there is limited formal evidence to establish the real benefit of these therapies in the rehabilitation of focal muscle spasticity.[15]

The important limitation of this study is the limited number of the sample size and its nonrandomized approach. Adjunctive treatment is required in several patients with spasticity in addition to botulinum injections. Nevertheless, these findings may have important clinical implications for physicians who treat children with cerebral palsy. Larger, prospective, randomized, controlled clinical trials in the pediatric population are needed to confirm and extend our findings.

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