RESEARCH ARTICLE

The Efficacy and Safety of Tizanidine in Treating Spasticity in Children with Cerebral Palsy

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Abstract

Objective

Spastic cerebral palsy (CP) is one of the most difficult and disabling conditions that requires medical attention and treatment. The aim of this study was to assess the efficacy and safety of oral tizanidine in treating spasticity in children with spastic CP.

Materials & Methods

Sixty children with spastic cerebral palsy were enrolled in a double-blind, placebo-controlled, randomized clinical trial. These patients were randomly assigned to receive tizanidine or a matching placebo. Sample normalization was not performed either before or after the study in these two separate groups. Nevertheless, no significant statistical difference was found between the two concerned groups in terms of age, sex, or type of spasticity. Each patient received the treatment for 2 weeks between May 2010 and February 2011.

Results

Thirty-one boys and 29 girls with a mean age of 7.3 ± 3.4 years were evaluated. Our study revealed that spasticity was reduced in 50% of the patients receiving the drug tizanidine compared to only 6.7% of the patients receiving the placebo. Additionally, 66.7% of patients reported less pain on the affected side receiving tizanidine (group A) compared to 13.3% of patients receiving the placebo (group B). No serious side effects were reported in this study.

Conclusion

Tizanidine is effective and safe in decreasing the spastic hypertonia associated with cerebral palsy in children.

Keywords: Tizanidine; spasticity; cerebral palsy; children

Introduction

Spastic cerebral palsy (CP) is one of the most disabling conditions in children. Indeed, CP is a nonspecific descriptive term pertaining to disordered motor function evident during the early infant stage. CP is characterized by changes in muscle tone (typically spasticity) and certain neurological abnormalities, such as ataxia, abnormal movements, and sensory, behavioral, and cognitive dysfunction (1). CP occurs in 1.2 to 2.5 children per 1000 live births, premature birth being the single most important risk factor (2,3). CP can be classified into two types: the predominant type of motor abnormality, which is further classified into six forms (spastic, choreathetotic, dystonic, hypotonic, ataxic, and mixed) and the distribution of limb

involvement into three forms (hemiplegic, diplegic, and quadriplegic) (4,5,6).

Many treatments have been proposed to treat spasticity under the assumption that spasticity is the main factor causing motor dysfunction and disability (7).

Tizanidine is an imidazole derivative in the same class as clonidine, which is known to be a potent α2-agonist (8). It is reported to be a presynaptic inhibitor that reduces the release of excitatory amino acids such as glutamate and aspartate. The drug may also facilitate the action of the inhibitory neurotransmitter glycine (9). Some of the most common side effects of tizanidine are dry mouth, sedation, dizziness, and hypotension.8 In this case, sedation may be a beneficial side effect if the drug is being used to improve spasms and comfort at night(10). Following two studies that have reported outcomes of tizanidine treatment in children with CP (11), we decided to evaluate the efficacy and safety of tizanidine for the treatment of spasticity in children affected with CP living in Tehran, Iran.

Materials & Methods

This double-blind, placebo-controlled, randomized clinical trial was conducted on children between the ages of 2 and 14 with spastic CP, who were referred to the pediatric neurology clinic at the children´s medical center between May 2010 and Feb 2011. The sample size of children with spastic CP was assessed to be 60 based on Z formula and a confidence interval (CI) of 95% with 20% power to detect any significant difference between two groups (A & B) with a level of 0.05. These patients were enrolled into two different groups (30 patients in each group) via balanced block randomization. Sample normalization was not performed either before or after the study in these two separate groups. Nevertheless, no significant statistical difference was found between the two concerned groups in terms of age, sex, or type of spasticity. Specifically, our main objective was to evaluate the efficacy of tizanidine on decreasing spasticity. Patients in group A received tizanidine (2 mg/day for age <7 years old and 4 mg/day for age >7 years old) and patients in group B received a matched placebo. We examined the patients before drug administration and assessed the severity of spastic hypertonicity using the Modified Ashworth Scale (MAS) (Table 1). After 2 weeks of drug administration, we re-examined these patients and the new scores were compared with the previous scores. Additionally, we evaluated the reduction in pain sensation after drug or placebo administration based on historical information and subjective sensation of patients or their parents' assessment.

Chi-square or Fisher exact tests were used for data analysis of qualitative variables and mean values were compared using a t-test. This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran.

Results

The efficacy and safety of tizanidine was evaluated in children with spastic CP. Thirty-one boys (51.7%) and 29 girls (48.3%) with a mean age of 7.3 ± 3.4 year (range = 2–14 year) were included in this study. In the evaluation of group statistics and t-test for equality of means for age, sex, and type of spastic CP, there was no significant statistical difference between groups A and B ($P > 0.1$). Indeed, the two groups were similar with respect to these variables.

After 2 weeks of treatment, the Ashworth Score on the affected side was decreased in 15 patients of group A (received tizanidine), whereas the score was only decreased in 2 patients of group B (received placebo) (50% vs. 6.7%). These results showed that there was a significant statistical difference between the two groups ($P < 0.0001$). Moreover, tizanidine was significantly better than the placebo for pain reduction in spastic upper and/or lower limbs (66.7% vs. 13.3%) ($P < 0.0001$) (Figs. 1, 2).

Discussion

The syndrome of spastic hypertonia develops when the supra segmental control over the spinal cord segmental reflexes is lost.12 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 hyperactivity of the stretch reflex(12). The most common cause of spasticity in childhood is cerebral palsy (CP) (13).

In this study, we evaluated the effect of tizanidine in treating spasticity in children with spastic CP. Tizanidine is an imidazole derivative and a potent α2-

agonist.8 This drug is also a presynaptic inhibitor that reduces the release of excitatory amino acids such as glutamate and aspartate. It may also facilitate the action of the inhibitory neurotransmitter glycine (9). In the present study, the Modified Ashworth Scale (MAS) was used to measure spastic hypertonia. In this scale, the resistance during passive muscle stretching at an unspecified velocity or body posture is evaluated (14). As mentioned in our study, 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 Maythaler et al. (2001), tizanidine treatment in 17 patients with spasticity due to acquired brain injuries significantly decreased the average Ashworth score for the affected side following 4 weeks of treatment (P<0.001) (15). In a separate double-blind study by Vasquez et al. (2006), 10 children suffering from spastic CP were treated with tizanidine and 30 children received a placebo for a 6-month period. Children receiving the placebo were thereafter unified with the group receiving tizanidine. Of the patients in the group receiving tizanidine, 78.8% reported having reduced spasticity compared with only 7.6% patients receiving the placebo (P<0.0001)(16). More recently, Palazon Garcia et al. (2008) reported the effect of tizanidine in 45 children with spastic CP. Their studies show that tolerance of tizanidine was excellent in 79% of children and was found to be good by 93% of their parents based on subjective assessment (17).

Unfortunately, there have been few and limited studies on the effect of tizanidine in children. Despite these limited evaluations, many neurologists recommend that tizanidine be considered for the treatment of spasticity in childhood CP.18 Additionally, our results show a statistically significant reduction in pain (66.7%) as opposed to only 13.3% in the placebo group, a study that was not directly related to amount of decrease in spasticity (P<0.0001). These findings have not been previously reported in the literature.

In conclusion,Tizanidine is an effective and safe drug for decreasing the spastic hypertonia associated with spastic CP in children. On the basis of our experimental findings, we conclude that tizanidine could be considered as a useful anti-spastic drug for the treatment of spastic CP in children.

Table 1: Modified Ashworth Scale Score(14)

Test	Description	Score
Modified Ashworth Scale Score	No increase in muscle tone	0
	Slight increase in tone with a catch and release or minimal resistance at end of range	1
	As 1 but with minimal resistance through range following catch	2
	More marked increase tone through ROM*	3
	Considerable increase in tone, passive movement difficult	4
	Affected part rigid	5

*ROM:Range Of Motion

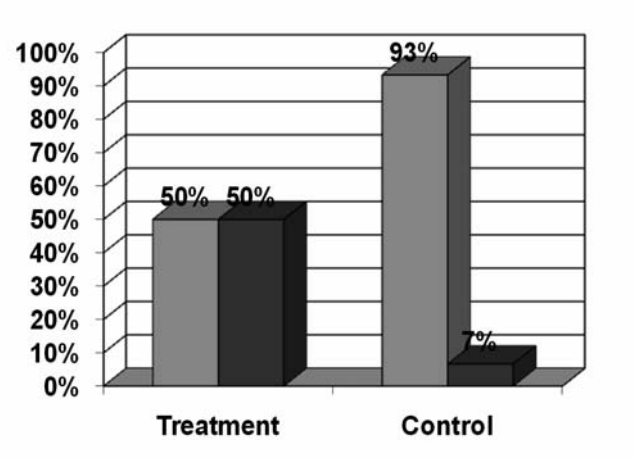

Fig 1. Changes in Ashworth Score between two groups of treatment. (Grey = no change, Black = better).

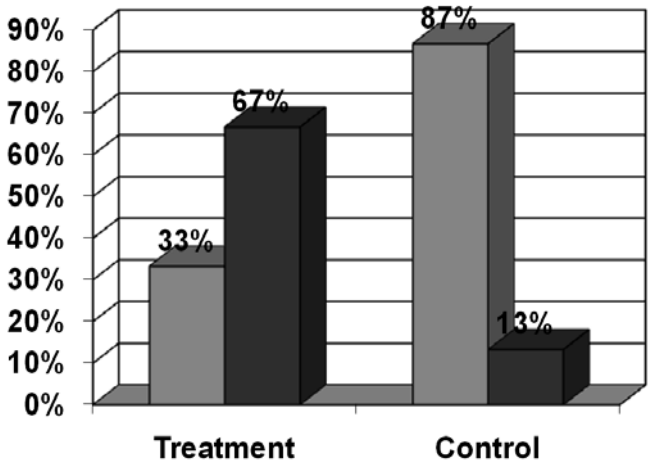

Fig2. Changes in pain reduction between two groups of treatment. (Grey = no change, Black = better)

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