Botulinum Toxin A Does Not Improve the Results of Cast Treatment for Idiopathic Toe-Walking

A Randomized Controlled Trial

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Background: There are many treatments for idiopathic toe-walking, including casts with or without injection of botulinum toxin A. Combined treatment with casts and botulinum toxin A has become more common even though there have been few studies of its efficacy and safety problems. Our aims were to conduct a randomized controlled trial to test the hypotheses that combined treatment with casts and botulinum toxin A is more effective than casts alone in reducing toe-walking by patients five to fifteen years of age, and that the treatment effect correlates with the extent of coexisting neuropsychiatric problems.

Methods: All patients who had been consecutively admitted to the pediatric orthopaedics department of our institution because of idiopathic toe-walking between November 2005 and April 2010 were considered for inclusion in the study. Forty-seven children constituted the study population. The children were randomized to undergo four weeks of treatment with below-the-knee casts either as the sole intervention or to undergo the cast treatment one to two weeks after receiving injections of botulinum toxin A into the calves. Before treatment and three and twelve months after cast removal, all children underwent three-dimensional (3-D) gait analysis. The severity of the idiopathic toe-walking was classified on the basis of the gait analysis, and the parents rated the time that their child spent on his/her toes during barefoot walking. Passive hip, knee, and ankle motion as well as ankle dorsiflexor strength were measured. Before treatment, all children were evaluated with a screening questionnaire for neuropsychiatric problems.

Results: No differences were found in any outcome parameter between the groups before treatment or at three or twelve months after cast removal. Several gait-analysis parameters, passive ankle motion, and ankle dorsiflexor strength were improved at both three and twelve months in both groups, even though many children still demonstrated some degree of toe-walking. The treatment outcomes were not correlated with coexisting neuropsychiatric problems.

Conclusion: Adding botulinum toxin-A injections prior to cast treatment for idiopathic toe-walking does not improve the outcome of cast-only treatment.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Several types of treatment have been suggested for idiopathic toe-walking, such as physical therapy, serial casts, and open or percutaneous Achilles tendon lengthening. Botulinum toxin A was first introduced for pediatric use in patients with spasticity, typically associated with cerebral palsy, in the early 1990s. Subsequently, the suggested indications for botulinum toxin A...
toxin A have expanded\textsuperscript{11}. Gradually, its use became more commonplace, despite a lack of studies on its efficacy and safety.

In the first study of botulinum toxin A for idiopathic toe-walking, published in 2004, ten children (two to seventeen years old) who exhibited idiopathic toe-walking were given injections of botulinum toxin A followed immediately by one to three weeks of treatment with below-the-knee walking casts, bracing, and physical therapy\textsuperscript{12}. All had ceased toe-walking three months later, but two children received repeated injections at three and twelve months. In another study, five children whose idiopathic toe-walking had been treated with botulinum toxin A and physical therapy without casts also showed an improved walking pattern\textsuperscript{13}, but two of the children received repeated botulinum toxin-A injections and splints after three months. The authors speculated about whether the outcomes would have been improved by cast treatment post-injection, particularly if an ankle plantar flexion contracture was present. In our own previous study, fifteen children exhibiting idiopathic toe-walking were treated with botulinum toxin A and physiotherapy and several of them had improvement in their walking pattern; however, it was difficult to predict which children would cease toe-walking\textsuperscript{14}.

Several studies have focused on the treatment of toe-walking with casts. Good results have been reported, with a high percentage of children ceasing toe-walking after three to ten weeks of cast treatment\textsuperscript{2-4}. Other studies, however, have shown contradicting results, with no long-term effect of cast treatment (at two to 21.5 years)\textsuperscript{7,15}.

It has been reported that children with autism spectrum disorders have a high prevalence of idiopathic toe-walking\textsuperscript{16}. A relationship between a delay in language and speech development and idiopathic toe-walking has also been described\textsuperscript{17,18}. However, it is unknown whether children with idiopathic toe-walking and accompanying neuropsychiatric problems respond as well to treatment as those without such problems.

We conducted a randomized controlled trial to evaluate whether botulinum toxin A improves the results of treatment of idiopathic toe-walking with below-the-knee walking casts.

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**Fig. 1**
Patient flowchart.
The specific hypotheses that we tested were that a combination of botulinum toxin A and casts is more effective than casts alone in reducing toe-walking by five to fifteen-year-old children, and that the overall treatment effect is correlated with coexisting neuropsychiatric problems. Evaluation methods included three-dimensional (3-D) gait analysis, parents’ perception of toe-walking frequency, passive ankle motion measurements, strength of ankle dorsal extensors, and a parental questionnaire for identifying neuropsychiatric symptoms.

Materials and Methods

This study received ethical board approval and was registered at ClinicalTrials.gov (NCT01590693). All consecutive children with idiopathic toe-walking evaluated at the pediatric orthopaedics department at Karolinska University Hospital between November 15, 2005, and April 15, 2010, were considered for inclusion. A child was considered to exhibit idiopathic toe-walking when, according to the parents’ perception, he/she walked at least 25% of the time on his/her toes and had done so for at least three months. Additional inclusion criteria included no other explanation for the toe-walking and no known congenital Achilles tendon contracture. Exclusion criteria were previous treatment for idiopathic toe-walking such as Achilles tendon surgery, casts, orthotics, and injection of botulinum toxin A as well as plantar flexion contracture beyond 10°.

A pediatric orthopaedic surgeon (P.E.) evaluated all children who exhibited idiopathic toe-walking. Seventy-eight children met the inclusion criteria, and their families were asked whether they would allow their child to participate in the study. The family received written and oral information about the study and were given time to discuss it at home before consenting to participate. Fifty-two families consented to participate (Fig. 1).

<table>
<thead>
<tr>
<th>TABLE I Demographic Characteristics</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>No. of patients</td>
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<tr>
<td>Sex (no.)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age† (yr)</td>
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<tr>
<td>Family history of idiopathic toe-walking (no.)</td>
</tr>
<tr>
<td>Cesarean section delivery (no.)</td>
</tr>
<tr>
<td>Age at independent walking† (mo)</td>
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</tbody>
</table>

*P value of the difference between the numbers of male and female subjects was determined with a chi-square test. †The values are given as the mean with the range in parentheses.

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<tr>
<th>TABLE II Gait Analysis Variables That Significantly Improved Between Pre-Treatment Evaluation and Three and Twelve-Month Evaluations</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Ankle angle at initial contact (°)</td>
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<tr>
<td>Ankle max. dorsiflexion (°)</td>
</tr>
<tr>
<td>Ankle dorsiflexion in swing (°)</td>
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<tr>
<td>Ankle max. plantar flexion (°)</td>
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<tr>
<td>Ankle max. dorsiflexion timing (% of gait cycle)</td>
</tr>
<tr>
<td>Ankle power minimum (W·kg⁻²)</td>
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<tr>
<td>Ankle power max. (W·kg⁻¹)</td>
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<tr>
<td>Ankle negative work (J·kg⁻¹)</td>
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<tr>
<td>Knee flexion max. in swing (°)</td>
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<tr>
<td>Knee extension in midstance (°)</td>
</tr>
<tr>
<td>Knee extension moment average (Nm·kg⁻²)</td>
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</tbody>
</table>

*Positive numbers = dorsiflexion or knee extension, and negative numbers = plantar flexion or knee flexion. †Norm = reference values from twenty-three able-bodied children from the current clinical database.
A pediatric neurologist with expertise in neuropsychiatric disorders examined all children to rule out any coexisting neurologic abnormality. The neurologic examination included evaluation of muscle tone, plantar reflex, deep tendon reflexes, and motor and cerebellar function. The neurologist confirmed that no child had any underlying neurologic or muscular pathology.

The children also underwent a neuropsychiatric assessment consisting of a neuropsychiatric history that included cognitive development, language development, and behavioral and/or social interaction problems. The parents filled out the Five to Fifteen (FTF) questionnaire, which was designed to identify problems and strengths most commonly encountered in five to fifteen-year-old children presenting with neuropsychiatric symptoms. The questionnaire has been validated in several studies.

Treatment randomization was done with use of sealed envelopes with randomly permuted blocks of four. A medical statistician prepared the envelopes, and a nurse performed the randomization. The randomization was done prior to baseline examinations, but the staff conducting the baseline examinations and the children and parents were blinded to which group the child had been allocated until after the baseline examinations. All children were randomized to four weeks of treatment with below-the-knee walking casts either as the sole treatment (CA group) or following botulinum toxin-A injection into the calf muscles (CA+BX group). Of the fifty-two children, four children and their parents withdrew from the study, citing recent media reports about adverse effects of botulinum toxin A, and one child moved from the area. These five children had all been randomized to the CA+BX group, leaving forty-seven children (median age, 9.6 years; range, 5.0 to 14.5 years; eighteen boys and twenty-nine girls) in the study, with twenty-six children in the CA group and twenty-one children in the CA+BX group (Table I). All children started walking independently before eighteen months of age except for one girl in the CA group who commenced walking at twenty-four months of age. In her neonatal period, this girl had been evaluated with several electroencephalograms (which indicated normal activity) and extending from the toes to the proximal part of the calf. The same nurse with special education in cast techniques applied all casts, with an aim of positioning the ankle in neutral. All children wore the casts for four weeks, but the children in the CA+BX group received their casts one to two weeks after botulinum toxin-A injections.

### Botulinum Toxin-A Treatment

The children in the CA+BX group underwent bilateral treatment with 12 units/kg body weight of Botox (Allergan, Irvine, California). One hour before injection, all children were given 40 mg/kg of oral paracetamol, and topical anesthetic cream (EMLA; AstraZeneca, Södertälje, Sweden) was applied at the injection sites. Just prior to and during injection, all children inhaled nitrous oxide for pain relief and sedation. Four injections in each calf—two in the proximal third of the lateral and medial gastrocnemius bellies and two distally in the gastrocnemius-soleus complex—were administered. Injections were performed with electromyogram-amplifier guidance to ensure intramuscular position.

### Stretching Program

After cast removal, all children/parents were given oral and written instructions by a physiotherapist to perform calf-muscle stretches five times per week and to walk on their heels at least fifty steps per day.

### Outcomes

#### Gait Analysis

Before treatment and three and twelve months after cast removal, all children underwent 3-D gait analysis, conducted by a single physical therapist.
Parents’ Perception of Toe-Walking Frequency and Side Effects

The parents rated the time that their child spent on his/her toes during barefoot walking to the nearest quartile (0%, 25%, 50%, 75%, or 100%) before treatment and at three and twelve months following cast removal. They were also asked whether they noticed any side effects of the treatment.

Joint Range-of-Motion Measurements and Strength of Ankle Dorsal Extensors

Before treatment and three and twelve months after cast removal, all children underwent an examination by a single experienced physical therapist, who measured the passive range of motion of the hip, knee, and ankle joints with a goniometer. Ankle passive range of motion was measured with the knees in both extended and 90° flexed positions. Ankle dorsal extensor strength was measured with a handheld dynamometer (MicroFET2; Hoggan Health Industries, West Jordan, Utah). Each child lay supine on an examination bed with the calves overhanging the bed. The moment arm was measured from the lateral malleolus to the midfoot dorsally. The physiotherapist held the dynamometer to the child’s midfoot dorsally (while stabilizing the heel) and resisted motion while the child pressed the dynamometer for five seconds. The highest of three force measurements was used for analysis. Strength measurements were normalized for each child’s weight.

The physical therapist had no information about group assignment, but sometimes the children and/or parents revealed this information.

Assessment of Neuropsychiatric Problems

The FTF questionnaire consists of 181 questions divided into eight domains: motor skills, executive functions, perception, memory, learning, language, social skills, and emotional/behavioral problems. Parents’ answers are calculated to determine a domain score. If a child’s score is above the 90th percentile of the reference value for a studied domain, he/she is considered to have difficulties with tasks in that domain.

Data and Statistical Analyses

Statistical analysis was based on the intention-to-treat principle. Power analysis was performed to perceive a difference of 5° in the ankle angle with a standard deviation of 9.5° (based on pilot data)—i.e., an effect size of 0.5 at the alpha = 0.05 significance level. A study population of n = 50 is equal to a sample power of 0.940, and with n = 40 the sample power is 0.881. In this study, n = 47.

Gait data and the passive range of ankle motion were analyzed with a mixed model. Measurements were performed before treatment and three and twelve months after treatment. The within-subject factors in the mixed model were time (three testing occasions) and side (left and right) and the between-subject factor was group (CA or CA+BX). In order to analyze the passive ranges of motion of the hip and knee, we fitted a generalized estimating equations (GEE) model with the GENMOD procedure (SAS, System 9.1) as the limited variability in measured angles is not suitable for the mixed model. Sex distribution was compared between groups with a chi-square test. Age distribution was compared between groups with the independent-samples t test. The within-group time effect of the parents’ perception of toe-walking and the classification of toe-walking severity was analyzed with the Friedman two-way analysis of variance by ranks, and the difference between groups at all testing occasions was analyzed with the Mann-Whitney U test.

To evaluate whether the presence of neuropsychiatric problems had any effect on treatment results, three parameters were used to express the overall treatment effect: ankle angle at initial contact, idiopathic toe-walking classification, and parents’ perception of toe-walking frequency. The difference between the pre-treatment and twelve-month post-treatment values for these three parameters was calculated. Correlations between the overall treatment effect and the number of domains in which the child scored above the 90th percentile were calculated with Spearman rank tests.

Source of Funding

Funding for this study was provided by research grants from the Centre of Competence Blekinge County Council, Promobilia Foundation, Samariten Foundation, and Society for Childcare. The funding sources did not play a role in the investigation.

Results

There were no differences between groups with regard to age or sex distribution.

One child in the CA+BX group was lost to follow-up after the three-month evaluation.

Gait Analysis

There were no significant differences in any gait parameter between the CA and CA+BX groups before treatment or at the three or twelve-month follow-up evaluation. In both groups, several gait analysis parameters had improved significantly at both three and twelve months (Table II). In both groups, the significant changes in nearly all parameters were found at the three-month post-treatment evaluation; almost no significant change occurred between the three and twelve-month follow-up evaluations. The only exception was an additional increase in maximal ankle power between the three and twelve-month follow-up evaluations in the CA+BX group.

At the time of follow-up, the initial ground contact was with the foot in a less planter flexed position in both groups. Maximal ankle dorsiflexion in stance shifted by an average of 9° from a plantar flexed position to dorsiflexion, and maximal dorsiflexion during swing phase improved from a plantar flexed to a neutral position. Maximal dorsiflexion occurred later in the gait cycle, so that it approached the timing for the gait laboratory reference group of able-bodied children. Maximal plantar flexion during gait decreased. Improvements in kinetic parameters included greater maximal ankle power generation, greater ankle power absorption, and greater negative work at the ankle.

Greater maximal knee flexion in swing and less knee hyperextension in midstance were observed, although the average changes in degrees were small. A greater average knee...
extension moment during stance, consistent with reduced knee hyperextension, was found. No significant changes were observed in cadence, normalized step length, or normalized walking speed.

Classification of idiopathic toe-walking severity showed no difference between the groups at any time. Both groups improved significantly between the pre-treatment and follow-up evaluations, with no change between the three and twelve-month follow-up evaluations (Table III).

Parents’ Perception of Toe-Walking Frequency and Side Effects (see Appendix)

There was no difference between the CA and CA+BX groups in toe-walking frequency before treatment. At the three-month follow-up evaluation, parents in the CA+BX group perceived a significantly lower toe-walking frequency than parents in the CA group (p = 0.033), although the difference between groups with regard to the improvement between the pre-treatment and three-month evaluations did not quite reach significance (p = 0.053). No between-group difference was observed at twelve months. Three children in the CA group and six children in the CA+BX group had ceased toe-walking, as perceived by their parents, by twelve months.

Parents reported no serious side effect in any child. In the CA group, two children had midcalf pain during the cast period and three children experienced itching and chafing from the casts. In the CA+BX group, one child reported calf pain after the botulinum toxin-A injection, three children had mild calf pain during cast treatment, and three children experienced minor skin problems.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cast Only</th>
<th>Cast + Botulinum Toxin A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Treat.</td>
<td>3 Mo</td>
</tr>
<tr>
<td>Ankle dorsiflexion with extended knee (°)</td>
<td>4.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Ankle dorsiflexion with knee flexed 90° (°)</td>
<td>11.5</td>
<td>16.0</td>
</tr>
</tbody>
</table>

Joint Passive Motion and Dorsiflexion Strength

Ankle dorsiflexion with the knees both flexed and extended increased in both groups at both follow-up evaluations (Table IV). No difference was observed between groups at any testing occasion. Prior to treatment, four children in the CA group lacked a neutral (90°) ankle position by 10° with extended knees and two in the CA+BX group lacked a neutral ankle position by 5° with extended knees; only one child (CA group) lacked a neutral ankle position by 5°, in one leg, with flexed knees. No changes in hip or knee motion were observed.

There were no differences between groups with regard to ankle dorsal extensor strength before treatment or at either follow-up evaluation. In the CA group, strength significantly increased between the pre-treatment and twelve-month evaluations (p = 0.011) and between the three and twelve-month evaluations (p = 0.031). In the CA+BX group, strength also significantly increased from the pre-treatment analysis to both the three-month (p = 0.01) and the twelve-month (p = 0.001) follow-up evaluation.

Influence of Neuropsychiatric Problems on Treatment Effect

As there was no difference in treatment effect between the CA and CA+BX groups, the correlations were performed for the entire group. No correlation was found between the number of domains in which the child scored above the 90th percentile and the treatment effect (difference in ankle angle at initial contact: r = −0.20, p = 0.18; difference in idiopathic toe-walking classification: r = −0.22, p = 0.14; and difference in parents’ perception: r = 0.09, p = 0.56).
Discussion

Administration of botulinum toxin-A injections prior to four weeks of treatment with below-the-knee casts for idiopathic toe-walking does not improve the treatment outcome. No differences could be seen between the treatment groups with regard to improvement of gait parameters, toe-walking severity classification, parents’ perceived frequency of toe-walking, passive ankle motion, or strength of ankle dorsal extensors at any evaluation. Both groups showed a marked improvement in all of these parameters after their respective treatments, at both three and twelve months, although thirty-eight of the forty-seven children still, to a varying extent, walked on their toes after treatment.

To our knowledge, no previous study has investigated this question. Two randomized controlled trials of children with cerebral palsy compared cast treatment alone with cast treatment and botulinum toxin-A injections with regard to gait parameters and passive range of motion after treatment. In both of those studies, the authors found that treatment with botulinum toxin A was no better than cast-only treatment.

The success rate following treatment of idiopathic toe-walking with below-the-knee walking casts is controversial. Several studies have shown favorable outcomes in the short or medium term (up to two years) and the cast’s effect has been postulated to result from elongation of noncontractile elements and increasing the number of sarcomeres in the calf muscles. In contrast, two other retrospective studies demonstrated no long-term improvement (at two to 21.5 years) after cast treatment compared with the results following no treatment at all. In our study, the majority of children in both groups spent less time toe-walking, had a better range of ankle motion, and had improvement in several gait parameters at twelve months, although only nine of the forty-seven children had completely ceased toe-walking according to their parents. Even though we did not include a control group that received no treatment, it seems unlikely that the improvements observed were not related to the treatment, as nearly all significant changes occurred between the pre-treatment and three-month post-treatment evaluations and not between the two follow-up evaluations. In order to evaluate longer-term effects, we have an ongoing follow-up plan for the children in the study.

We are unaware of any previously published study assessing the effect of neuropsychiatric problems on the outcome of treatment of idiopathic toe-walking. We found that a greater prevalence of neuropsychiatric problems had no influence on treatment results. Even though our study population is too small for us to draw any firm conclusions about this question, the general belief of many clinicians that children with idiopathic toe-walking are more difficult to treat successfully if they have neuropsychiatric problems was not confirmed.

A limitation of this study is that the questionnaire regarding parents’ perception of toe-walking frequency is not a validated tool. Nevertheless, we consider parents’ opinion very important, as it provides a good indication of the child’s walking pattern in an unobserved environment, complementing information gained from observations of walking. Also, five children originally assigned to the CA+BX group withdrew from the study after randomization but before treatment. There is, however, no reason to believe that inclusion of these children would have changed the overall results, as their reasons for withdrawal were not related to their toe-walking severity or frequency. Also, the fact that group allocation was occasionally revealed by the children to the physical therapist should be considered a limitation, although a minor one.

The primary aim of this randomized controlled trial was to determine whether botulinum toxin A adds any benefit to cast treatment for idiopathic toe-walking. We conclude that it did not in the group that we studied.

Whether the effect of botulinum toxin-A treatment for idiopathic toe-walking can be improved with repeated injections, addition of bracing, or more vigorous physiotherapy programs is unknown and should thus be studied in future randomized controlled trials. In general, high-quality studies exploring a wider variety and combination of treatments are required to find an optimal treatment strategy. Until such evidence is obtained, we cannot recommend that clinicians complement cast treatment with botulinum toxin-A injections in children with idiopathic toe-walking.

Appendix

A table showing parents’ perception of toe-walking frequency is available with the online version of this article as a data supplement at jbjs.org.

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