

Does Botulinum Toxin A Combined with Bracing Prevent Hip Displacement in Children with Cerebral Palsy and “Hips at Risk”?

A Randomized, Controlled Trial

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Background: Cerebral palsy is the most common cause of childhood physical disability in developed countries, affecting two children per 1000 live births. Hip displacement affects about one-third of children with cerebral palsy and may result in pain, deformity, and impaired function. The prevention of hip displacement has not been studied in a randomized trial as far as we know.

Methods: A randomized, controlled trial was conducted to examine the effect of intramuscular injections of botulinum toxin A combined with use of a variable hip abduction brace on the progression of hip displacement in children with cerebral palsy. The patients in the treatment group received injections of botulinum toxin A to the adductor and hamstring muscles every six months for three years and were prescribed a hip abduction brace to be worn for six hours per day. In the control group, no hip bracing was used nor were injections performed. The primary outcome measure was hip displacement from the acetabulum as determined by serial measurements of the migration percentage.

Results: Ninety children with bilateral cerebral palsy and so-called hips at risk (a migration percentage of >10% but <40%) were entered into the study. Fifty-nine patients were boys, and the mean age was three years. Progressive hip displacement, as determined by serial measurements of the migration percentage, was found in both the treatment and control groups. The rate of hip displacement was reduced in the treatment group by 1.4% per year (95% confidence interval, -0.6% to 3.4%; $p = 0.16$) when weighted for the uncertainty in rates due to the differing numbers of migration percentage measurements per subject.

Conclusions: There may be a small treatment benefit for the combined intervention of intramuscular injection of botulinum toxin A and abduction hip bracing in the management of spastic hip displacement in children with cerebral palsy. However, progressive hip displacement continued to occur in the treatment group, and our data do not support recommending this treatment.

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

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Fig. 1-A

The SWASH brace (sitting, walking, and standing hip orthosis) seen from the front (Fig. 1-A) and above (Fig. 1-B). The SWASH brace consists of a pelvic component, with rods attached to two variable hinges and two adjustable thigh cuffs. The hips are maintained in abduction and the degree of abduction can be adjusted. When the hips are extended (Fig. 1-A), the hips are abducted to a smaller degree so that the child can experience standing and stepping without scissoring. In the sitting position, with the hips flexed, the brace ensures a much wider degree of abduction (Fig. 1-B).

Cerebral palsy is the most common cause of childhood physical disability in developed countries and affects two children per thousand live births, in our community¹⁻³. Silent lateral hip displacement may progress to painful hip dislocation and later arthritis³⁻⁵. The incidence of hip pain may be underreported because of cognitive and communication difficulties in some children^{6,7}. Hip dislocation may impair higher motor functions, such as running and walking, in children who are able to walk and may impair more basic functions, such as the ability to stand or to sit comfortably in a wheelchair, in children with severe motor impair-

ment^{8,9}. In the early stages, spastic hip displacement is difficult to detect clinically, and regular radiographs of the hip are recommended as the best method for early detection¹⁰. The aim of surveillance is to detect hip displacement at a time when intervention to prevent further displacement may be effective¹¹. Systematic hip surveillance, leading to early diagnosis of hip displacement and followed by prompt preventative surgery, results in a marked decrease in late hip dislocation and its sequelae^{11,12}. However, we know of no clinical trial that has investigated the effects of nonoperative interventions on the progression of hip displacement in children with cerebral palsy.



Fig. 1-B

Nonoperative treatments for hip displacement include various braces and postural alignment systems in which the common aims are to maintain adequate hip abduction and to prevent progressive contractures of the hip adductor muscles and hamstring muscles and consequent hip dislocation¹³. However, fixed abduction braces are not well tolerated in children with cerebral palsy⁹. Compliance is often poor, and there is no evidence that they are effective^{8,9}. A new brace, the variable hip abduction orthosis (SWASH brace; CAMP, Helsingborg, Sweden) allows sitting, lying, standing, and walking with the hips maintained in a variable degree of abduction (Figs. 1-A and 1-B). We know of no prior controlled trial of hip abduction braces to prevent hip displacement in children with cerebral palsy.

Intramuscular injections of the neurotoxin botulinum toxin A are effective in reducing adductor spasticity in children with cerebral palsy and in improving the passive range of hip abduction¹⁴⁻¹⁶. However, injections alone may not result in lengthening of the adductor muscles in sitting and standing without the use of a brace to stretch them¹⁷. A small, prospective pilot study has suggested that intramuscular injections of botulinum toxin A to the hip adductors and medial hamstrings combined with the use of the variable hip abduction orthosis could reduce spasticity and stretch the hip adductor muscles better than the brace alone. Our study tests the hypothesis that intramuscular injection of the hip adductor and hamstring muscles with botulinum toxin A, combined with abduction bracing with use of the SWASH brace, would reduce the progression of hip displacement in children with spastic cerebral palsy, in a single-blind, randomized clinical trial. Secondary study aims were to examine safety, utility, and compliance issues associated with the use of the variable hip abduction orthosis in combination with the intramuscular injections of botulinum toxin A. We undertook a study across four states with a three-year outcome to address these issues.

Materials and Methods

Study Design

This investigation was a multicenter, phase-III, randomized, controlled trial. Subjects were recruited between 1997 and 2001. The control group received standard care but no hip abduction bracing or injections of botulinum toxin A. The treatment group received injections of botulinum toxin A to the hip adductor and hamstring muscles every six months, when specific criteria were met (Fig. 2). Subjects were followed for a three-year period. The children entered the study from five centers. The institutional review board at each center approved the study protocol, and all families or legal guardians gave written informed consent. Entry criteria for each potential subject were verified centrally by at least two chief investigators.

Randomization

Eligible patients with cerebral palsy were allocated to the intervention or the control limb according to a predetermined randomization list developed by the Clinical Epidemiology and Biostatistics Unit at the coordinating center. Randomization was stratified by motor distribution (diplegia or quadriplegia), age at the time of entry (twelve to thirty-six months or thirty-seven months to a corrected age of five years at the time of entry), and the severity of displacement for the hip that was most severely displaced (a migration percentage of 10% to 20%, 21% to 30%, or 31% to 40% at study entry). This gave fourteen possible groups, with each group containing equal numbers allocated to treatment and control.

After consent was obtained and the child had been allocated to the appropriate group, personnel at the coordinating center opened the next numbered opaque envelope in the list and treatment allocation was conveyed by telephone to the treating physician. Neither participants nor personnel involved with assessment and treatment were blind to the treatment allocation. However, the decision to exit from the study to

surgery was made by an observer who was masked to group allocation.

Inclusion Criteria

Children were entered into the study if they had bilateral spastic cerebral palsy, were between one and five years of corrected age at study entry, and had hip adductor spasticity and scissoring postures with hips at risk. These criteria were verified on videotaped recordings of patients with supine, supported standing, and stepping postures. For the purpose of this study, *hips at risk* were defined as those having a migration percentage between 10% and 40%^{18,19}.

Exclusion Criteria

Children were excluded if they had a fixed muscle contracture of the hip adductors with an abduction range of $<20^\circ$ in either hip. They were also excluded if they had had previous hip surgery, an initial migration percentage of $>40^\circ$, a hip flexion contracture of $>30^\circ$, or scoliosis with a Cobb angle of $>20^\circ$. Children with pseudobulbar palsy were excluded because of an increased risk of aspiration and respiratory complications after injection of botulinum toxin A¹⁷. Pseudobulbar palsy was diagnosed on the basis of a history in the medical record of disordered pharyngeal and/or laryngeal function, including feeding problems, choking on food or fluids, aspiration of food or fluids, speech problems, and airway or respiratory difficulties.

Interventions

Subjects in the intervention group received intramuscular injections of botulinum toxin A to both hip adductor and medial hamstring muscles. The dose was 4 U/kg of the botulinum toxin-A preparation (Botox; Allergan, Irvine, California) to each muscle, for a total maximum dose of 16 U/kg of body weight. A standard dilution of botulinum toxin A was used by reconstituting 100 U in 1.0 mL of normal saline solution. Injections were repeated every six months if indicated, according to clinical criteria. The criteria for repeated injections were spasticity on clinical examination, a modified Ashworth scale score of 1+ or greater, and a reduced dynamic range according to the modified Tardieu scale of $<40^\circ$ of abduction or $<45^\circ$ of popliteal angle^{20,21}.

The modified Ashworth scale is a six-level, ordinal grading system that is widely used to describe the increase in passive resistance to movement, which is commonly felt in spastic limbs (see Appendix)²⁰.

The modified Tardieu scale measures the point of initial resistance (catch) through the range of passive motion of a limb segment. The test is conducted at a consistent, fast angular velocity, starting from a standardized limb position. It permits an assessment of the velocity-dependent component of hypertonicity and is considered to be a valid and reliable method for measuring spasticity in children with cerebral palsy²¹.

With use of these two clinical measures of spasticity, it was possible to identify when the effects of the previous injection of botulinum toxin A had worn off and when a particular muscle group should be reinjected.

Botulinum toxin A was injected, according to previously described protocols, with use of mask anesthesia^{14,22}. With the child in the supine position, the hips were flexed and abducted. The pubic tubercle and adductor longus tendon were identified by palpation and marked with a skin-marking pen. Two sites were injected in each adductor group. The first was 2 cm distal to the pubic tubercle, just posterior to the adductor longus, and the second was 4 cm distal to the pubic tubercle, again just posterior to the line of the adductor longus tendon.

During hamstring injections, the hips were flexed to 90° and the knee was extended until it was restricted by hamstring spasticity, as when measuring the popliteal angle. The ischial tuberosity was palpated and marked. The hamstrings were identified by palpation running from the ischial tuberosity along the posterior aspect of the thigh. A 23-gauge needle was inserted into the palpable mass of the medial hamstrings, and the position was confirmed by flexing and extending the knee and observing reciprocal movements of the needle. Once satisfactory needle position was confirmed, the syringe containing the botulinum toxin-A solution was attached. Two sites were injected. The first was proximally, at 2 to 4 cm from the ischial tubercle, and the second was in the midpart of the thigh, directly into the mass of the medial hamstrings.

The injecting physician at each center used the same dose, dilution, and injection protocol that had been standardized before the trial commenced. All children were evaluated three weeks after the injection to determine the maximum clinical response and to record adverse events related to the injection or anesthesia.

Injections of botulinum toxin A were combined with the use of the SWASH brace, which was worn for six to eight hours per day. The brace was used predominantly during the day, when the child was in sitting positions, but also for lying, crawling, standing, and walking according to the functional abilities of the child. An experienced pediatric orthotist fitted each SWASH brace, and repairs and minor adjustments were performed at regular intervals. A single orthotist managed the bracing program at each center. The range of hip abduction in the orthosis was set at between 15° and 30° of hip abduction in extension. The duration of brace wear was recorded by parents in diaries and was monitored by the child's community physiotherapist. Records were kept of the estimate of brace wear made by both the parents and the therapist. No limits were placed on the amount of physiotherapy, specialized seating, or the use of standing frames, gait aids, and below-the-knee orthoses for both groups, but amounts of these concomitant therapies were monitored at each six-month review. At the initial visit, parents and caregivers received an educational session to explain the trial, the importance of hip surveillance, and the relevance of the measures performed during the study to determine the child's progress.

Follow-up Procedures and Outcomes

All children were evaluated in hip surveillance clinics at tertiary referral centers every six months by the research physical

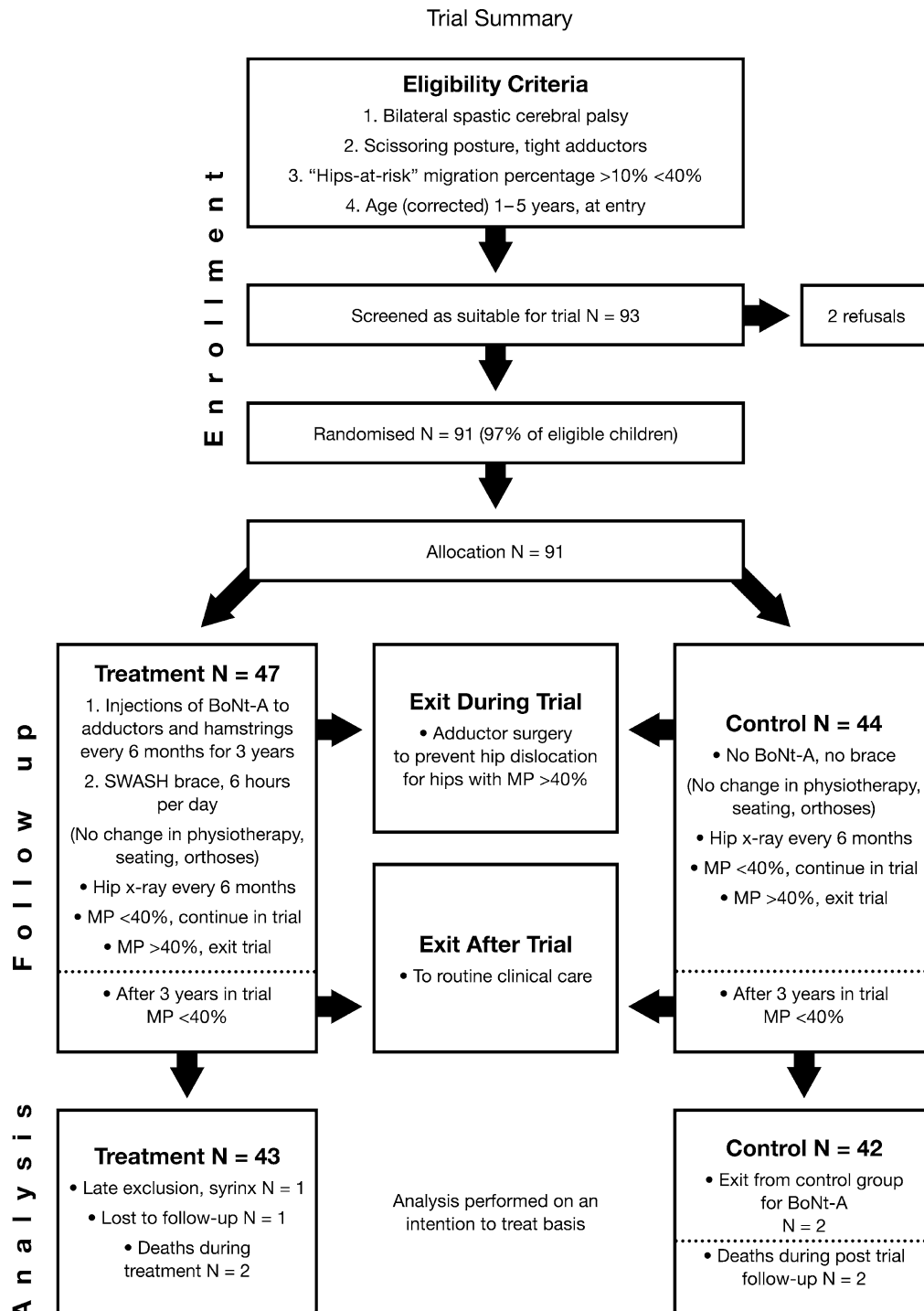


Fig. 2

Trial summary. MP = migration percentage, and BoNT-A = botulinum toxin A.

therapist, orthopaedic surgeon, and/or pediatrician. The gross motor function of each child was classified according to the Gross Motor Function Classification System (GMFCS) at the time of entry into the study and at each subsequent visit²³. The GMFCS is a five-level, ordinal grading system, which is

based on self-initiated movement, with particular emphasis on sitting (truncal control) and walking. The descriptors vary according to age and have been fully described and illustrated elsewhere. The GMFCS is valid, reliable, and relatively stable over time. For this study, four age-range descriptors were used:

TABLE I Demographic Data on the Patients and a Summary of Treatments Used in the Treatment Group

Variable	Treatment Group (N = 47)	Control Group (N = 44)
Mean age at entry (y + mo)	3 + 2	2 + 11
Gender		
Male	28	31
Female	19	13
Motor distribution (no. of patients)		
Diplegia	15 (32%)	14 (32%)
Quadriplegia	32 (68%)	30 (68%)
GMFCS level* (no. of patients)		
II	3 (6%)	2 (5%)
III	12 (26%)	6 (14%)
IV	13 (28%)	21 (48%)
V	19 (40%)	15 (34%)
Migration percentage at study entry†		
Right hip	22.8 (10.1)	23.0 (9.9)
Left hip	22.9 (8.1)	24.2 (9.2)
Treatments†		
Botulinum toxin A (U/kg)	13.9 (2)	
Brace wear† (hr)	5.6 (2.06)	
Concomitant therapy		
Individual physiotherapy sessions (no. of patients)	43 (91%)	43 (98%)
Group physiotherapy sessions† (hr/mo)	272 (3.9)	242 (4.0)
Postural management (no. of patients)		
Special seating	23 (49%)	20 (45%)
Standing frame	34 (72%)	30 (68%)
Gait aids	32 (68%)	30 (68%)
Wheelchair	24 (51%)	20 (45%)

*GMFCS = Gross Motor Function Classification System. †The values are given as the mean, with the standard deviation in parentheses.

before the second birthday, between the second and fourth birthday, between the fourth and sixth birthday, and between the sixth and twelfth birthday.

Hip displacement was measured from an anteroposterior radiograph of the hips, with use of a reliable protocol to measure the migration percentage²⁴. The primary study outcome measure was the hip migration percentage. The secondary outcome measure was the progression of hip displacement that led to surgery.

Exit Criteria

When hip displacement exceeded the migration percentage by 40% or the increase in migration percentage was >10% in six

months, children were considered to have hips at high risk of rapid displacement and dislocation^{11,12,19}. The decision to exit from the study was made not by the treating surgeon but by a colleague, masked to group allocation, using the following process. The treating surgeon and therapist, with full knowledge of the group allocation, identified a child who was thought to have reached the radiographic criteria to exit the study and proceed to surgery. The child and the series of radiographs that had been made up to that time were presented to a colleague who was masked to group allocation. The masked observer judged whether exit criteria were met and whether the child should continue in the study or exit to surgery. The child and the radiographs were then evaluated by a surgeon, and the patient was offered adductor-lengthening surgery to prevent hip dislocation. The progression of fixed deformities, such as contractures of the hip adductor and hamstring muscles, was also considered, secondarily to radiographic criteria, in the decision to exit from the study.

All pelvic radiographs meeting the exit criteria were checked at the lead center by an observer who was masked to group allocation.

Sample Size

The primary measure for sample size calculation was the migration percentage from a natural history study in which migration percentage increased by a mean of 6.4% per year without treatment²⁵. At the age of thirty months, children in the control group were expected to have a mean migration percentage of 16% and were expected to have deterioration to 32% at five years of age. Halving the annual progression from 6.4% to 3.2% would result in a migration percentage of 24% at the age of five years in a typical patient in the treatment group. Assuming a standard deviation of 5.2%, it was determined that to have 80% power to detect a difference of 3.2 percentage points in annual rates of change in the migration percentage and with use of a significance level of 0.05 in a two-sided two-sample t test, a sample size of forty-four children in each group was required. We aimed to recruit forty-four children per group with the benefit of two hips being monitored per subject, providing improved power to an extent that would depend inversely on the strength of the intrachild correlation.

Statistical Analysis

For progression of the migration percentage, a summary statistic was calculated for each hip²⁶—the slope of the line of best fit by linear regression through the migration percentage measurements over time. These slopes were compared between groups with use of a two-sample t test for univariate analysis and linear regression when adjusting for GMFCS level. Standard errors were adjusted for the clustering of hips among subjects with use of the information sandwich formula (release 8.0, 2003; Stata Statistical Software, College Station, Texas). The analysis was performed (1) without any weighting of the summary statistics, (2) with each hip weighted according to the number of migration percentage measurements for that

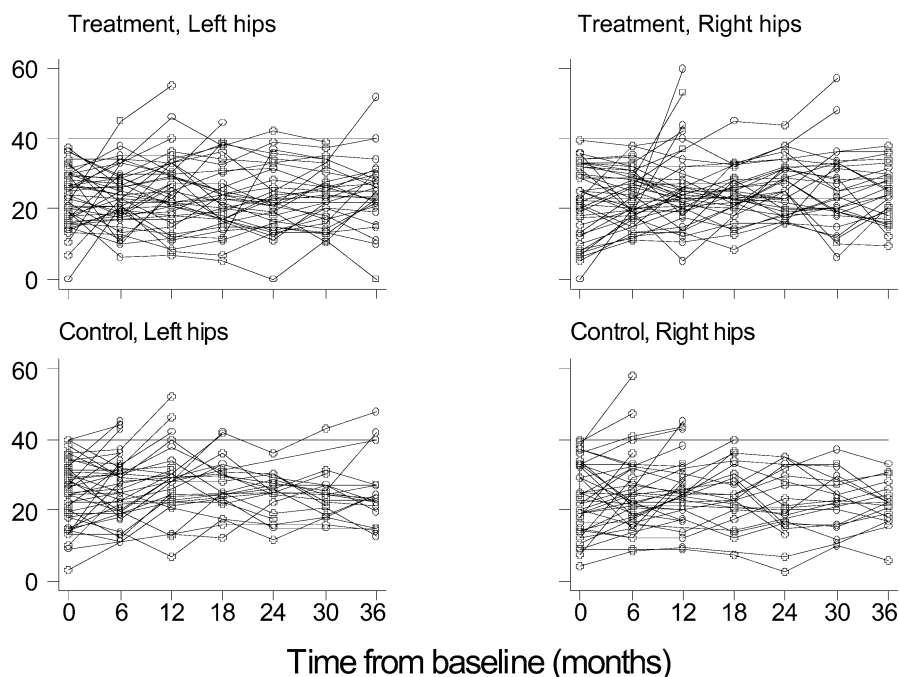


Fig. 3

Changes in the migration percentage in the treatment (botulinum toxin A combined with variable hip abduction bracing) and control groups at the six-month reviews during three years of follow-up. Each line represents the migration percentage data for a single hip, and the circles indicate the migration percentage at that interval. The horizontal line is at a migration percentage of 40%. It can be seen that the migration percentage values for some hips quickly crossed from <40% to $\geq 40\%$. In other hips, the migration percentage remained close to the 40% line for a longer period. In these children, the timing of exit from the study was more difficult to determine.

hip, and (3) the inverse of the variance (squared standard error) of the slope from the line of best-fit analysis. The analyses assume that missing data were missing at random, i.e., unobserved migration percentages were predictable given observed migration percentages, time, and study group. Analysis was performed on an intention-to-treat basis.

Results

Study Population

Ninety-one of ninety-three eligible children entered the study, for a 98% recruitment rate (Fig. 2). One child was later excluded from the treatment group because of a diagnosis of a cervical level syrinx in addition to a static brain lesion. The treatment and control groups were evenly balanced by center (Fig. 2). The two groups had similar baseline characteristics apart from GMFCS levels (Table I). The numbers of children with epilepsy, respiratory illness, feeding tubes, and ventriculoperitoneal shunts are reported in a table in the Appendix.

Adverse Effects and Safety

The occurrence of adverse events related to botulinum toxin-A injection and/or anesthesia was determined by questioning the parents at an examination three weeks after the injection, as most, if not all, botulinum toxin-A-related events occur within

this time²⁷. Younger children with severe cerebral palsy are prone to respiratory infections and gastrointestinal problems, and our data may overestimate the incidence of botulinum toxin-A-related adverse events. The mean dose (and standard deviation) of botulinum toxin A was 13.9 ± 2.1 U/kg per child for a total of 204 episodes of treatment in forty-six patients. The mean weight of the children in the treatment group was 14.4 ± 3.7 kg (range, 8 to 32 kg). The mean total dose of botulinum toxin A was 196.8 ± 51.8 U, with a total usage of 39,180 units in the study.

During the study, two children in the intervention group and none in the control group died. The two deaths that occurred during the trial were at 3.1 weeks and 26.4 weeks after injection of botulinum toxin A. Autopsy findings suggested that the deaths resulted from asphyxiation related to epilepsy.

Adverse events were classified as major if they required medical consultation, treatment, or hospital admission.

There were twelve major adverse events following 204 injection episodes, an incidence of 6%. These included the two deaths, which were not thought to be injection related. There were four episodes of respiratory infection. One child was managed with antibiotics at home, and three were treated in the hospital for two to three days. Two children had bronchospasm during recovery from general anesthesia. Three chil-

TABLE II Patient Progression to Surgery and Withdrawal During the Three-Year Follow-up Period

Status	Months from Baseline (<i>no. of patients</i>)						Total
	6	12	18	24	30	36	
Group treated with botulinum toxin A and bracing* (n = 47)							
Completed follow-up							32 (70%)
Surgery			5	3	1	2	11
Deceased		1	1				2
Withdrawn		1				0	1
Control group (n = 44)							
Completed follow-up							21 (48%)
Surgery	10	9	1	1		1	22
Deceased							0
Withdrawn		1					1

*One of the forty-seven patients in the group was excluded because of a cervical level syrinx.

dren had urinary incontinence, lasting from one to four days before spontaneous resolution. One child had a flu-like illness, characterized by fever, vomiting, weakness, and lethargy, that began twenty-four hours after the injection and lasted for six days.

Minor events were mild, transient, and self-limiting and did not require additional consultation, treatment, or hospital admission. There were thirty-three minor adverse events following 204 injection episodes (an incidence of 16%). Six children had a mild fever, and four had an urticarial rash. Ten children had symptoms of an upper respiratory tract infection. Parents reported focal weakness in the injected muscles on three occasions and generalized weakness on two occasions. Three children had pain and bruising at one or more injection sites. Two children had vomiting, two had diarrhea, and one had vomiting and diarrhea within forty-eight hours following injection.

In the treatment group, each child used a mean of 1.3 braces over the three years, with major refurbishments required in eleven (19%) of the fifty-nine braces and minor adjustments in thirty-nine braces (66%). Three braces had cracks on the pelvic band, which led to a design and material modification for the new low-profile SWASH brace. The mean number of hours of brace wear as reported by the parents was 5.6 ± 2.6 hours per day.

Efficacy

Migration Percentage

The serial changes in migration percentage are shown in Figure 3. The unweighted mean of the hip-specific regression line slopes, i.e., a summary of migration percentage change per year, was 2.6% in the botulinum toxin-A-treated group and 5.7% in the control group, a difference of 3.1% (95% confidence interval, 0.0% to 6.2%; $p = 0.05$). When analyses incorporated a weighting of the individual hips by the inverse of

the variance of their slope, there was no significant difference between the control and botulinum toxin-A groups in the annual rate of change; the weighted mean difference between the control and treatment groups was 1.4% per year (95% confidence interval, -0.6% to 3.4% per year; $p = 0.16$). The same conclusion was reached when the analysis was weighted by the number of migration percentage measurements per child. Adjusting for the GMFCS level at baseline reduced the unweighted and weighted differences slightly; the unweighted analysis difference was 2.7% per year ($p = 0.08$), and the weighted analysis was 1.2% per year ($p = 0.21$).

Progression to Surgery

Children in the intervention group progressed to surgery at a lower rate than those in the control group (Table II). The decision to exit from the study for some children was influenced by the progression of contractures as well as by radiographic criteria. Two children from the control group exited from the trial to have surgical correction of hamstring and adductor contractures when their migration percentages were just below the 40% threshold. However, the migration percentage in both had been noted to be increasing by $>10\%$ in six months. Although the exit radiograph was assessed by an observer masked to group allocation, presentation of the child and the radiograph for an exit decision was more likely because of the presence of progressive contractures.

Discussion

The two most common deformities that affect children with cerebral palsy are spastic equinus, which causes toe-walking, and spastic hip displacement, which may result in painful hip dislocation^{2-5,11,12}. Botulinum toxin A has been used successfully in the management of toe-walking in children with cerebral palsy for more than a decade^{17,22}. Benefits include delaying or avoiding surgery and giving time for the child to

make gains in gross motor function. Parents and therapists are frequently reluctant to consider surgery to prevent hip displacement in children with cerebral palsy because of postoperative pain, transient increased spasticity, and developmental regression⁵. Hip displacement is often detected when it is asymptomatic and when the child is involved in therapy programs designed to maximize gains in gross motor function, when surgery may be seen as an unwelcome and unnecessary intrusion. Given the documented success of botulinum toxin-A therapy in the management of spastic equinus, we chose to investigate whether hip displacement could be prevented by a similar treatment strategy.

Hip bracing is not well tolerated by children with spastic cerebral palsy because the stretch reflex in the spastic hip adductors is activated by passive abduction in the brace^{5,11}. Chemodenervation of spastic muscles is effective when the muscles are stretched during functional activities. Following injection of the gastrocnemius-soleus for spastic equinus, the relaxed calf muscle is stretched during walking^{17,22}. Little active stretching of the hip adductors is possible in younger children with limited walking abilities^{5,23,28}, which was the rationale for investigating the combined intervention of abduction bracing and injection of the hip adductors with botulinum toxin A. Chemodenervation should reduce the overactive stretch reflex, and the SWASH brace would passively abduct the hips. It was theorized that the combined effect might be to center the femoral head within the acetabulum and prevent fixed contractures of the hip adductors, and this combined intervention was successful in a small pilot study. We previously reported the limited effects of this intervention on gross motor function in a subset of the study population²⁸. We acknowledge that the parental self-reporting of brace wear times may not be accurate.

This present study is, to our knowledge, the first randomized, controlled trial of nonoperative management for early hip displacement in children with bilateral spastic cerebral palsy. Serial injections of botulinum toxin A to the hip adductor and hamstring muscles combined with use of a variable hip abduction brace may have had a small effect on the rate of progression of hip displacement. The exact difference was difficult to quantify because the subjects with the largest increase in migration percentage progressed most rapidly to surgery and therefore had the fewest migration percentage measurements from which to estimate the rate of migration percentage change. From the unweighted analysis, the rate of displacement in the intervention group was reduced by 3.1% compared with the control group, although the annual change remained a 2.6% increase in migration percentage. Weighted analyses indicated a much smaller difference (1.4%) between groups. In overall management terms, the results indicate that treatment might lead to a delay for some children in the timing of surgery, but they suggest that a similar number of children would eventually require surgery, with or without botulinum toxin-A injections and bracing.

Weighting the individual hips in the statistical analysis by the number of migration percentage measurements or, simi-

larly, the inverse of the variance of the slope from the least-squares line of best fit through the migration percentage measurements of the hips over time gives greater weight to children who did not exit the study early. As these children tended to progress less rapidly, as evidenced by not exceeding the exit criteria, this weighting potentially dampens any difference between the groups. Correspondingly, subjects who exited the study early and hence potentially had the greatest increase in migration percentage also had the fewest migration percentage measurements taken and therefore the most uncertainty in estimates of the rate of change in the migration percentage. We do not view either approach as “the correct answer” but consider both to be valid interpretations of the trial data. Only by considering both analyses can the uncertainty in the study conclusions be fairly represented.

There was no evidence of a beneficial effect of treatment that was clinically important. It is possible that a small benefit exists although the clinical relevance of such a benefit is debatable, and the evidence provided by this study of such an effect is weak. Fewer children progressed to surgery in the intervention group, but this was not based purely on the radiographic criteria but on the clinical criteria of the progression of contractures. The combined intervention, botulinum toxin-A injections and bracing, may have been more effective in preventing the progression of contractures than in preventing hip displacement^{5,17,22}. This would explain the discordance between the weak effect of the intervention in preventing hip displacement compared with the strong effect in delaying progression to surgery. The quality of the trial may have been impaired by differences in the GMFCS levels at trial entry. When the trial was designed, we were not aware of how closely the rate of hip displacement is affected by GMFCS level². However, the *increased* number of patients at GMFCS level IV in the control group may have been balanced by the *decreased* numbers at GMFCS levels III and V.

The combined intervention of repeated injection of botulinum toxin A under mask anesthesia and use of abduction bracing is expensive and invasive. It is not sufficiently effective in improving gross motor function or in preventing hip displacement for us to recommend this therapy, and we no longer use it. Questions with respect to safety remain unanswered. The mortality rate for the treatment group during the three years of the study was sixteen per 1000 life years (95% confidence interval, two to fifty-nine deaths per 1000 life years). The mortality rate for children with epilepsy and a neurological condition has been estimated to be ten per 1000 life years²⁹. Children with severe cerebral palsy have a high incidence of respiratory disease, and the combination of mask anesthesia and high-dose botulinum toxin-A therapy increases the risk of an acute respiratory event^{27,30,31}, and such events might be difficult to distinguish from epilepsy-related asphyxia.

In retrospect, the largely negative outcome of this trial is not surprising. The strongest association with hip displacement in children with cerebral palsy is the level of gross motor function, which is not affected by the injection of botulinum toxin A and bracing^{2,28}. The incidence of hip displacement in

children with cerebral palsy is directly related to gross motor function and is not related to the type of movement disorder. In a recent study, children with hypotonic, spastic, and dystonic cerebral palsy had similar rates of hip displacement². Thus, spasticity is probably not as important as once thought. In terms of the musculoskeletal factors, which predispose the hip to progressive displacement, spasticity is but one factor. Osseous deformities such as femoral anteversion and valgus are important and are not affected by chemodenervation of the adductor muscles. Finally, injection of the adductor muscles with botulinum toxin A may not be the most effective way to maintain reduced muscle tone and improved hip abduction^{5,11}.

Appendix

eA Tables showing the modified Ashworth scale and the comorbidities seen in the study patients are available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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