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Long-term use of botulinum toxin type A in children with cerebral palsy: Treatment consistency

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ABSTRACT

At the University Hospital of Pellenberg (Belgium), more than 1000 patients have been treated with Botulinum toxin type A (BTX-A) over the last decade. Ten percent of these patients ($n = 106$) received multiple (at least four times), multi-level, high-dosage treatments. The aim of this study was to evaluate the stability of dosage and treatment intervals in long-term, multi-level, high-dosage treated children with cerebral palsy and to evaluate the evidence for a safe and stable response to this treatment. Data on disease, age, dosage and target muscles were extracted for each treatment session of 106 patients who received multiple BTX-A treatment sessions. Patients had a follow-up of 4 y 6 mo (range 1 y 8 mo–8 y 9 mo) on average and received 4 to 12 BTX-A treatments within the period of January 1996 and December 2005. Patients received a mean dosage of 23.5 ± 5.2 U/kg bw at first treatment with stable subsequent values. Mean dosages for children with diplegia, hemiplegia and quadriplegia were 24.5 ± 4.7 U/kg bw, 15.9 ± 3.7 U/kg bw and 22.0 ± 4.8 U/kg bw, respectively. Mean age at first treatment was 4 y 6 mo (range 1 y 11 mo–18 y 10 mo) with a majority of patients (76.4%) first treated within 2 and 4 y of age. Treatment intervals of approximately 1 y remained stable within four, five and six subsequent treatments. Long-term, high-dosage, multi-level BTX-A applications can be considered as a safe and stable treatment option for children with cerebral palsy and the formation of antibodies, responsible for secondary non-response, can be indirectly precluded.

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1. Introduction

Botulinum toxin type A (BTX-A) is a local, reversible and commonly used and accepted treatment option for spasticity in children with cerebral palsy.[1–5] The toxin produces, to some extent, dose-related and reversible chemodenervation of agonist muscles by impairing the release of acetylcholine at the neuromuscular junction. Molenaers et al.[6] investigated the influence of multi-level, high-dosage botulinum toxin type A on the prevalence, frequency and timing of orthopaedic surgical procedures of 424 children with cerebral palsy at the University Hospital of Pellenberg (Leuven, Belgium). Their outcomes suggest that BTX-A treatment decreases the frequency and delays the need for orthopaedic surgical procedures until gait is mature when carefully applied to conscientiously selected patients.

A multitude of BTX-A studies has been published in the last decade. Most of them, however, focus on single, one-level BTX-A treatment in cerebral palsy.[7–19] A few studies, though, highlight the need and overall better response of multi-level injections.[20–23] As several muscles are injected simultaneously within one treatment session, multi-level treatments may request a higher total dosage when compared to single-level treatments to achieve optimal treatment outcomes.[24,25]

Nevertheless, it is generally accepted that for repeated injections of multi-level, high-dosage BTX-A, there may be a risk of the development of neutralizing antibodies. Evidence of developing antibodies was mainly investigated in long-term studies on cervical dystonia by performing a mouse neutralisation bioassay.[26–29] In cerebral palsy studies, little evidence for the development of antibodies following repeated, high-dosage, multi-level injections was found.[30,31] There are, however, many differing opinions about treatment strategies, extent of dosage and treatment intervals in cerebral palsy studies.[7–20,25] Additional information on long-term efficacy and safety of high-dosage, multi-level BTX-A is required in order to expand the current knowledge of BTX-A treatment in cerebral palsy.

This study investigates a long-term strategy of multi-level, high-dosage BTX-A treatments in children with cerebral palsy, thereby focusing on safety data and excluding the formation of antibodies that interfered with clinical response. The standard examination of antibodies by mouse neutralisation bioassay, as performed by several investigators, is an expensive and complex venture. Therefore it was decided to consider an alternative approach to antibody formation by evaluating the consistency of dosage and treatment intervals over a long-term follow-up period.

We hereby partly followed the approach of Brashear et al.[32] who investigated the dose consistency and treatment intervals over a period of 3 y in cervical dystonia patients to eliminate the formation of antibodies as an alternative to the mouse neutralisation bioassay.

Antibody formation was correlated with secondary non-response in former studies[27,31] and discovered that risk factors for secondary non-response were high dosages of BTX-A per treatment session and frequent injection intervals.[26,28,31,33] The long-term stability of dosage and treatment intervals can therefore be considered as an indirect indication that the patient is continuing to respond to BTX-A treatment, thereby excluding the formation of antibodies. Although response to BTX-A treatments was not specifically examined in the study of Brashear et al.[32] treatment efficacy and safety were supported by stable intervals, dosages and the patient's returning for subsequent treatments. Adult cervical dystonia patients, however, generally receive low-dosage treatment over a longer time period and within shorter treatment intervals[26–29,32] which is different to the treatment of children with cerebral palsy. BTX-A in the latter patients is usually a treatment option together with conservative treatment at an early age (<5 y) and may require higher dosages and longer treatment intervals when compared to cervical dystonia treatment.[6,34] These different approaches can therefore not be directly compared which deepens the need for long-term safety and efficacy data in patients with cerebral palsy.

In former studies at Pellenberg Hospital,[6,35] efficacy data of high-dosage, multi-level BTX-A treatment of children with cerebral palsy have already partly been investigated.

The purpose of this study is to evaluate the stability of dosages and intervals between treatment sessions, in order to evaluate the safety of repeated multi-level, high-dosage BTX-A injections to children with cerebral palsy. It is hypothesised that (i) the mean total BTX-A dosage does not increase and (ii) the mean intervals between treatments do not decrease within the longitudinal follow-up.

2. Materials and methods

2.1. *Patients and treatment concept*

For this retrospective study, adequate patients have been selected from the general patient database and the database of the Clinical Motion Analysis Laboratory at Pellenberg University Hospital.

The following inclusion criteria were established: the diagnosis of predominantly spastic cerebral palsy and at least four treatments with BTX-A from January 1996 to December 2005. The Surveillance of Cerebral Palsy in Europe (SCPE) describes spastic cerebral palsy as one of the subtypes of cerebral palsy.[36] The spastic subtype is further divided by the SCPE into a unilateral (limbs on one side of the body are involved, hemiplegia) and a bilateral (limbs on both sides of the body are involved) type. In this study, the spastic bilateral type was further subdivided into diplegia and quadriplegia.

Patients were excluded when having received BTX-A treatment only of the upper limbs and when having been treated with a combination of surgery and BTX-A in the same session, for reasons of biased dosage and interval measures.

The patients with spastic cerebral palsy received an integrated approach of BTX-A, as formerly described by Molenaers et al.[37] According to this approach, the reduction in muscle tone, induced by BTX-A injections, was intended to provide an opportunity to optimise the effects of casting and orthotic management and enhance both motor ability and functional skills.

Three-dimensional gait analysis including kinetics, kinematics and electromyography (EMG) was performed before and after each treatment with BTX-A to detect abnormal

muscle activity during gait, to define possible target muscles and to evaluate treatment outcome. Very young or less functional children received video recordings. Apart from the gait evaluation, a standardised clinical examination (muscle tone, passive and active range of motion and selectivity) was also performed at each evaluation time. All of the patients were once more examined under general mask anaesthesia directly before the application of the toxin.

BTX-A (Botox®, Allergan, Irvine, CA) was administered by using multiple injection sites with dosages that did not exceed 50 Units per treated site. The extent of dosage depended on the muscle size, patients body weight, gait analysis, clinical examination, evaluation under anaesthesia and individual treatment goals. The placement of the needle (usually 26 gauge × 23 mm) was controlled by stretching the target muscle and moving the above- or beyond-located joint and thereby examining the needle movement. Ultrasonography has also been used to confirm the correct needle placement. A majority of the children with cerebral palsy received serial casting, day and night splinting and physiotherapy after treatment sessions with BTX-A, as part of the integrated approach, in order to receive optimal individual treatment outcomes.[37]

2.2. *Statistical analysis*

Information on disease, age at treatment, dosage and target muscles was extracted for each patient and treatment session from the electronic patient files, operation reports and database of the gait laboratory at Pellenberg University Hospital. Mean dosages, decrease/increase of dosage for consecutive treatment sessions, mean age at treatment sessions, decrease/increase of treatment intervals and frequency distribution for target muscle combinations were evaluated for the whole treatment group ($n = 106$), separated groups (diplegia, hemiplegia and quadriplegia) and subgroups with five ($n = 32$) and six ($n = 12$) repeated treatments.

A mixed model procedure was used to gain statistical significance for repeated interval/ratio data for four repeated treatments of all patients ($n = 106$) taking diagnoses as covariate, and for groups with five ($n = 32$) and six ($n = 12$) repeated treatments. The level of significance was defined at $p = 0.05$.

3. Results

A total of 1020 patients have been treated with BTX-A from January 1st 1996 to December 31st 2005 at the University Hospital of Pellenberg. Approximately half of all treated patients (51.7%) were diagnosed with diplegia, 24.3% with hemiplegia, 15.3% with quadriplegia and 9.7% had other diseases including hemiplegia after stroke, torticollis, idiopathic clubfoot and tip-toe walkers, plexus brachialis lesions and myelomeningocele. Approximately 10% of all treated patients (10.4%, $n = 106/1020$) received multiple (four or more) BTX-A treatments. The numbers reported in the following section refer to this latter group of patients unless noted otherwise.

Eighty-four children (79.2%) who received at least four BTX-A treatments were diagnosed with diplegia, 13 with quadriplegia (12.3%) and 9 with hemiplegia (8.5%). Sixty-five patients were male (52.8%) and 50 patients were female (47.2%).

At time of the first examination, the Gross Motor Function Classification System (GMFCS)[38] level was I in 18 children (17%). Twenty-eight children (26.4%) were GMFCS II, 44 children (41.5%) were classified as GMFCS III, 12 children (11.3%) as GMFCS IV and 4 children (3.8%) as GMFCS V.

Patients in this study ($n = 106$) were followed 4 y 6 mo on average (±1 y 7 mo; range 1 y 8 mo–8 y 9 mo) within the period of January 1996 and December 2005. Patients who received five treatments had a mean follow-up period of 5 y 3 mo (±1 y 7 mo; range 2 y 11 mo–8 y 10 mo) and patients with six treatments had a mean follow-up period of 4 y 10 mo (±1 y 0 mo; range 3 y 5 mo–7 y 2 mo). Patients ($n = 106$) received 4 to 12 treatments of BTX-A. Fifty percent of the patients (53 children) received four treatments, 30.2% (32 children) were treated five times, and 11.3% (12 patients) received six BTX-A treatments. Approximately 8% of the patients (8.5%, 9 children) received seven or more treatments.

3.1. *Levels of treatment and treated muscles*

The majority of patients (94.2%) received multi-level treatment (levels of pelvis/hip, knee and ankle) or treatment of two proximal levels (levels of pelvis/hip and knee). The toxin has been applied to one or two distal levels (levels of knee and ankle) in only 2.9% of the patients. Regarding the first treatment session, children with diplegia mainly received multi-level treatment. The treatment strategy changed at the 3rd and 4th treatment session, when multi-level treatment decreased in favour of the treatment of two proximal levels (Fig. 1). All patients with hemiplegia received multi-level BTX-A applications at their first treatment session. This remained largely unchanged within the first four treatment sessions. Most of the patients with quadriplegia (23 out of 25 treated limbs) received either multi-level treatment or treatment of the two proximal levels at their first treatment session. The most

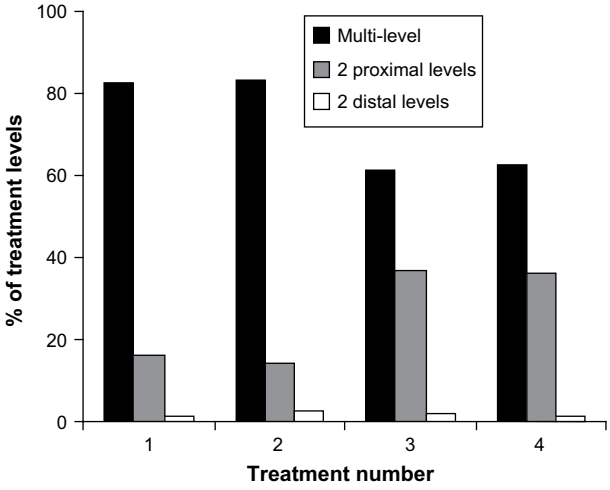

Fig. 1 – Development of treated levels in patients with diplegia over four consecutive treatment sessions.

frequently treated muscles for the total group were M. Psoas, Hamstrings, Adductors and M. Gastrocnemius. The same combination of muscles was treated most frequently in patients with diplegia. The Hamstrings, Adductors and M. Gastrocnemius were most frequently treated in patients with hemiplegia and M. Psoas, Hamstrings and Adductors were most frequently treated in patients with quadriplegia (Table 1).

3.2. Dosages

The mean dosage for the study group was 23.5 ± 5.2 U/kg bw at the first BTX-A treatment session with a stable continuing trend ($p = 0.1202$). Mean total dosages were reported up to the 4th, 5th and 6th treatment sessions (Fig. 2, Table 2) even though several patients received up to 12 treatments. Because one of the inclusion criteria was that patients had to have received at least four treatment sessions with BTX-A, patient numbers remain stable for the first four treatment sessions ($n = 106$). The patient numbers for the 5th and 6th treatments ($n = 32$ and $n = 12$, respectively) were also considered sufficient to perform statistical analysis. The low patient numbers with increasing numbers of treatment sessions, however, would have affected the statistical analysis.

The group with five BTX-A treatments ($n = 32$ patients) had a significant decrease of the total dosage from the 1st to the 5th ($p = 0.0013$), from the 2nd to the 5th ($p = 0.0019$) and from the 4th to the 5th treatment session ($p = 0.0008$). Values for the group with six treatments ($n = 12$ patients) showed a significant decrease of the total dosage from the 2nd to the 6th treatment session ($p = 0.04$) (Table 2).

The separated mean dosages for groups of diplegia, quadriplegia and hemiplegia were significantly different from each other ($p < 0.0001$). Children with diplegia received a significant higher dosage of BTX-A compared to children with hemiplegia ($p < 0.0001$) and children with quadriplegia ($p = 0.0053$). Patients with hemiplegia, however, received a significant lower dosage of BTX-A compared to patients with quadriplegia ($p = 0.0004$) (Fig. 2, Table 2).

Side effects were spontaneously reported by the children and/or their parents, in only 3 of the 522 treatments (0.57%). One patient reported back pain for 2 weeks, one showed a deterioration of gait pattern for less than 5 days and one experienced an impaired stability while walking for more than 5 days.

3.3. Time of treatment and treatment intervals

Mean age at first treatment for patients with at least four treatments of BTX-A ($n = 106$) was 4 y 6 mo (age range 1 y 11 mo–18 y 10 mo). Patients who received five and six treatments were first treated at a mean age of 3 y 8 mo (age range 2 y–8 y 7 mo) and 3 y 11 mo (age range 2 y 2 mo–10 y 4 mo), respectively.

Patients with diplegia were first treated at a mean age of 4 y (age range 1 y 11 mo–18 y 10 mo) and patients with hemiplegia received their first treatment with a mean age of 4 y 10 mo (age range 2 y 1 mo–14 y 10 mo), which was not significantly older when compared with diplegia. Patients with quadriplegia, however, were significantly older at first treatment (7 y 1 mo, age range 2 y 10 mo–14 y 11 mo, $p = 0.0003$) compared to patients with diplegia. The majority of patients (76.4%) received the first treatment with BTX-A between 2 and 4 y of age.

The elicited treatment intervals of approximately 1 y remained stable within the entire follow-up period (Fig. 3, Table 3). The intervals between first and second treatment with BTX-A in patients with hemiplegia and quadriplegia (1 y 2 mo both, ±4 mo and 9 mo) were found to be similar to intervals of patients with diplegia (1 y 0 mo ± 5 mo) (Fig. 3, Table 3). Patients who were treated five times showed an increasing trend regarding treatment intervals. The first and the third, and the first and the fourth treatment intervals were significantly different ($p = 0.0098$, $p = 0.0049$). Treatment intervals within the patient group with six BTX-A treatments did not differ significantly.

3.4. Surgical treatment

Surgery was indicated in children who developed secondary problems (bony deformities, fixed muscle contractures and lever-arm dysfunction) which profoundly limited motor function. Soft-tissue and bony deformities were corrected as formerly described by Molenaers et al.[6] Thirty-two patients (30.2%) of the study group were treated with soft-tissue and/or bone surgery before (2 patients), during (17 patients) or after (13 patients) their BTX-A treatment period, if indicated. Surgical procedures included an Achilles tendon lengthening (1 patient), multi-level soft-tissue surgery (8 patients), bone surgery (4 patients), combinations of soft-tissue and osseous surgical procedures (17 patients) and intrathecal baclofen

Table 1 – Frequency distribution of most frequent muscle combinations.

Combination of muscles	Diagnosis (treated limbs within 1996–2005)			Total
	Diplegia ($n = 948$)	Hemiplegia ($n = 47$)	Quadriplegia ($n = 126$)	
M. Psoas, Hamstrings, Adductors, M. Gastrocnemius	237 (21.1)	4 (0.4)	20 (1.8)	261 (23.3)
M. Psoas, Hamstrings, Adductors	144 (12.9)	0 (0.0)	40 (3.6)	184 (16.4)
M. Psoas, Hamstrings, M. Gastrocnemius	138 (12.3)	1 (0.1)	6 (0.5)	145 (12.9)
Hamstrings, Adductors, M. Gastrocnemius	108 (9.6)	7 (0.6)	6 (0.5)	121 (10.8)
M. Psoas, Hamstrings	79 (7.1)	0 (0.0)	18 (1.6)	97 (8.7)
Hamstrings, M. Gastrocnemius	64 (5.7)	4 (0.4)	0 (0.0)	68 (6.1)

Numbers in parentheses are percent values of the total ($n = 1121$ treated limbs from 106 patients in 4 to 12 BTX-A treatments).

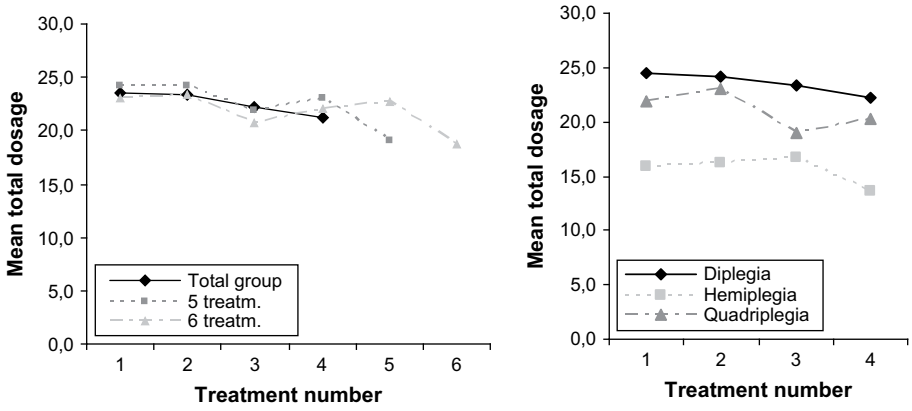

Fig. 2 – Left: development of the mean dosage in U/kg bw for the total study group ($n = 106$) and for groups with five ($n = 32$) and six treatments ($n = 12$). Right: development of the mean dosage in U/kg bw for diplegia ($n = 84$), hemiplegia ($n = 9$) and quadriplegia ($n = 13$).

pump implantations (two children). Twenty-six patients who received surgical procedures had diplegia, five patients had quadriplegia and one patient had hemiplegia. Most of these patients (20 patients) received one surgical treatment, 10 patients received two and 2 patients received three surgical treatments.

3.5. *Follow-up*

Fifty percent of the patients in the study group continued with BTX-A treatments after the four investigated BTX-A treatments. Data from consecutive treatments of these patients are included in this study. Another 19.8% of the patients received their last treatment in 2005 (data collection ended in December 2005). The latter group may or may not continue the treatment sessions with BTX-A (follow-up treatment is unsure). Approximately 18% of the patients (17.9%) stopped treatment after four sessions of BTX-A and 12.3% received surgery. Elicitation of detailed information on reasons for stopping with BTX-A was beyond the scope of this study.

Follow-up data after five treatment sessions disclosed 39.6% of patients who continued treatment and 22.6% who received their last injection of BTX-A in 2005 (and may or may not continue treatment). Another 26.4% stopped treatment with BTX-A and 11.3% were treated surgically after five BTX-A treatments.

4. Discussion

A multitude of studies on short-term outcomes of BTX-A in children with cerebral palsy have been performed so far.[7–19] Long-term investigation of BTX-A, however, has mainly taken place in the fields of cervical dystonia, hemifacial spasm and blepharospasm.[29,32,39–41] Only a small number of studies investigated long-term effects of BTX-A in cerebral palsy.[42–44] The present retrospective study indirectly estimated the safety of long-term, high-dosage BTX-A treatment in 106 children with cerebral palsy by evaluating the stability of consecutive levels of treatment, dosages and treatment intervals.

Ten percent of the patients who were treated with BTX-A within the period of January 1996 and December 2005 at the Pellenberg University Hospital received at least four repeated injections of BTX-A. It should be noted, however, that the proportion of diagnoses within the studied group ($n = 106$, repeated treatments) did not match the proportion of diagnoses for less often treated patients ($n = 1020$, one to three treatments). Comparatively more children with diplegia and fewer children with hemiplegia and quadriplegia received four and more BTX-A treatments compared to the group of one to three BTX-A treatments.

Patients in this study received constant mean BTX-A dosages of approximately 23 U/kg bw, which is notably higher

Table 2 – Development of mean dosages for the total group, patients with five and six treatments and for separate groups of diplegia, hemiplegia and quadriplegia.

No. of treatment interval	Total group ($n = 106$)	Four treatments ($n = 106$)			Five treatments ($n = 32$)	Six treatments ($n = 12$)
		Diplegia ($n = 84$)	Hemiplegia ($n = 9$)	Quadriplegia ($n = 13$)		
1	23.5 (5.2)	24.5 (4.7)	15.9 (3.7)	22.0 (4.8)	24.3 (4.9)	23.0 (5.8)
2	23.4 (5.5)	24.2 (5.2)	16.3 (5.2)	23.0 (4.2)	24.2 (5.8)	23.4 (3.8)
3	22.2 (5.7)	23.3 (5.4)	16.7 (4.1)	19.0 (5.1)	21.9 (5.9)	20.7 (6.6)
4	21.3 (6.2)	22.3 (5.8)	13.7 (5.5)	20.2 (5.4)	23.0 (5.5)	22.0 (5.1)
5	–	–	–	–	19.0 (6.7)	22.6 (4.4)
6	–	–	–	–	–	18.7 (5.1)

Mean dosages are noted in U/kg bw. SD in parentheses.

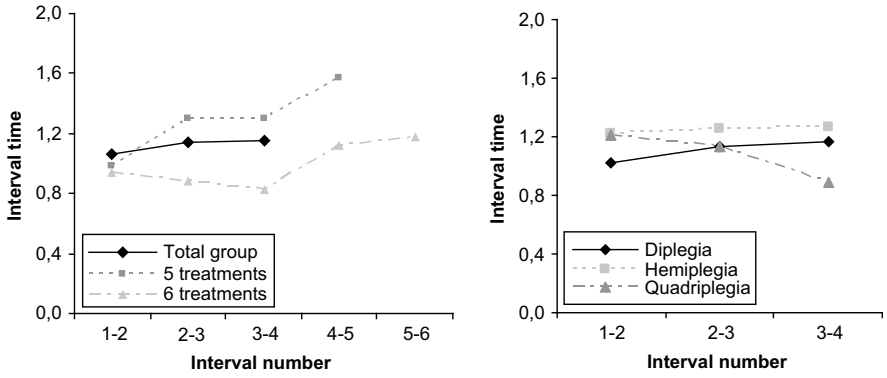

Fig. 3 – Left: development of treatment intervals in years for the total group ($n = 106$) and for groups with five ($n = 32$) and six treatments ($n = 12$). Right: development of treatment intervals in years for diplegia ($n = 84$), hemiplegia ($n = 9$) and quadriplegia ($n = 13$).

compared to other cerebral palsy studies.[42–44] The majority of previous studies of children with lower limb BTX-A treatment for spasticity have used relatively low doses of Botox®. Delgado[42] examined 104 children with cerebral palsy in a retrospective chart review over a 2-y period. Mean total dosages of 6.3–9.1 U/kg bw (Botox®) were used, which remained constant across eight injection sessions. It should be noted that the number of patients in the study of Delgado[42] decreased with increasing treatments. In the retrospective study of Gormley et al.[43] who investigated the patterns of BTX-A use (Botox®) at three different American treatment centres, injected total dosages ranged from 7.7 to 10.8 U/kg bw. Dosages in the study of Gormley et al.[43] increased with increasing treatment sessions over the study period of 2 y in two centres and remained constant in one treatment centre.

Linder et al.[44] performed a prospective study with repeated BTX-A injections (Botox®) on 25 cerebral palsy children. A standardised BTX-A dosage of 12 U/kg bw was applied to the patients at each treatment session in their study which may suggest that previous treatment outcomes were not considered an indication for dosage considerations. This is contrary to the BTX-A treatment concept at Pellenberg Hospital, where dosages are 'result-driven', that is, former BTX-A treatment outcomes, amongst others, play an important role in subsequent dosage considerations.

Regarding the values of total dosage in the latter studies, it should be noted that patients did not receive treatment of more than two muscle groups[44] or had an standardised dosage or an upper limit of maximal 400 U of Botox®,[42,43] whereas the majority of patients in this study received multi-level treatment or treatment of at least two proximal levels with higher doses of BTX-A. The treatment of spasticity in children with cerebral palsy often requires BTX-A injections in more than one muscle group resulting in a higher dose exposure to gain optimal treatment outcomes compared to single-level BTX-A treatment. Increasing doses of BTX-A may increase the risk for site effects. In our study, minor side effects were reported in only 0.57% of the treatments. Other studies with doses in the range of those used in this study, also support the safety of multi-level, high-dosage BTX-A treatments in children with cerebral palsy. Molenaers et al.[37] studied a group of 156 children with spastic cerebral palsy after multi-level BTX-A treatment. The mean dose was 19.4 U/kg bw for children with diplegia, 13.0 U/kg bw for those with hemiplegia and 20.4 U/kg bw for those with quadriplegia. No major side effects related to BTX-A were reported. In the study of Desloovere et al.,[45] 34 children with spastic cerebral palsy received a total mean dose of 24.4 U/kg bw for diplegia or 16.4 U/kg bw for hemiplegia. Minor complications were noted in 14 children, including 12 children who had generalized weakness for 1 of 2 weeks and three children with incontinence. Heinen et al.[46] reported 495 multi-level treatments with a mean dose of 16.6 U/kg bw in patients with spastic diplegia, with a mean adverse event rate of 8.8%. Goldstein[47] reported a retrospective study of 94 children and 14 adults who received a mean injection dose of 19.1 U/kg and 15.2 U/kg,

Table 3 – Treatment intervals for the total group, groups with five and six treatments and for separate groups of diplegia, hemiplegia and quadriplegia.

No. of treatment interval	Total group ($n = 106$)	Four treatments ($n = 106$)			Five treatments ($n = 32$)	Six treatments ($n = 12$)
		Diplegia ($n = 84$)	Hemiplegia ($n = 9$)	Quadriplegia ($n = 13$)		
1–2	1 y 1 mo (7 mo)	1 y (6 mo)	1 y 2 mo (5 mo)	1 y 2 mo (10 mo)	1 y (5 mo)	11 mo (4 mo)
2–3	1 y 1 mo (8 mo)	1 y 1 mo (8 mo)	1 y 4 mo (6 mo)	1 y 1 mo (10 mo)	1 y 4 mo (1 y)	11 mo (4 mo)
3–4	1 y 2 mo (6 mo)	1 y 2 mo (6 mo)	1 y 4 mo (7 mo)	11 mo (5 mo)	1 y 4 mo (6 mo)	10 mo (4 mo)
4–5	–	–	–	–	1 y 7 mo (1 y)	1 y 1 mo (6 mo)
5–6	–	–	–	–	–	1 y 3 mo (5 mo)

Mean intervals are given in years and months. SD in parentheses.

respectively, with the total dose divided into multiple muscle groups. Adverse event after a single injection was reported in three patients.

Multi-level BTX-A therapy and the concomitant use of higher dosages led to concern about a possibly higher rate of antibody formation. In general, application of higher doses of BTX-A are linked with a higher probability to develop antibodies. In the study of Herrmann et al.,[31] neutralizing antibodies were present in one-third (31.8%) of the paediatric patients after BTX-A treatment. This prevalence value is similar to those reported by Koman et al.,[30] who found antibodies in 33 of the 177 (28%) of their paediatric patients. Antibody formation was an important cause of treatment failure in the study of Herrmann et al.,[31] but not in those of Koman et al.[30] In these two studies, neutralizing antibodies to BTX-A were detected using direct tests, respectively, the mouse phrenic nerve hemidiaphragm test and the mouse protection bioassay. Because direct tests are complex, expensive and time-consuming, in this study, it was decided to eliminate the formation of antibodies following an alternative approach. Patients who develop neutralizing antibodies often require progressive higher doses at shorter intervals to maintain clinical effectiveness of the BTX-A treatment.[48] Thus, the consistency of dosage and treatment interval over a long-term follow-up period may be considered an indirect indication that the patient is continuing to respond to treatment and thereby excluding the formation of antibodies that cause secondary non-response. With mean total dosages and mean treatment intervals of approximately 1 y that remained stable within four, five and six subsequent BTX-A treatments, our data may provide stable response to long-term, high-dosage BTX-A treatments and thereby the formation of antibodies, responsible for secondary non-response, can be indirectly precluded.

It is commonly accepted that children with diplegia and hemiplegia show more functional abilities compared to the more involved children with quadriplegia. Treatment goals may have focused more on relieving spasticity for the facilitation of hygienic care and positioning in patients with quadriplegia. Decreasing treatment intervals in this subgroup compared with stable, slightly increasing treatment intervals in children with diplegia and hemiplegia support this assumption. Treatment goals for more functional children with diplegia and hemiplegia may have primarily focused on improving gait performance.

Ambulation comes along with the possibility of improving walking patterns during chemodenervation of the target muscles and may result in functional carry-over effects, which – in turn – may have caused stable treatment intervals of approximately 1 y in our study. These treatment intervals of approximately 1 y were higher than usual re-injection periods of 3–6 mo reported in other cerebral palsy[42–44,49] and cervical dystonia studies.[29,32,41]

In the studies of Delgado,[42] Gormley et al.,[43] Linder et al.,[44] and Metaxiotis et al.,[49] however, patients did not receive multi-level treatment or treatment of muscle combinations, like in this study. Delgado and Gormley et al.[42,43] state that patients with short treatment intervals in their studies would probably have required treatment of more target muscles at any one injection visit. The treatment of target muscles, however, was split up in order to avoid going beyond the 300 U limit of Botox®. Delgado and Gormley et al.[42,43] moreover also used the treatment combination of BTX-A and phenol. Another reason for short treatment intervals in the latter two studies were, that once chemodenervation and relieve of spasticity started in the injected muscles, it was found that other muscles also required treatment with BTX-A and patients were re-injected.

The chemodenervation of the overactive muscles after multi-level BTX-A treatment creates basic conditions that are necessary to improve muscle length, muscle strength and function. Therefore, an adequate follow-up treatment including orthotic management, serial casting and physical therapy seems to be crucial for a maximal profit of the BTX-A injections. Serial casts should be applied to stretch shortened muscles and thus increase muscle length.[37] Day and night orthoses are important in maintaining muscle length and their provision of stability to distal joints.[37] Intensive physical therapy is indicated to improve muscle strength and length and to allow optimal motor learning during the limited period of tone reduction. For all patients included in this study, an ultimate treatment strategy was set up according to an integrated therapy concept. The integrated treatment approach in combination with high dosages at Pellenberg Hospital may have prolonged the duration of BTX-A treatment, resulting in a duration of about 1 y between injections.

Another aspect of this study is that the majority of patients were first treated within an age of 2–4 y, which is different from the findings of Metaxiotis et al.[49] who evaluated the long-term effects of BTX-A (Dysport®) on 21 children with diplegia. Patients in their study had a mean age of 5 y 8 mo at first treatment. Former BTX-A studies, nevertheless, suggest superior treatment outcomes with an earlier treatment start.[10,34,50] Linder et al.[44] reported a tendency to attain higher functional outcomes for younger (<5 y) and moderately impaired children in their study. Boyd et al.[34] pointed out the main emphasis for BTX-A treatment within the age period of 1–5 y in order to gain optimal outcomes.

Children with diplegia and hemiplegia in our study fit to the latter suggested age intervals. Patients with quadriplegia, however, were significantly older at first treatment (mean age 7 y 1 mo). This may be the result of a more severe impairment and different treatment goals for this patient group. The most frequently treated muscles in patients with quadriplegia were M. Psoas, Hamstrings and Adductors. Treatment of the Hamstrings and Adductors is common in less functional children to facilitate positioning, handling and hygiene. There is also a high incidence of hip subluxation in children with quadriplegia. Injection of M. Psoas, Hamstrings and Adductors is a common solution for this problem.[43] Less impaired children with diplegia and hemiplegia in this study, on the other hand, most frequently received a multi-level BTX-A treatment combination including M. Psoas, Hamstrings, Adductors and M. Gastrocnemius. Treatment of the calf muscles is often indicated to facilitate gait performance and therefore indicative of the ability of ambulation.[7–19,43]

Thirty percent of the treated children received surgical procedures before, during or after their treatment periods with BTX-A. As surgical treatment is only considered a treatment possibility for secondary problems, BTX-A can be

regarded as an adjunct for superior surgical treatment outcomes when applied after or in combination with surgery. Surgical treatment which follows a period of BTX-A treatment, however, may simply indicate that the child reached an age where gait had become mature and other treatment strategies were more appropriate.[6,34]

Patients in this study were followed 4 y 6 mo on average, which has been the longest follow-up period within BTX-A studies in cerebral palsy so far. The previously mentioned studies reported follow-up periods of up to 2 y.[42–44,49]

Ongoing treatment strategies after BTX-A treatments show that 69.8% of the patients who received four treatments and 62.2% who received five treatments continued with their BTX-A treatment, which indicates safety and efficiency. Patients (19.8%) with four treatments and 22.6% with five treatments had their last treatment in 2005 (end of data collection). With treatment intervals of approximately 1 y, further treatment is not to be excluded. The overall results of our study are similar to the outcomes of the study of Brashear et al.,[32] who investigated the long-term dose consistency of BTX-A, and the intervals between treatments in 172 cervical dystonia patients during a 2-y treatment period. Their outcomes demonstrated consistent dosages and intervals within this period of time, thereby indirectly indicating the non-development of antibody formation.

Our treatment intervals of approximately 1 y widely exceed the commonly used re-injection period of at least 3 mo to prevent antibody resistance.[42–44,49,51] With mean total dosages that did not increase and mean intervals between treatments that did not decrease across repeated treatment sessions our data may provide stable response to long-term, high-dosage BTX-A (Botox®) treatments in children with cerebral palsy, thereby excluding the development of antibodies that are responsible for secondary non-response. A specific investigation of long-term treatment effects and efficacy, however, should be performed to further confirm the results on efficacy of Molenaers et al.[6] and Desloovere et al.[35] and expand the results of this study.

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