Botulinum toxin (BoNT) is a well established treatment in cerebral palsy. A uniform dose strategy is, however, missing. We reviewed 35 children with spastic cerebral palsy treated with BoNT according to a newly-developed Key-Muscle concept. All patients received at least 4 BoNT treatments. Systemic side effects or secondary non-response were not observed. After a mean follow-up of 30.3 months, none of these patients needed bone surgery whereas 6 underwent soft tissue procedures. The Key-Muscle concept is a safe and effective treatment in spastic cerebral palsy. It respects the need for long-term therapy during motor development. Contractures and lever arm disease can be avoided.

**Keywords**: cerebral palsy; Botulinum toxin; Key-Muscle Concept.

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**INTRODUCTION**

Since the first report of its use in children with cerebral palsy in 1993 (14), Botulinum toxin (BoNT) treatment has been regarded as a well established, safe and effective therapy module (5,7, 15,18,24,25). However, even more than 15 years later, a uniform dosage is not yet agreed upon (Fig. 1). The dose applied in these patients has increased over time (8,17). Compared to the high-dose regimen suggested lately for Botox®, the first guidelines from Russmann et al (23) and Graham et al (10) recommended 12 units/kg body weight. Later publications reported a high-dose multi-level concept with doses of up to 30 units Botox®/kg body weight (16,20). A European (13) and a German (12) Consensus paper recommending doses up to 25 units Botox®/kg body weight as a safe range are based on these studies. This dose was decreased to 20 units Botox®/kg body weight by an updated European Consensus paper (11). The safe range of Dysport® recommended by the manufacturer is up to 20 units/kg body weight at first application, and
up to 30 units/kg body weight for the subsequent applications (2). Although recent high-dose papers showed excellent short-term results, data on long-term follow-up, especially knowledge on secondary non-response and antibody production is lacking.

The purpose of this study is to examine the outcome, safety and efficiency of a new regimen that we called the key-muscle concept (KMC) consisting of long-term multi-level injections of the key spastic muscles strictly following the dose recommendations of the manufacturers. It is hypothesised that this treatment is possible without increased secondary bony deformities, muscle contractures or lever-arm dysfunction and provides a better quality of life by performing the injections at the outpatient clinic whenever possible.

PATIENTS AND METHODS

Fifty-seven children (37 boys and 20 girls) who ranged in age between 2.1-16.1 years (mean: 8.1 ± 3.9 years) and suffered from spastic cerebral palsy were treated with BoNT between January 1998 and December 2004 at the neuro-orthopaedic department of Berlin University Hospital according to the key-muscle concept. Inclusion criteria were spastic cerebral palsy (unilateral or bilateral) according to the Surveillance of Cerebral Palsy in Europe (SCPE) and administration of at least four BoNT treatments. Children with ataxic or dyskinetic cerebral palsy were not considered. The severity of handicap was classified by the Gross Motor Function Classification System (GMFCS). Patients were excluded when treated only for the upper limbs and when having a surgery and BoNT in the same session for reasons of biased dosage and interval measures. Children with indication for surgery before starting BoNT therapy due to secondary problems like bony deformities, fixed contractures or lever arm dysfunction were also excluded. A written informed consent was obtained from all parents.

The study children received an integrated approach, as described by Molenaers et al (19) where the reduction in muscle tone was intended to provide an opportunity to optimise the effects of casting and orthotic management and enhance both motor ability and functional skills. Injections were performed primarily at the outpatient clinic to avoid interrupting the child’s social setting. Injection sites were determined based on thorough clinical examination, accurate palpation and video-based motion analysis at every outpatient visit to determine the key spastic muscles that prevent reaching the next motor
milestone. Additionally, muscles at acute risk for contracture or even muscles with initial contracture were injected. Spastic muscles were not injected as long as the elevated tone did not impair function, there was no acute risk for developing contractures or, if the tone permitted, compensatory mechanisms. In the lower extremities, one injected site per muscle was selected and, if necessary, the injection was done fan-shaped. Needle placement was controlled by palpating spastic muscles without anaesthesia. General anaesthesia was used only in irritable or uncooperative children or for the iliopsoas muscle. Ultrasound-guidance was performed in few cases to confirm correct needle placement (e.g. in the tibialis posterior). No EMG-guidance was used, taking into account that BoNT is known to diffuse across fascial planes, so that paralysis may still be produced despite suboptimal injection.

In de novo patients we used Dysport® (Ipsen Pharma GmbH, Ettlingen, Germany) because of its higher specific biological potency with 115 equivalent mouse units/ng BoNT compared to Botox® (Allergan, Irvine, CA) with 60 equivalent mouse units/ng BoNT. A long-term treatment combining multi-level injections was ensued under strict abidance to the manufacturers’ dose recommendation: 20 (de novo patients) to 30 units of Dysport®/kg, and up to 12 units of Botox®/kg. The standard solution takes into account the findings of Bigalke et al: 500 units Dysport® in 5 ml saline solution 0.9%; 100 units per 1 ml solution. The mean number of injections was 5.5 ± 3.7 (range: 2-16) with a minimum interval of 3 months between injections. Children were integrated into a multimodal treatment including intensive physiotherapy and orthotics. Casts were not used because they increase muscle tone causing pain, agitation and sleeplessness in cerebral palsy children. Night-splints were applied to prevent fixed contractures.

Every child was examined clinically and video-documented 2 to 4 weeks after injection to document the effect of treatment and after 12 to 14 weeks to decide for a reinjection. All patients with adductor spasticity had radiological pelvic examination for hip laterisation or subluxation. In every outpatient visit, parents were asked about the occurrence of side effects (fever, weakness, hypotonia and tiredness).

RESULTS

Thirty-five children with 4 or more BoNT treatment sessions according to the KMC were reviewed after a mean follow-up period of 30.3 months (range 14-69). There were 22 boys and 13 girls with a mean age of 103 months (range 25-188). Twenty-seven patients (77%) suffered from bilateral spasticity and eight (23%) had monolateral involvement. At the initial examination, a GMFCS-Level II was found in 12 (34%) and a GMFCS-Level III in 17 (49%) patients. Two patients were classified as GMFCS-Level I, 2 as Level IV and 2 Level V (5.7% each). Thirty-three patients were treated at least at 2 levels.

The average dose of Dysport® was 25 (range: 14 to 30) units/kg body weight, always under the limit of the European recommended manufacturer dose of 30 units/kg body weight. This amounted to a mean patient dose of 423 ± 223 (range: 60-1500) units. The interval between injections averaged 4 months (range: 3-6).

None of the patients who got 4 or more injection sessions underwent bony surgery. Six patients underwent soft tissue procedures: 4 children had percutaneous Achilles tendon lengthening (3 unilateral, 1 bilateral) and 2 underwent bilateral lengthening of the adductor muscles due to structural contractures. No systemic side effects or antibody-induced non-response were encountered (Fig. 2-3).

DISCUSSION

We present a retrospective clinical study of cerebral palsy patients treated with low-dose BoNT according to our key-muscle concept. In contrast to the widely used high-dose treatments, this concept allows long-term therapy and strictly follows the dose recommendations of the manufacturers. Special consideration is given to the developmental state of the child and aims to promote optimal motor development. The KMC avoids new contractures, bone deformities, lever arm disease, antibody-induced non-response and systemic side effects which are shown to be dose-dependent.

The motor development in a child with cerebral palsy is similar to that of a healthy child but it takes longer. If not reaching a motor-milestone, motor growth can stagnate. The KMC selectively treats spastic muscles that impede reaching the next motor milestone. Because of longitudinal growth, the lever arm changes in disfavour of force development. As
Graham stated: “In children with cerebral palsy a race takes place between growth of spastic muscle and the neighbouring long bone. The race is concluded at skeletal maturity” (9). Here, BoNT improves gait and prevent contractures.

Our patients had twice the age of those in the high-dose study of Molenaers et al (21) while the onset age of treatment at 23 and 25 months is comparable. From their 106 patients receiving 4 treatment sessions, 32 (30%) received 5 and 12 (11%) received 6 injections. In comparison, among our 35 patients who received 4 treatments, 86% received 5 and 69% received 6 treatment sessions. Our patients had a higher monolateral spasticity (23%) compared to 8% in Molenaers et al study (21). The time interval between injections was a year in their study and 4 months in our study. Regarding motor development and contractures during growth, a treatment interval of one year seems less flexible to cover the steps of motor development. Specially during the early motor development, a shorter injection interval appears favourable.

Children may be at special risk for secondary non-response due to BoNT-antibodies. Risk factors for antibody production include the amount of BoNT applied at each injection and the interval between injection series (7). Furthermore, a risk of severe side effects due to overdosage specially in severely diseased children exists (6,22,26). Forced by a case of death after BoNT treatment with the dose recommended in the 2006 consensus paper of the Swiss health administration (22), a joint letter of Allergan and Globopharm (1) emphasized that the European Consensus paper does not reflect the dose limit recommended by health authorities and the manufacturers.

Concerning limitations of this study, the data presented consisted of video-documented patients without examination score. Due to the multiple clinical patterns in cerebral palsy, its classification is challenging and a scored evaluation alone will be less informative without a control group. This is,
however, ethically debatable with our current state of knowledge. Other measurement tools like GMFM, modified Tardieu scale or a tool with a multi-domain approach like the Functional Independence Measure for Children (WeeFIM) would be used in further studies.

In conclusion, the key-muscle concept is an adequate low-dose BoNT therapy for children with spastic cerebral palsy with a long-term treatment setup that offers an alternative to the commonly used high-dose schemes. We recommend that the upper dose limits set by the manufacturers be strictly respected to reduce the risk of antibody development and systemic side effects. Despite the results being based on a small number of patients, a follow-up time till 69 months with up to 16 injections where 61% of children received 4 or more injections without significant side effects indicates the success of this concept. Larger randomised controlled studies are needed to validate its superiority over other treatment schemes in current clinical practice.

REFERENCES


