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Evidence-based review of safety and efficacy in cerebral palsy

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ABSTRACT

The introduction of botulinum toxin has been a major advance in the care of children with cerebral palsy. Clinically the positive effects of treatment with botulinum toxin are seen in patients with all levels of GMFCS. Botulinum toxin has been established in multiple studies to reduce spasticity in the upper and lower extremities, although there is some conflicting evidence regarding function. The medication is felt to be generally safe with a low incidence of adverse events which are temporary and self-limited. However there is the recognition that severe weakness may rarely occur. Ultimately it is incumbent upon the physician to consider both risks and benefits in determining the best treatment plan for the individual patient.

Cerebral palsy (CP) is the most common movement disorder in children, occurring in 2–3 of every 1000 live births with a prevalence of 3.3 per 1000 in eight year olds (Yeargin-Allsopp et al., 2002). It is significantly more common in preterm and low-birthweight infants, and half of all cases occur in infants with a birthweight of less than a kilogram. Previous definitions often focused exclusively on CP as a motor disorder. The definition of CP was revised by the Executive Committee for the Definition of Cerebral Palsy and in that statement the definition was significantly broadened. "Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder." (Bax et al., 2005).

Patients with CP demonstrate a diverse group of movement disorders, which all have in common that they are caused by static injury to the developing brain. The definitive diagnosis of CP can only be made after a period of observation in which no progression of symptoms is observed. The child with CP may also have significant non-motor impairments, including communication, intellectual function, learning disabilities, behavioral disturbances, epilepsy, and sensory impairment including hearing and vision disturbances. Any worsening of motor function over time warrants a further evaluation to identify possible complications due to orthopedic or other comorbid issues. If none are revealed then an alternative diagnosis to cerebral palsy must be sought.

Cerebral Palsy encompasses a heterogeneous group of etiologies with wide variations in clinical presentation. Even standardized terminology for the clinical aspects of the disorder have been lacking, making comparisons of populations and outcome measures problematic. Some progress in this areas has been made by the Task Force on Childhood Motor Disorders (Sanger et al., 2003). This NIH-supported effort developed detailed operational definitions of spasticity, dystonia, and rigidity, which are applicable to clinical features of hypertonic movement disorders in children. The majority (approximately 80%) of patients with CP have spasticity as the predominant symptom of their motor dysfunction. The remaining have a dyskinetic form of movement disorder including primarily dystonia, athetosis, ataxia, and atonia (Yeargin-Allsopp et al., 2002). Clinically it is apparent that many patients have some component of both spasticity and dyskinesia. A further problem in CP research is the difficulty of conducting blinded, placebo-controlled trials in this disorder.

As an upper motor neuron disorder, CP gives rise to both positive and negative symptoms (Mayer, 2002). The positive symptoms include muscle overactivity and increased flexor reflexes, while the negative symptoms include weakness and loss of fine motor dexterity. In general, only the positive symptoms are amenable to pharmacologic therapy. Unfortunately, in many cases the negative symptoms have a greater effect on patient function.

This article focuses on the treatment of movement disorders in patients with cerebral palsy with botulinum toxin. The specific emphasis is on safety and efficacy in this patient population.

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1. Safety of botulinum toxin in cerebral palsy

For over 20 years, botulinum toxin has been widely used in clinical practice for treatment of muscle overactivity in cerebral palsy. Over this period, reports of adverse events have raised some concerns about safety. The severity of the reported events has ranged widely. In response to these adverse events, formal warnings have been issued by regulatory agencies.

A systematic review of 20 randomized studies of botulinum toxin A, enrolling 882 participants between 1990 and 2008, reported the range of adverse events, including pharyngitis, nonspecific pain, falls, respiratory tract infection, bronchitis, vomiting, seizures, urinary incontinence, asthma, and infections (Albavera-Hernández et al., 2009). There have also been separate reports of flu-like feeling and fever. The majority of reported adverse events are described as localized and minor.

The production of muscle weakness is Intrinsic to the mechanism of action of botulinum toxin; therefore there has been the continued concern about the possibility of generalized weakness or weakness remote from the injection site. The German Federal Institute for Drug and Medical Devices (BfArM) produced a “red hand letter” in 2007 documenting the possibility of severe side effects. Of note, in September 2008 the German Federal Institute for Drugs and Medical Devices published a statement stating that currently “there is no evidence showing a causal connection” between the fatal outcome of 5 patients and their prior treatment with botulinum toxin (BfArM, 2008).

Warnings were issued from regulatory agencies in several countries in 2008, including from Health Canada, the Swiss Agency for Therapeutic Product and the US Food and Drug Administration. Responding to a petition concerning safety, the FDA warning was formalized on April 30, 2009, with safety level changes including black box warnings and a requirement for a “risks, evaluation and mitigation strategy” (REMS), applicable to all types of botulinum toxin products. The FDA further stated that physicians must be aware of these warnings and inform and educate the patients and their families, especially those physicians whose practice was directed toward children. They expanded that, however, to say that adults also experience these symptoms and these had been seen in both approved and unapproved indications. The black box warning from the FDA ultimately said that there may be a distant spread of toxin effect beyond the treatment area, with the possibility of breathing and swallowing difficulties, and the risk of death. Adverse events could occur within hours of injection, or weeks later.

The incidence of any adverse events varies by toxin type. A report from Toxin 2013 indicated the overall rate of adverse events for botulinum neurotoxin type A was between 6.2% and 10% and were described as mild (Papavasiliou et al., 2013). A 2013 report on botulinum type B noted a rate of adverse events of 29.8% with none requiring hospitalization. The adverse events with the use of botulinum toxin type B included bowel and bladder incontinence, dry mouth, swallowing difficulty, weakness, hypotonia, and increased seizures (Brandenburg et al., 2013).

With the successful use of botulinum toxin in children two years of age and older more attention has turned to the use and safety of the medication in children under two years of age. Safety data for onabotulinum toxin A for the treatment of club foot in children less than two years of age at a single center indicated only a single adverse event in the treatment of 361 feet in 239 subjects over a 12 year period (Chhina et al., 2014). Safety data on the use of botulinum toxin type A in a Spanish cohort under two years of age were reviewed by Pascual-Pascual (Pascual-Pascual and Pascual-Castroviejo, 2009). Treatment in the first year of life was predominantly for obstetric brachial palsy (72%) and cerebral palsy (25%). By the second year the indication was predominantly for cerebral palsy representing 74% of the patients injected. Their adverse events were only 3.6% in the first year and 6.5% in the second year of life. Mild weakness or tiredness was reported, but not observed by the physicians in the study. There was no difference in rate of events between type A preparations, nor any relation to the dose by muscle or the total dose given.

Other factors that physicians may be concerned about regarding adverse events include the level of the patient's motor function, as captured by the Gross Motor Function Classification System (GMFCS). Evaluation of 1980 injections in 1147 children (distributed across the GMFCS spectrum) indicated that 1% of injections were associated with incontinence (Naidu et al., 2010). Another 1.3% led to hospital admission for respiratory symptoms. Neither effect was related to GMFCS level. Patients with oropharyngeal dysfunction, pseudobulbar palsy and a high GMFCS level were considered to be at a higher risk for complications, but interpretation was difficult due to the concurrent use of inhalation anesthetics. The authors recommended caution in patients at levels IV and V with a history of aspiration and respiratory disease. In a study of 334 patients with all levels of GMFCS, again at a single center, the incidence of adverse events occurred in all groups and were temporary at 9.6% (O'Flaherty et al., 2011). Lower respiratory infections in the GMFCS level 4 and 5 were reported, but of note, there were fewer events after the injections than before. The average dose was 16 u/kg. Further supporting the above authors a recent retrospective study reviewed the safety of botulinum toxin A in sixty patients age 20 months to 16 years with predominantly spastic type (89% spastic and 11% dyskinetic) cerebral palsy Gross Motor Functional Classification level IV and V. This more severely involved group is often considered the most vulnerable to complications. The comorbidities were consistent with those previously described including cognitive disabilities epilepsy, gastrointestinal, and orthopedic. In a total of 242 treatments the patients received between 3 and 21 U/kg of botulinum toxin A with a maximum of 400 U. The majority of injections were provided in the lower extremities but some patients received upper extremity injections either separately or in conjunction with the lower extremities. Only 13% were done under general anesthesia with the remainder in the outpatient setting with relaxation and distraction techniques. Twelve of the 242 treatments resulted in local side effects such as swelling, bruising, or localized weakness. These side effects lasted only a few days and were all considered transient by the parents. No one required hospitalization. The authors added that their lower rate of side effects may reflect the reduced use of general anesthesia in this group (Mesterman et al., 2014).

Both incontinence of bowel and constipation have been reported. Naidu reported an approximately one percent incidence (19 patients) of incontinence in their review of almost two thousand injection episodes across all GMFCS levels and age groups. The majority of patients (15) had involvement of both bowel and bladder but either could be independently involved. The incidence of incontinence occurred across all GMFCS levels, with higher doses associated with systemic complications. The authors contend that bowel or bladder incontinence is a good marker of systemic involvement. They further argue that incontinence is due to systemic spread and not local spread of the toxin as evidenced by patients who experience incontinence after injections of their calf muscles. The incontinence is thought to be due to the involvement of cholinergic mediated external sphincters of the bowel and bladder, especially in children who may have borderline control of continence. The urinary incontinence resolved in all children within six weeks. Separately constipation has also been reported and there the authors theorized that the constipation is related to the systemic spread and the autonomic effects of the toxin (Vles and Vles, 2010).

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Sedation is another major safety factor that has been a consideration in several reports. In a retrospective study of 356 patients over 1382 sessions, 3.3% were associated with adverse events (Papavasiliou et al., 2013). Five were related to sedation and were seen specifically in GMFCS V. Twenty-three were toxin-related adverse events, including weakness, pain, restlessness, flu-like feeling, swallowing, strabismus and possibly seizure, although the relationship to seizure has been hotly debated. The incidence was related to GMFCS level and epilepsy, but not related to dose.

The relationship between dosing and adverse events has continued to be debated, with reports of dose-related increase in events in some cases, and reports of no relationship in others. Further studies are indicated to explore this important question. It is incumbent on the individual treating physician to weigh the potential for complications when calculating the dosing regimen.

2. Efficacy of botulinum toxin in cerebral palsy

In 1994, Cosgrove and Graham showed that treatment with botulinum toxin type A prevented contractures in the hereditary spastic mouse model of cerebral palsy (Cosgrove and Graham, 1994). Spastic mice injected at postnatal day six developed mature calf muscles within 2% of normal length, versus 16% shorter muscles in untreated mice. In 1999, the same group looked at the effects of gastrocnemius injection in 39 ambulatory CP patients, showing that there was a short-term, though not a long-term, effect on gastrocnemius length after botulinum toxin injections (Eames et al., 1999). Based on this, the authors argued that injections may be indicated to delay the need for surgical lengthening procedures.

The literature rapidly expanded soon afterward, such that in 2010, the American Academy of Neurology and Child Neurology Society published a Practice Parameter evaluating evidence from 148 studies (Quality Standards Subcommittee et al., 2010), and in 2013, Novak published a systematic review of 166 treatment interventions for children with cerebral palsy, including botulinum toxin (Novak et al., 2013).

Of the studies considered in the American Academy of Neurology/Child Neurology Society (AAN/CNS) Practice Parameter, 15 studies encompassing treatment of 573 patients rose to the Class 1 (highest) level, and five studies rose to the Class 2 level. All used botulinum toxin type A. Spasticity reduction was seen in all but three studies, with the duration of response approximately three months. When compared to physical therapy alone, toxin treatment plus physical therapy was superior for its spasticity reduction effect at six months (Reddihough et al., 2002).

A Class 1 study of gait analysis showed improved ankle dorsiflexion and swing, with a longer duration of effect at higher dose (Polak et al., 2002). On the Gross Motor Function Measure walking dimension, a class 1 study showed 37% improvement versus 7% for placebo at 12 weeks (Ubhi et al., 2000). That same study also showed that the mean gait improvement at 12 weeks was twice as great in the treated group, as measured on the Physicians Rating Scale.

There were four class 1 studies of treatment effects in the upper extremities. Here, the main outcome measure was the Quality of Upper Extremity Skills Test (QUEST). A common theme emerging from these studies is early and limited functional improvement, with no residual benefit by six months. Lowe et al. showed superiority for toxin treatment plus occupational therapy versus occupational therapy alone at one month and three months, but not at six months (Lowe et al., 2006). Wallen et al. also demonstrated than the combination of the two was superior to occupational therapy alone (Wallen et al., 2007).

Based on their review, the AAN/CNS reviewers concluded that botulinum toxin A is established to reduce spasticity in the upper and lower extremities. Conflicting evidence was found regarding functional improvement. They also concluded that treatment with botulinum toxin A is generally safe in children with CP, however severe generalized weakness may occur. Their recommendation was that for localized and segmental spasticity, botulinum toxin A should be offered as an effective and generally safe treatment. There was insufficient evidence to support or refute the use of botulinum toxin A for improved motor function. Neither was their sufficient evidence to evaluate the use of botulinum toxin B, phenol, or alcohol injections as a treatment for spasticity. It should be noted that this lack of endorsement does not imply that these interventions do not work, but simply points out that there is insufficient evidence at this point.

As part of their 2013 review of 166 articles and 131 outcomes, Novak et al. (2013). classified interventions based on a “traffic light” scheme, with green indicating “do it”, yellow “probably do it,” and red “clearly do not do it.” Only 16% or 21 out of 131 rose to the level of green. Among the interventions rated green were botulinum toxin therapy and OT after botulinum toxin treatment. There were eight studies considered for reduction of lower extremity tone, where it was thought to be effective and safe. The quality of evidence was high and the strength of the recommendation was strong. In reducing upper extremity tone, there were three studies. The quality of evidence was thought to be moderate and the strength of recommendation was strong at green. It was felt that there was insufficient evidence when function was measured over spasticity reduction and extrapolated from the lower extremity to the upper extremity. In the review of reduced hypertonia of the neck, there was only one study, which was insufficient for recommendation, with extrapolated data from treatment of non-CP dystonia, it was felt to be effective. The quality of evidence was not applicable and the recommendation was yellow. In improved walking function three studies revealed that it was probably effective if combined with physiotherapy. The quality of evidence was moderate and the recommendation was green. In studies of efficacy, improved hand function and activities were seen in four studies. It was effective in combination with occupational therapy. The quality of evidence was high, the strength of recommendation again was green. There were four studies where it was proven to be effective in combination with occupational therapy, and further studies supporting therapy in upper extremities were recommended. One study discussed reduced pain, but the quality of evidence was very low and the strength of the recommendation was a weak yellow. Decreased drooling was seen in three of the reviewed studies. It was effective short-term and, given the adverse social outcome for patients who do drool and do not have treatment, the overall recommendation was green.

Newer studies have continued to add to the body of evidence evaluating use of botulinum toxin for CP. In a retrospective study of 438 patients, higher scores on a goal attainment scale were found in children who were younger than age 10, had multi-level injections, and had distal versus proximal injections (Desloovere et al., 2012). The Goal Attainment Scale which evaluates parent or patient defined functional goals was also the metric used in another report from the same group, who found again that success correlated with multi-level injections, younger age at treatment, and distal versus proximal injections. Molenaers et al. (2013) reviewed a data base of all botulinum toxin treatments at their institution over a ten year period to study two important aspects of the treatment of the lower extremities with botulinum toxin in children with cerebral palsy. First, they sought to identify the factors that might predict the outcome. In the second study they evaluated the efficacy of repeated injections of botulinum toxin. They utilized gait analysis and the Goal Attainment Scale (GAS) to assess the functional outcome of the treatment sessions. The authors concluded that

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based on the GAS, 67% of the treatments were successful. The GAS scores indicated successful treatment in the mildly involved children with cerebral palsy and those patients who received multilevel injections or distal only injections (when compared to proximal muscle injections only). Other factors that correlated with successful outcome included increasing the frequency of physical therapy, casting post injection, and increased use of orthotics. In the second study, 444 treatments were evaluated and the GAS confirmed that repeated injections showed efficacy (Molenaers et al., 2013). Potential benefits included delay of surgery.

3. In summary

In clinical practice, botulinum injection is appropriate for a patient for whom the weakening of a limited number of muscles has the potential to provide meaningful benefit in care, comfort, or active function. The focus of the injections of botulinum toxin are those muscles involved in the common clinical patterns in the upper motor neuron syndrome. In the lower extremity, the injections are typically directed to the adductors, hamstrings, gastrocnemius, and soleus. In the upper extremities the most frequent distribution is in the flexors of the arm, wrist, and fingers. Botulinum toxin may be used in conjunction with other treatments, such as oral medications or intrathecal baclofen, to provide focal tone reduction. Electromyography, electrical stimulation, or sonography are frequently utilized to guide injections. This is especially important in difficult to reach or identify muscles. Clinical benefit is usually seen within several days, and the peak benefit occurs at approximately four weeks. Benefit gradually declines, typically requiring reinjection in three to four months.

The introduction of botulinum toxin has been a major advance in the care of children with cerebral palsy. Clinically the positive effects of treatment with botulinum toxin are seen in patients with all levels of GMFCS. Botulinum toxin has been established in multiple studies to reduce spasticity in the upper and lower extremities, although there is some conflicting evidence regarding function. The medication is felt to be generally safe with a low incidence of adverse events which are temporary and self-limited. However there is the recognition that severe weakness may rarely occur. Ultimately it is incumbent upon the physician to consider both risks and benefits in determining the best treatment plan for the individual patient.

Transparency document

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