Botulinum toxin and cerebral palsy: time for reflection?

Review

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Botulinum toxin A (BTX-A) is increasingly being used in early management of spasticity in ambulant children with cerebral palsy (CP), with the aim of improving function, promoting muscle growth, and delaying the need for surgical intervention. However, there is a lack of evidence about the long-term outcome of BTX-A injections. The focus on spasticity as the predominant problem in younger children with spastic CP may not fully consider the associated muscle weakness. It also raises concern that although BTX-A may improve function in the short term, it has the potential to affect muscle growth and function adversely in the long term. A cautious approach to the early use of BTX-A, with the use of objective outcome measures within a specialized multidisciplinary setting, is recommended, particularly in ambulant children with spastic diplegic CP, until further evidence is available on the long-term outcome of early BTX-A injections in children with CP.

The use of botulinum toxin A (BTX-A) has been recommended in the management of spasticity in ambulant children with cerebral palsy (CP) to improve function and to delay the development of fixed deformity and, thus, the need for surgical intervention.[1] Although its immediate positive effect on joint passive range and function had previously been described in several randomized control studies,[2–4] Ade-Hall and Moore concluded in 2000 that there was not enough evidence to support or refute the use of BTX-A in the management of lower-limb spasticity.[5] There have been further randomized controlled studies since then,[6–9] but a recent review[10] noted that the number of cases studied remained small and that further work in this area was required. Although it seems to provide a short-term functional benefit,[6–9] there is limited objective evidence for a continuing effect of BTX-A on function[7,11] or muscle growth[12] in children with spastic CP. However, there is increasing interest in the early use of BTX-A in this area, with some authors suggesting that BTX-A might prevent the development of deformity in ambulant children with spastic diplegic CP, possibly avoiding[13,14] the need for orthopaedic surgery. Given that the natural history of the development of deformity in children with CP is still unclear, that some children with spastic diplegic CP show a deterioration in their mobility with growth,[15–18] and that the long-term prognosis for mobility in adults with spastic diplegic CP is likely to be poor,[19,20] it seems appropriate to consider whether there are any long-term implications of the early use of BTX-A. The use of BTX-A in ambulant children with CP has been comprehensively reviewed recently in this journal[21] and elsewhere.[10,22] Rather than duplicate those reviews this paper looks at the evidence for the use of BTX-A in the context of our current understanding of the development of deformity in CP, particularly in children with spastic diplegia, and considers the implications of this for our clinical practice.

Current ideas about the development of deformity in children with CP and the treatment or prevention of deformity have been largely developed from animal models,[23–26] with a generally held view that the development of deformity in muscle is related to a combination of increased tone, altered joint

position, and a decrease in muscle fibre length.[27] Although BTX-A was initially used in humans to weaken the extra- ocular muscles in strabismus,[28,29] after a study on the effect of BTX-A on muscle growth in the hereditary spastic mouse[30] it was used in children with CP with the aim of reducing hypertonicity to allow more control of movement and to allow increased stretch of the involved muscle, thus, promoting longitudinal muscle growth.[31] Subsequent studies on the use of BTX-A in children with CP[2–4,6–9] have continued to emphasize treatment of spasticity. The rationale behind the use of BTX-A as a focal treatment for spasticity is unclear: the temporary chemodenervation of a muscle may mask the clinical features of spasticity by weakening the muscle but it is unlikely to otherwise alter the upper motor neurone syndrome with which spasticity is associated as a positive feature.[32] This focus on management of spasticity has meant that the potential effects of BTX-A on negative features of the upper motor neurone syndrome, such as muscle weakness and tendency to fatigue, are not generally considered.

The use of BTX-A is based on the concept that muscle fibres in children with spastic CP are short, and that weakening the muscle with BTX-A injections will allow them to be stretched and, thus, to grow longitudinally: the progression from a dynamic to a fixed deformity may, therefore, be delayed.[31] The evidence for this is limited. The findings of the two studies to date that have looked at muscle fibre length in children with spastic CP[33] are not consistent with the theory behind the use of BTX-A. Shortland et al.[34] used ultrasound to assess the medial gastrocnemius in children with spastic diplegia who had fixed deformity of the muscle: no difference in length was noted between the muscle fascicles of children with spastic diplegia and those of children developing normally with a normal passive joint range. They suggested that because of the pennate nature of the medial gastrocnemius, fixed deformity of this muscle in children with spastic diplegia may be related to decreased muscle fibre diameter and shortening of the aponeurosis secondary to muscle atrophy rather than shortening of the muscle fascicles. Lieber and Friden,[35] using intraoperative laser diffraction, did not find any evidence of decreased muscle fibre length in the flexor carpi ulnaris in children with CP with a fixed flexion deformity of the wrist. These findings are supported by a study by Fry et al.,[36] who used three-dimensional ultrasound to assess medial gastrocnemius muscle belly length in children with spastic diplegia with fixed shortening of the calf muscles and in children developing normally. They found that gastrocnemius muscle belly lengths were significantly shorter in the group with diplegia. This was independent of the reduced ankle joint range and suggested a relative increase in tendon length and a decrease in muscle belly length within the musculotendinous unit, again indicating that fixed deformity might be related to muscle fibre atrophy rather than a change in muscle fibre length. Muscle weakness in children with CP is well described. Wiley and Damiano[37] showed that children with spastic diplegia had significant weakness of their lower-limb muscles, in particular their hip extensors, and ankle plantarflexors and dorsiflexors. They recommended caution in the use of any intervention that could unmask or exacerbate muscle weakness in these children. Engsberg et al.[38] found that children with spastic diplegia had greater lower-limb muscle weakness distally compared with proximally, and suggested that weakness rather than spasticity might be the prevailing impairment in children with diplegia. Despite this, the focus on spasticity as the main problem in these children persists.

If the calf muscles in children with spastic diplegic CP are weak and have an altered morphology, will BTX-A injections lead to increased muscle growth or to further weakness? There is, as yet, no histopathological study looking at the immediate effect of BTX-A on human muscle morphology, although there have been a few animal studies. Cosgrove and Graham[30] showed that BTX-A improved muscle growth in the hereditary spastic mouse homozygote, but the relevance of this finding to children with diplegia is unclear. Although termed the spastic mouse, the homozygote mouse develops a myoclonus, rather than spasticity, owing to a mutation in the glycine receptor gene[39] in which all four limbs are involved.[26] The main features of the condition are tremor, episodic spasms, and a disturbed righting response, and the clinical picture is not thought to be equivalent to spasticity in humans.[40] The only other study (to our knowledge) of the effect of BTX-A injections on muscle growth was reported by Chen et al.[41] They looked at the effect of BTX-A injections on growth of normal juvenile rat gastrocnemius muscle, and found that BTX-A injections led to decreased muscle fibre cross-sectional area and decreased muscle mass, which was not reversed fully by exercise. They suggested that BTX-A injections could compromize the maturational growth of muscle.

There is recent evidence of the effect of BTX-A on normal adult animal muscle. Kim et al.[42] assessed the effect of different dilution volumes of BTX-A injections in adult rabbit gastrocnemius muscles together with the use of passive stretching and electrical stimulation designed to simulate eccentric muscle action. Their results showed that uninjected control muscle was not altered by a combination of stretching and stimulation. Gastrocnemius muscles injected with BTX-A showed muscle fibre atrophy and necrosis. Marked deterioration was seen when injection volume was increased by dilution and by a combination of stretching and electrical stimulation, which caused pronounced variation in muscle fibre size with associated muscle fibre splitting and fatty infiltration, similar to that noted by Castle et al.[43] in severely atrophic soleus muscles with marked fixed deformity in children with CP. Although Kim et al.[42] felt that these muscle changes, which appear to represent a deterioration, represented a promising strategy for increasing the beneficial effects of BTX-A treatment, the possibility that BTX-A might cause pathological changes in normal adult animal muscle subjected to eccentric loading is a cause for concern in the context of its use in the management of equinus in children with spastic CP.

The ability of BTX-A to weaken muscle is the basis for its use in adult cosmetic intervention. BTX-A has been used to reduce masseteric hypertrophy because of the predictable and permanent degree of muscle atrophy noted after injection. Von Lindern et al.[44] described the use of BTX-A in seven adults with masseteric hypertrophy; the outcome was assessed by clinical photography. Four patients had reduction of their hypertrophic muscles after a single injection, three needed a second injection, and one needed a third injection. Atrophy was noted 3 to 8 weeks after injection, and persisted at follow-up 25 months after injection. To et al.[45] described the outcome in nine injected hypertrophic masseter muscles, and found that the muscle bulk, when assessed by ultrasound, was still decreased in six patients 1 year after a single injection. The other three muscles needed a second injection to maintain the reduction in their masseter muscle bulk. Both studies advocated the use of

BTX-A as an effective means of reducing masseteric hypertrophy, which was preferable to surgical debulking of the muscle. Lee et al.[46] described the use of BTX-A in the deliberate reduction in medial gastrocnemius muscle bulk in adult Korean women, for the purpose of aesthetic contouring. The decrease in muscle bulk in these cases was assessed subjectively and by clinical photography. It is not clear how BTX-A can be used to apparently promote longitudinal muscle growth in children with spasticity and to promote muscle atrophy when used in adult muscle: it is probable that the apparent reduction in spasticity, the improvement in equinus seen in children after injection and the short-term improvement in function are due to the exacerbation of underlying muscle weakness.

Should we be concerned that BTX-A works by weakening muscles, in view of its positive short-term effects? To answer this question, we need to look at the broader context of the natural history of mobility in children with spastic diplegic CP. Children with spastic diplegic CP are not a homogeneous group. Some children with spastic diplegic CP, despite an initial improvement in mobility,[47] show a progressive deterioration in mobility in childhood[15–18] which can continue after skeletal maturity.[19,20,48,49] It is not clear from the literature whether those children with spastic diplegic CP who present with dynamic equinus and those who later develop multilevel fixed lower-limb deformities are different subgroups or represent different stages of the natural history, but there is evidence for a progression in children with diplegia from an equinus gait to crouch gait. Rodda et al.[50] described a classification system for sagittal plane kinematics in children with spastic diplegic CP, ranging from dynamic equinus to crouch gait. Their paper included a longitudinal study, which showed that some children seemed to deteriorate with time while other children improved. Half of the children who developed crouch gait had not had previous surgical intervention to lengthen the calf muscles, indicating that a progression from equinus to crouch gait may reflect the natural history of gait for some children with spastic diplegia. Could this be affected by the use of BTX-A? Sutherland et al.[51] studied the effects of temporary denervation of the calf muscles in healthy adult volunteers by a tibial nerve block: the denervation resulted in increased ankle dorsiflexion, increased knee flexion, and subsequent increased knee extensor activity. The potential for isolated surgical intervention to the calf muscles in children with spastic diplegia to accelerate the development of crouch gait is well known,[52] but the potential long-term effect of BTX-A does not seem to have been considered. The possibility that BTX-A might reduce the ability of the calf muscles to cope with eccentric loading,[42] which is increased in dynamic equinus,[53] causes particular concern here: if the gait of children with spastic diplegic CP is likely to deteriorate, then anything that could further weaken the ankle plantarflexor muscles could hasten the development of crouch gait by leading to an increased reliance on the knee extensors for support and progression.[54] Such a deterioration might not be attributed to the use of BTX-A, either because the effects are masked by the early improvement in mobility that seems to be part of the natural history[47] and may be attributed to the effect of the early intervention, or because those children with early development of deformity may have been referred onwards for consideration of surgical intervention, making long-term outcome studies by the clinicians who initially performed the BTX-A injections more difficult.

The use of BTX-A in CP has previously been questioned and the need for outcome studies discussed[55,56] together with the importance of its use within a specialized multidisciplinary setting. We do not wish to imply that BTX-A is inappropriate for children with spastic diplegic CP, but we are concerned that the current focus on the management of spasticity does not take into account the associated muscle weakness or consider the potential long-term effects of injection in the context of the natural history of mobility in these children. We lack information about the medium-term to long-term effects of BTX-A: a current outcome assessment of those children who participated in the studies mentioned on BTX-A[2–4,6–9] would be very useful. Objective outcome assessment should ideally be performed on all children having BTX-A injections,[56] and more formal studies of the effect of BTX-A on muscle morphology in children with CP should be considered. The use of ultrasound to assess the effect of surgical intervention on the architecture of the medial gastrocnemius in children with diplegia has been described;[57] similar techniques could be used to assess the effect of BTX-A on muscle.

Given the present lack of evidence about the long-term effect of BTX-A, a cautious approach to the early use of BTX-A in ambulant children with spastic diplegia without fixed deformity, with the use of objective, standardized outcome measures within a specialist multidisciplinary setting,[56] seems appropriate. In the subgroup of children with spastic diplegic CP who have early development of fixed deformity, particularly those with early development of proximal fixed deformity or with a pre-existing increase in knee flexion on walking, an initial approach that emphasizes muscle strengthening and focuses on long-term function and mobility, limiting the use of BTX-A, is recommended. Further studies may then show whether the short-term benefit gained from injecting muscles with BTX-A in children with spastic diplegia is associated with a long-term benefit in function, mobility, and improved muscle growth.

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