Does botulinum toxin prevent or promote deformity in children with cerebral palsy?

MARTIN GOUGH MCH FRCSI(ORTH)
One Small Step Gait Laboratory, Guy's Hospital, London, UK
E-mail: Martin.Gough@gstt.nhs.uk
See related article on page 120.

In this issue, Tedroff et al. report the outcome of a prospective uncontrolled study on the effect of botulinum toxin A (BoNT-A) on the lower limb muscles of children with spastic cerebral palsy (CP). The study group is heterogenous in terms of age, Gross Motor Function Classification System (GMFCS) level, topographical pattern of CP, and level of deformity. It consists of children with CP having BoNT-A treatment for spasticity which interfered with function or the use of orthoses, or which was associated with a reduction in joint range of motion. Children awaiting orthopaedic surgery were excluded. BoNT-A was not used in isolation: most (92%) of the children used ankle-foot orthoses, and serial casting was performed in addition for 3 weeks following injection in children who did not have ankle dorsiflexion past neutral. Outcome measures were limited to the modified Ashworth scale and joint range of motion measures. Injections were repeated, to a maximum of 8 injections per muscle, when the authors and families noted a favourable outcome from previous injections. They found a persistent reduction in muscle tone in the muscles injected but a progressive reduction in joint passive ranges, following an initial improvement. They concluded that BoNT-A was not effective in preventing muscle deformity and suggest that it may instead promote the development of deformity. They also concluded that deformity is not necessarily linked to spasticity and that reduction of spasticity may not prevent deformity. This is similar to the conclusion reached by Graham et al.[1] in their recent randomized controlled study on hip dysplasia.

Tedroff et al. found that the rate of progression of deformity did not appear to be influenced by age, GMFCS level, or pattern of CP. This is interesting as progression of deformity in children with CP has been shown to be influenced by the severity of involvement of the child;[1] given the heterogenous nature of the study group a wide variation in outcome would have been expected. Variation in the number of courses of BoNT-A was noted, however: 14 of 94 children had a single injection only, due to an adverse reaction or a lack of response, and 28 more children left during the study period, 13 of whom required orthopaedic surgery for progressive deformity. Although they do not have control data, the children who completed the study and had the greatest number of BoNT-A injections may represent a subgroup who would normally have a better prognosis and have less risk of development of deformity. Could repeated BoNT-A injections have adversely altered muscle growth in this selective subgroup, as the authors suggest?

Tedroff et al. did not measure muscle volume or muscle belly length so it is difficult to be specific about where the observed reduction in length of the musculotendinous units occurred. There is evidence that BoNT-A causes deleterious changes in muscle fibres. Minamoto et al.[2] showed that a single BoNT-A injection to adult rat muscles caused up to 80% reduction in muscle fibre size 1 month following injection, which was associated with a similar reduction in muscle force generation. Muscle fibre atrophy of this magnitude could lead to the development of deformity in the muscle because the length of the muscle belly in most pennate muscles is highly dependent on average fibre diameter.[3] Ma et al.[4] looked at the effect of physiological doses of BoNT-A on muscle mass and force in juvenile rats. They found that muscle mass decreased by almost one-third 2 weeks following injection, but returned to near-normal 6 months following injection. In terms of musculoskeletal growth, however, 10.5 rat days is equivalent to 1 human year:[5] if we are to extrapolate the results of animal studies this would suggest that peak loss of muscle mass may occur 16 months following injection of BoNT-A in children and that it may be necessary to wait over 17 years for a human muscle to recover before repeating the injection. Similarly, the marked reduction in muscle fibre size seen in adult rats 1 month following injection[2] could persist in adult humans over a year following injection.[5] These comments relate to the effect of BoNT-A on normally-developing muscle. Muscles in children with CP may not be developing normally, and the concern expressed by Tedroff et al. that repeated injections of BoNT-A may have a cumulative adverse effect on muscle growth in children with CP appears valid and needs to be addressed.

Function and participation in adults with CP may be influenced by a range of factors including communication skills, epilepsy, availability of assistive devices, and

the local environment. It may also however be influenced by available muscle mass. Given the lack of evidence of a long-term functional benefit of BoNT-A in children with CP prospective longitudinal studies of its effect on muscle morphology and growth are needed if we wish to optimize long-term function in adults with CP.

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Thrombolysis in paediatric arterial ischaemic stroke

V GANESAN MD

Neurology Unit, Institute of Child Health, University College, London, UK.
E-mail: v.ganesan@ich.ucl.ac.uk

See related articles on pages 151 and 155.

Two papers in the current issue of the journal present accounts of the use of intra-arterial thrombolysis to treat children with arterial ischaemic stroke (AIS). Although these reports discuss thrombolysis in very specific contexts, as the view that stroke in adults should be treated as 'brain attack' becomes a reality, paediatric neurologists are increasingly questioning whether childhood AIS should be treated in a similar way. This is a complex issue and clearly there is potential to do significant harm for a benefit that is, as yet undefined. For example, Gupta et al.[1] reported that although some degree of clot resolution was seen in 85% of cases, only 30% of 80 children (65 with AIS) treated with tissue plaminogen activator did not experience any treatment complications. Unfortunately, the bulk of the current literature on this topic comprises a multitude of single case reports from which it is only possible to infer feasibility and not more generalizable data regarding safety and efficacy.

Why not just apply the adult guidelines (of administering intravenous tissue plasminogen activator to adults with AIS within 3 hours of symptom onset and no intracranial haemorrhage)[2,3] to children? First, the diagnosis of childhood AIS is usually not made for many hours, if not days, after symptom onset[4,5] and there is a need to raise awareness and recognition. However, it is possible that the time window for salvaging tissue at risk may be different in children compared with adults or, as Janmaat et al. point out, in the posterior compared with the anterior circulation. Second, the pathophysiology of AIS in childhood is variable and is not, unlike in adults, dominated by the consequences of atheromatous cerebrovascular disease. Although arterial abnomalities are apparent in 80% of children with AIS,[6] complete arterial occlusion is relatively unusual and, thus therefore, the logic of universally administering thrombolysis is flawed. Patients could be screened and selected on the basis of imaging; given the wide differential diagnosis for acute focal neurological deficits in children this would need to be done with magnetic resonance imaging (MRI). However, acute access to brain imaging in young children remains challenging in the UK. For example, nearly two thirds of children with acute hemiparesis do not have any brain imaging within the first 24 hours and less than 10% are investigated with brain MRI during that period.[4] These resource issues would need to be addressed if they precluded access to clinically proven treatments. There are no data on the optimal thrombolytic agent, dosing regime (an important consideration given the differences in the coagulation system between adults and children), nor on the optimal mode of delivery. Intra-arterial thrombolysis, as described in the papers by Tan et al. and Janmaat et al., would require the skills of an interventional neuroradiologist with paediatric experience. Finally, robust data on the outcome of childhood AIS are scanty and are necessary to compute the risk to benefit ratio of a high risk intervention such as thrombolysis. Although the majority of children have some residual impairment after childhood AIS, the nature and severity of this is not predictable in the acute stage and death is relatively unusual. Thus counselling families, even in the context of a clinical trial, will be very challenging.