Use of botulinum toxin A in management of children with cerebral palsy

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Abstract

Question What is the role of intramuscular botulinum toxin injections in the management of spasticity and related morbidity in children with cerebral palsy?

Answer When botulinum toxin A is injected into the limbs of children with spastic paresis, it induces temporary reduction in muscle tone. It also promotes better motor function when used in combination with conservative treatments such as physiotherapy. Although there is a growing body of evidence for its effective and safe treatment, there is still a lack of consensus on dose, treatment regimens, and the best integration with other clinical modalities.

La toxine botulique A dans la prise en charge de la paralysie cérébrale

Résumé

Question Quel est le rôle des injections intramusculaires de toxine botulique dans la prise en charge de l'hypertonie spastique et de sa morbidité afférente chez les enfants atteints de paralysie cérébrale?

Réponse Quand on injecte de la toxine botulique A dans les membres d'un enfant ayant une parésie spastique, il se produit une réduction temporaire du tonus musculaire. Cela favorise aussi une meilleure fonction motrice lorsqu'elle est utilisée en combinaison avec des traitements conservateurs comme la physiothérapie. Même si les données probantes en sa faveur comme traitement sûr et efficace se multiplient, il y a toujours un manque de consensus quant aux doses, aux régimes thérapeutiques et à son intégration optimale à d'autres interventions cliniques.

Cerebral palsy (CP) is a clinical syndrome characterized by a persistent disorder in motor control and posture, and results from nonprogressive brain damage.[1] Cerebral palsy is the most common cause of physical disability in children, with a reported incidence of 2 to 2.5 per 1000 live births.[1] Approximately 90% of affected children present with clinical symptoms of spastic paresis, a muscle-tone and muscle control–regulation disorder.[2] Static muscle contractures and bony deformities develop slowly over time and are secondary consequences of spasticity. Children with CP require management by a multidisciplinary team to address each child's particular needs. A treatment program usually focuses on the reduction or normalization of tone to prevent the development of secondary complications. The most common interventions are physiotherapy, use of orthotics, serial casting, electrical stimulation, and, more recently, the intramuscular injection of botulinum toxin type A (BtxA).

Botulinum toxin

Botulinum toxin type A is 1 of the 7 different serotypes of botulinum toxin (A to G) produced by the anaerobic bacterium *Clostridium botulinum*.[3] Botulinum toxin type A selectively blocks the release of acetylcholine at the cholinergic nerve terminal, ensuring a temporary reduction in muscular activity in the injected muscles.[3] The process is reversible and the return of synaptic function to the original neuromuscular junction takes approximately 90 days. The period of clinically useful relaxation is usually 12 to 16 weeks.[4]

Botulinum toxin type A injections were first given therapeutically for strabismus in the early 1980s.[5] The treatment was adopted for other neurologic conditions, such as blepharospasm, cervical dystonia, and hemifacial spasm. In 1993, Koman et al[6] produced preliminary results of the first clinical trials using BtxA for spasticity in CP patients. The rationale for using BtxA for CP management was that the reduction of spasticity after BtxA injection opened a "therapeutic window" for interventions, enhancing both motor ability and functional skills and preventing contracture formation.[7] Although at first BtxA was applied to one muscle at a time, it became apparent that many of the common limb dysfunctions

and gait patterns in CP could be adequately treated only if several muscles were treated simultaneously.

Effectiveness of BtxA in CP management

In the past 2 decades, numerous trials have assessed the effectiveness of BtxA injections on motor function in children with CP.[8-15] While several studies found statistically significant beneficial effects,[8-10,13-15] others failed to demonstrate benefits.[11,12] The use of distinct assessment tools and primary outcome measures, in addition to the diversity in clinical approaches, cointerventions, and subjects' characteristics, partly accounts for the variability of the reports. Lack of consensus on recommended dose and diverse pharmacokinetic properties of commercially available BtxA preparations contribute to the challenge in interpreting the results of currently available literature.

In 2010, a Cochrane systematic review assessed the effectiveness of BtxA alone or in combination with occupational therapy for upper-limb treatment in children with CP. Ten randomized controlled trials (RCTs) were included. An analysis of data showed that a combination of BtxA and occupational therapy is more effective than occupational therapy alone in reducing impairment and improving activity-level outcomes, but not for improving quality of life or perceived self-competence. When BtxA was used alone there was moderate evidence that it was not effective.[9]

Several systematic reviews also analyzed the effectiveness of BtxA therapy in the management of lower-limb spasticity and gait in children with CP.[10-12] In 2001, Boyd and Hays[10] summarized results of 10 RCTs and found evidence for a moderate, dose-dependent treatment effect of BtxA on gait and lower-limb function. Koog and Min[11] reviewed 15 RCTs and reported less-favourable results. When botulinum injection was compared with a non-sham control, it was effective in improving muscle tone, ankle range of motion, gross motor function, and gait speed; however, when sham injection was used as control, botulinum injection had affected gross motor function only when measured after 4 months. Koog and Min[11] suggested that BtxA might not be as effective as commonly believed and might be overprescribed for CP patients. Recently, Ryll et al[12] systematically reviewed 8 RCTs in order to assess treatment effects of BtxA on gait of children with CP. When compared with physiotherapy alone, adding BtxA treatment had a moderate positive effect after 2 to 24 weeks of follow-up. This effect was not demonstrated when BtxA treatment was compared with casting alone.

Age and long-term effects

Spasticity most commonly develops within the first few years of life in children with CP. Therefore, BtxA treatment is recommended at 2 to 6 years of age, when gait patterns and motor function are still flexible.[8] Evidence relating to long-term outcome of treatment with BtxA is scarce. Desloovere et al[13] demonstrated that BtxA injections delay and reduce the frequency of surgical procedures and result in a favourable gait pattern at 5 to 10 years of age. Similarly, Molenaers et al[14] reported that BtxA treatment can delay and reduce the need for surgery in the follow-up of children with CP, provided that the treatment is started while gait patterns are still flexible. A recent prospective study on children with CP treated with BtxA included 57 children with a mean age of 6 years who were followed up for a year. Results demonstrated larger reduction in spasticity and better functional prognosis after BtxA injection in younger children. Botulinum toxin type A treatment also correlated with improvement in quality-of-life measures.[15]

Adverse effects

Botulinum toxin type A is considered to be one of the most potent poisons. However, when used in recommended doses, adverse events of BtxA are usually transient, mild, and local.[16] Adverse events attributed to systemic spread of the toxin are uncommon and include flulike symptoms, generalized weakness, dysphagia, and subsequent aspiration caused by diminished airway protection.[16] In 2008, the US Food and Drug Administration expressed concern about potential severe adverse effects (respiratory compromise and death) of BtxA based on reports of children treated for CP-associated limb spasticity.[17] These concerns were contrary to previous safety-profile information.[18] In a meta-analysis of safety with 20 RCTs and 882 participants, BtxA use was associated with respiratory tract infection, bronchitis, pharyngitis, muscle weakness, urinary incontinence, falls, seizures, fever, and unspecified pain. Two deaths were reported in one study and were found not to have causal relation to the toxin. The authors concluded that BtxA had a good short-term safety profile, but advocated careful monitoring, especially in children with more severe CP.[19]

Conclusion

Treatment of spastic-movement disorders associated with CP requires an interdisciplinary team approach with a range of conservative and surgical strategies. There is growing evidence that BtxA is effective in reducing spasticity and improving motor function when it is used in combination with other treatment measures. However, there is a lack of data about optimal dosing and injection schemes, and safety concerns demand strict monitoring of potential adverse effects, especially in children severely afflicted with CP.

Competing interests
None declared

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PRETx Pediatric Research in Emergency Therapeutics

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