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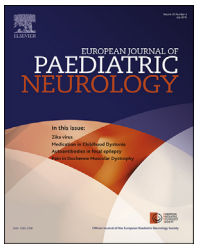

Original Article

Safety profile of incobotulinum toxin A [Xeomin®] in gastrocnemious muscles injections in children with cerebral palsy: Randomized double-blind clinical trial

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ABSTRACT

Background: The only two preparations of botulinum toxin A for which there are published evidences of efficacy in children with cerebral palsy are onabotulinum toxin A (Botox®) and abobotulinum toxin A (Dyport®); these toxins should be considered generally safe and appropriate in the treatment for localized upper and lower limb spasticity.
Aims: To establish the safety profile of incobotulinum toxin A (Xeomin®) in children with cerebral palsy and muscle spasticity.
Methods: Randomized double-blind controlled trial that involved the recruitment of children of both sexes with spastic hemiplegia or diplegia in cerebral palsy, aged between 3 and 18 years. Children were randomized to either the study group (SG, incobotulinum toxin A) or the control group (CG, onabotulinum toxin A) both to be injected with 5units/kg on gastrocnemius (medialis and lateralis) muscles. The occurrence of adverse events at baseline, after 48 h, 10 days and 3 months was recorded by the caregivers in a checklist that listed both common and uncommon side effects.
Results: 35 patients were treated (CG = 18; SG = 17); the 2 groups were well balanced regarding demographics and anthropometry characteristics. At least 1 adverse event occurred in 49% of patients within first 2 days, 46% between 2 and 10 days, and 12% between 10 and 90 days. All the reported events were minor; no serious adverse event was recorded. Fatigue was the most frequent complaint. There was no significant difference in frequency and type of events between the 2 groups.
Conclusion: Incobotulinum toxin A and onabotulinum toxin A share similar profile of safety in the treatment of lower limb spasticity in CP children.

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1. Introduction

Botulinum toxin type A (BTX-A) is one of the seven different serotypes of botulinum toxin (A to G) produced by the anaerobic bacterium *Clostridium botulinum*.[1,2] 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. The neuromuscular synaptic blockage is irreversible, but the denervation is transient since the synapsis is reconstituted within an average of 90 days.[3] The onset of muscle weakness occurs within 14 days of treatment, even though usually after few days the weakening of the injected muscles is already apparent and the duration of action in children averages 3–6 months.[2]

BTX-A injections were first given therapeutically for strabismus in the early 1980s.[3] The treatment was adopted for other neurologic conditions, such as blepharospasm, cervical dystonia, and hemifacial spasm. In 1993, Koman et al.[4] produced preliminary results of the first clinical trials using BTX-A for spasticity in cerebral palsy (CP) patients. There are three commercial formulations of BTX-A available at present: onabotulinum toxin A (Botox®), abobotulinum toxin A (Dysport®), and incobotulinum toxin A (Xeomin®). These formulations have different manufacturing process, as well as different excipients and advised dosages. Interchangeability and conversion algorithms have been widely criticized and indeed find little justification in the clinical practice. In fact the Italian regulatory agency AIFA has highlighted the need that each formulation is treated as a separate product. However some clinical development programme of incobotulinum toxin A showed a 1: 1 incobotulinum toxin A to onabotulinum toxin A dose ratio.[5]

The rationale for using BTX-A for CP management was that the reduction of spasticity after BTX-A injection opened a "therapeutic window" for interventions, enhancing both motor ability and functional skills and preventing contracture formation.[3] The efficacy of BTX-A in the management of spasticity in children with CP was recently confirmed.[6] BTX-A is not approved for treatment of spasticity or children younger than 12 years of age but use of off-label medications such as BTX-A in children with CP is very common.[2] Therefore, for safety reasons, the lowest dose necessary should be injected and always determined on the basis of the child's weight. The use and dosage of BTX-A in CP, depending on body weight and age, were established in the European Consensus Table of 2009[7]: in that occasion the researchers highlighted as the only two preparations of BTX-A for which there are published evidences of efficacy in children with CP are onabotulinum toxin A and abobotulinum toxin A.

A meta-analysis of data from 37 randomized clinical trials across a wide range of BTX-A showed that adverse events occurred in 25% of individuals who were treated with onabotulinum toxin A.[8] Adverse events are reported with the use of onabotulinum toxin A with a frequency of 23.2% in children with CP[9] and may be grouped into two broad categories: local and general.[8] Local reactions to BTX-A at the administration site commonly include pain, oedema, erythema, ecchymosis, short-term hyperaesthesia and excess weakness in the muscle injected. In addition, local reactions can occur following migration of the toxin into adjacent muscles. The general events reported with a certain consistency are nausea, fatigue, malaise, flu-like symptoms and rash, allergic reactions and generalization of the effect, with weakness beyond the injected muscles "causing symptoms similar to those of botulism". Those symptoms include potentially life-threatening swallowing and breathing difficulties and even death.[10] Most serious adverse events have been reported in children with CP treated for spasticity; this problem, which led the FDA to require in 2009 a "black box" warning on BTX-A and might condition the way in which the toxin is used especially in children,[11] highlights the importance of accurately report describe the adverse events associated with any BTX-A preparation especially in children. No controlled study explored the safety (and efficacy) of incobotulinum toxin A in children with spastic CP. To our knowledge in literature there are one study that describe the use of incobotulinum toxin A in children with spasticity[12] and two in children with different pathologies (obstetrical brachial plexus palsy,[13] strabismus due to brain damage[14]).

One of the supposed advantages that incobotulinum toxin A may have over other botulinum toxin formulations for its use is the lower antigenic potential due to lower protein content.[15] A systematic review[16] of randomized control trials with BTX-A (abobotulinum toxin A and onabotulinum toxin A) in spastic CP suggests that BTX – A has a relatively good safety profile during the first months of use but no randomized clinical trial with incobotulinum toxin A. Recent studies[17–23] demonstrated the safety and efficacy of incobotulinum toxin A in adult spasticity.

Aim of our study was to evaluate the safety profile of incobotulinum toxin A on CP children, using the same standard dose of onabotulinum toxin A in the management of children with lower limbs muscle spasticity.

2. Methods

2.1. Population

We recruited 35 consecutive CP patients referred to our Institute for rehabilitation and treatment. They had diagnosis of spastic diplegia, hemiplegia or quadriplegia due to CP, as verified by history, clinical/instrumental examination and neuroimaging findings; they were between 3 and 18 year of age. Subjects were excluded from the study if was present one of the following criteria: peripheral nervous system disorders/myopathies; previous treatments for spasticity other than BTX-A to the lower limbs (<1 years); previous orthopaedic surgery to lower extremities; bone or joint deformities and fixed contractures; medications that could have had an impact on the study findings (es. Intratechal baclofen, benzodiazepines, muscle relaxant,…).

All the patients had a clinical indication to treatment with BTX–A in the gastrocnemius muscle.

The study was approved by the competent IRB (Prot. N° 057/11_CE, Ethical Committee). After complete description of the study, written informed consent was obtained from all the patients' relatives.