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INVITED LECTURE

NEW CONSENSUS ON BOTULINUM TOXIN APPLICATION IN TREATMENT OF CEREBRAL PALSY

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ABSTRACT

Cerebral palsy (CP) is a most common cause of spastic movement disorders with children. One of methods of treating spasticity is application of Botulinum toxin (BoNT). BoNT therapy has widely been used for 20 years now during which time it has proven to be a safe treatment. Botulinum toxin is natural purified protein and the strongest biological toxin – neurotoxin. Its medicinal application in USA dated back to year 1981 and in Europe – 1992.

Botulinum toxin blocks neuromuscular conductance, i.e. it blocks transmission of acetyl-holin and in neuro muscular presynaptic – this is so called temporary (reversible) local chemodenervation. It does not influence synthesis of acetyl-holin. During 2-6 months neural collaterals are formed so that neuromuscular conductance is reestablished and spasm develops again. Botulinum toxin therapy can become inefficient due to three reasons. First is improper application of the toxin itself, second reason is predominant muscular fibrosis and third is presence of antibodies.

Interdisciplinary European group of clinical experts in field of movement disorders and experienced users of Botulinum toxin (BoNT), updated its Consensus on Botulinum toxin application dated 2006. Consensus is based on two types of proof: published works and works based on application praxis. In the first part of consensus, authors have formed tables and collected proof, merging data and experience from 36 institutions in 9 European countries, that include more than 10,000 patients and over 45,000 particular treatments. In second part, graphs of motor development, based on Gross Motor Function Measure (GMFM) and Gross Motor Function Classification System (GMFCS), are updated in such a way to get a graphical representation of how motor disturbances with children with cerebral palsy should be treated. Name of this graph is "CPGraph Treatment Modalities – Gross Motor Function". Its purpose is to ease communication between parents, therapists and doctors, dealing with reachable motor functions, setting realistic goals and perspectives for children with cerebral palsy.

Keywords: *cerebral palsy, Botulinum toxin*

INTRODUCTION

An interdisciplinary European group of clinical experts in the field of movement disorders and experienced Botulinum toxin (BoNT) users has updated the consensus for the usage of BoNT in the treatment of the children with Cerebral palsy (CP). A problem-orientated approach was used focusing on both published and practice-based evidence. In part I of the consensus the authors have tabulated the supporting evidence to produce a concise but comprehensive information base, pooling data and experience from 36 institutions in 9 European countries which involves more than 10000 patients and over 45000 treatment session. In part II of the consensus the Gross Motor Function Measure (GMFM) and Gross Motor Function Classification System (GMFCS) based Motor Development Curves have been expanded to provide a graphical framework on how to treat the motor disorders in children with CP. This graph is named "CPGraph Treatment Modalities – Gross Motor Function" and is intended to facilitate communication between parents,

therapists and medical doctors concerning achievable motor functions, realistic goal-setting and treatment perspectives for children with CP. The updated European consensus 2009 summarizes the current understanding regarding an integrated, multidisciplinary treatment approach using Botulinum toxin for the treatment of children with CP. [1]

UPDATED EUROPEAN CONSENSUS 2009 FOR USE OF BONT IN TREATMENT OF THE CHILDREN WITH CP

The Consensus update 2009 presents a conceptual framework for best practice in the use of BoNT in children with CP. Since the first European consensus table on BoNT for children with CP in 2006 basic research, clinical trials, new treatment strategies and safety regards have evolved in the expanding field of CP management. The aim of this updated, annotated, and tabulated evidence report which contains epidemiology and etiology of CP, medico-legal and medico-economic aspects of CP, BoNT and integrated therapy, is to incorporate the recent advances in knowledge into all sections of the earlier consensus table.

Besides literature enhancement, the updated European consensus table is based on data from an extended number of 36 European centers. The authors were able to draw upon the combined experience of more than 280 treatment years, more than 10000 treated patients, and more than 45000 treatment sessions to condense the knowledge in the consensus table. [1,2]

ESSENTIALS OF 2009 CONSENSUS

1. Changing the Paradigm from "Botulinum toxin" to "Activity is supported by Botulinum toxin": Activity is supported by BoNT and vice versa: due to its mechanism of action, BoNT only reduces muscle tone in the active, non-fibrotic, "non-contractured" part of the muscle. However, by reducing tone in the muscle it allows stretch to be applied, which is in itself a stimulus for muscle growth. Activity, which means function, (e.g. dorsiflexion of the foot during the gait cycle) is dependent on the agonistic activity of a particular muscle (in this case tibialis anterior muscle). To improve function, activity, participation and development of a child with CP additional therapies have to be included.
2. "Safety and publicity": BoNT reflects all the benefits and controversies of modern medicine: strong and ongoing medical success as well as a fashion-driven presence on "how to design a perfect body", oversimplified enthusiasm, mass media presence, and headline catching criticism. Due to the wide number of indications pharmaceutical houses have had to document the possibility of severe systemic side effects in a "red hand letter" in Europe in June 2007, followed by an FDA statement in February 2008, and a statement produced by Swissmedic in June 2008. In September 2008 the German BfArM published the conclusive statement that currently "there is no evidence showing a causal connection" between the fatal outcome of 5 patients and their prior treatment with Botulinum toxin. A follow-up statement of the FDA was published in May 2009 stating that FDA has notified the manufacturers of licensed Botulinum toxin products of the need to strengthen warnings in product labeling and that manufacturers have to develop and implement a Risk Evaluation and Mitigation Strategy (REMS) to provide more information regarding the risk of distant spread of Botulinum toxin effects after local injection in the future. It rests in the hand of the treating physician to be up to date on the ongoing safety and labeling discussions using the above mentioned health agencies.

The members of the consensus group are strongly com mitted to emphasize the ongoing need for a careful, unbiased and transparent documentation of any adverse events in the children with CP who are treated with BoNT, ideally stratified by GMFCS levels (1 to 5). [3,1]

CEREBRAL PALSY

CP is the most common cause of spastic movement disorders in children. Epidemiologic data has shown that with the advanced care in neonatal medicine the incidence and severity of CP in premature children of very low birth weight in Europe and northern America is decreasing.

Our understanding of the etiology, or at least the pathogenesis, of the disease has been greatly advanced by the development of Magnetic Resonance Imaging techniques, which allow the identification of the underlying structural changes in the brain and gives information on topography and the extent and potential timing of the causative lesion. Although the cerebral lesion in CP is viewed as caused by a single event, CP has to be understood as a developmental disorder described over time as an individual develops. The development of the European consensus on CP definition and classification and its illustration by a video-based manual provides a practical basis for a unified approach with respect to diagnosis. A whole body approach to classification (and reclassification) is facilitated by the use of the Gross Motor Function Classification System (GMFCS), which describes disease severity.

Reclassification of a child is recommended during every appointment, especially when the child is under the age of four years. Classification according to GMFCS may also be used for decision-making concerning which treatment intervention is appropriate over the course of time. The GMFCS classification system is a useful tool for hip surveillance programs as was shown by a Swedish group in 2007. Classifications by GMFCS and 'limb distribution' or by GMFCS and 'type of motor impairment' are significantly correlated. However, an analysis of function (GMFCS) by impairment (limb distribution) indicated that the limb distribution did not add prognostic value over GMFVS, although classification of CP by impairment level seems useful for clinical and epidemiological purposes. These recommendations are in line with a report on the definition and classification of cerebral palsy as published by an international consensus group. [4,5]

MEDICO-LEGAL AND MEDICO-ECONOMIC ASPECTS

BoNT treatment of children with CP is often performed under unlicensed conditions, using dosages and body segments or muscles which are not supported by relevant licensing bodies. However, the off-label use of medications is accepted and common practice in many pediatric fields and will continue until there is a significant increase in research directed at children. Typically the licenses for BoNT treatment show a great variety between countries and are restricted to specific preparations, specific indications and dose limitations. Licensing does not reflect the clinical need, especially for children with CP. Individualized variations in BoNT dosage, BoNT dilution, and clinical indications and the muscle groups treated represent appropriate, although unlicensed, use where such treatment is in line with clinical experience. Careful decision-making on dosage, dilution and injection control rests in the hands of the treating physician and has to be adapted to the individual patient. [1]

BOTULINUM TOXIN AND INTEGRATED THERAPY

The use of BoNT in children with CP represents a major therapeutic intervention but should never be considered a stand-alone treatment. The treatment approach to the spastic movement disorders associated with CP must include the whole range of conservative and surgical strategies and regularly requires an interdisciplinary team approach. Recent developments in the field show that the advanced use of BoNT combined with different conservative (or non-conservative) treatment options, has the potential to achieve functional benefits for children with CP. However, there is insufficient evidence to either support or refute the use of these interventions before or after BoNT injections.

A combination of therapy procedures is common in daily practice, but addressing this by research is far from being easy. Robotic assisted therapy can serve as an intervention model where activity parameters can be measured during therapy intervention. This may allow a better understanding about the correlation of effect of dosing to activity and whether this has any effect on participation. [6]

BOTULINUM TOXIN AND COMMON INDICATIONS

Spastic movement disorders in children with CP are a result of the involvement of the brain, central motor pathways, spinal circuits and musculo-skeletal system. With ongoing child motor development spastic movement disorders develop into distinctive motor patterns, which need to be recognized and should be used to guide treatment. Starting in 1990s an increasing number of focal indications emerged such as pes equinus, pes equinovarus, knee and hip flexion spasticity, adductor spasticity, and spasticity of upper extremity (e.g. finger flexion, wrist flexion, ulnar deviation, elbow flexion and shoulder adduction). In non – focal conditions such as CP, a number of muscle groups may need to be targeted. This has led to development of a multi-muscle, multi-level treatment approach, in which a number of overactive muscle groups are treated with BoNT to achieve an improvement of limb motion and posture. The use of classifications, e.g. for sagittal gait patterns may facilitate the development of more standardized pattern-guided treatment approaches. [7,6]

DOSAGE AND DOSE MODIFIERS OF BOTULINUM TOXIN THERAPY

To date two preparations of BoNT Serotype A – Botox® (Allergan Inc.) and Dysport® (Ipsen Ltd.) – have demonstrated focal efficacy and functional gains for children with CP. A third BoNT/A preparation (Xeomin®, Merz Pharma, Germany) was introduced to the market in 2005 with circumstantial reports on beneficial effect in children with neuro–pediatric indications. All Botulinum toxin products are distinct concerning their molecular structure and manufacturing process and methods used for determining biological activity are different. For children with CP, these pharmacological differences have significant implications for clinical use. Individual dosages must be calculated independently for each BoNT preparation.

Dosage calculation for each preparation is based on:

1. Total units per treatment session
2. Total units per kg body weigh per session
3. Units per muscle
4. Units per injection site
5. Units per kg body weight per muscle (unit / kg / muscle)

It has to be respected that the term "unit" represents a different biological potency for each BoNT preparation. Additional dose modifiers which have to be considered when planning the injection protocol may be: severity of CP according to GMFCS, accompanying diagnoses (e.g. dysphagia, aspiration, breathing problems), predominance of movement disorder (spasticity, dystonia), activity of the injected muscle, muscle size, dynamic versus fibrotic muscle, knowledge about the distribution of motor endplates in the injected muscle. Dilution will depend on body region and muscle size (e.g. forearm versus upper leg). In animal models higher dilutions showed greater dissemination, but clinical evidence to support this information is missing. [8]

SAFETY OF BOTULINUM TOXIN

BoNT therapy has been widely used for over 20 years during which time it had proved to be a safe treatment option. In general, the occurrence and severity of adverse events after BoNT therapy for children with CP are rare. With the development of the multi – level treatment strategy over the last years it has become apparent that an adequate focal treatment effect can only be achieved when the injected dose / muscle remains the same. Consequently, the total dose/session increases with the number of treated muscles, but this needs to be differentiated from "overdosing" a single muscle. Adverse events can be differentiated into focal, generalized and procedural adverse events.

It is important to emphasize that it remains the responsibility of the treating physician to "check and balance " dosing, dose modifying effects and procedural risks (as general anesthesia) for each child on an individual basis keeping in mind the treatment goal(s), national and institutional rules. The GMFCS helps to anticipate severity-related co-morbidities which should be taken into account in every BoNT treatment session. According to the Surveillance of Cerebral Palsy in Europe the GMFCS was distributed at Level I in 32%, Level II in 29%, Level III in 8%, Level IV in 15%, and level V in 16%. Learning disability was present in 40%, epilepsy in 33%, and severe visual impairment in 19% of the children. More severe GMFCS levels correlated with larger proportions of accompanying impairments and a greater incidence of brain stem pathology and cranial nerve dysfunction that needs to be assessed prior to BoNT treatment. The potential additional risk for the different subgroups of GMFCD evolving from treatment with BoNT remains to be clarified and Is currently under investigation in different centers worldwide. [9,10]

BOTULINUM TOXIN THERAPY AND PROCEDURES

In children with CP, pain management is an important issue. Procedural pain such as BoNT injections requires appropriate, effective analgesia, especially because BoNT therapy requires repeated multiple, painful, but elective injections. Therefore, appropriate, effective analgesia and as the case arises in combination with sedation is fundamental and an ethical necessity. The optimal regimen will vary between individuals and will be influenced by the age of the child, the GMFCS, the number of muscles to be treated and the institutional setting and resources. The procedural pain management includes pharmacological as well as non – pharmacological techniques and already starts prior to the procedure. Children should receive injections delivered using accurate localization technique. Classical neurophysiological localization methods (EMG) have recently been amended by sonography which allows precise identification of any target muscle using readily available, noninvasive equipment. [6,9]

ASSESSMENT AND EVALUATION OF TREATMENT WITH BONT IN CHILDREN WITH CP

The development of new CP assessment tools has been stimulated by the therapeutic possibilities offered by BoNT therapy. Purpose – built classification tools and standardized clinical assessments enable people to speak the same language and to evaluate interventions using consistent and valid instruments, matched to the dimensions of the international classification of functioning, disability and health. A large number of studies in literature report about the effect of BoNT predominantly only on the level of body structure and function. Gait analysiis data provide important information for delineating the problems of children with CP. The following issues are important:

1. Stratification of patients according to age, Gross Motor Function/Manual abilities and type/characteristic of movement disorder
2. Randomization centrally organized, independent from the physician doing the intervention
3. Blinded rating of treatment effects
4. Standardization of co – interventions
5. Intention – to – treat analysis of drop – out patients.[9,10]

EFFICACY OF BOTULINUM TOXIN THERAPY

In a randomized controlled clinical trial 48% of children treated with BoNT showed clinical improvement, compaired to 17% of placebo treated children. The mean duration of BoNT exposure was 1.46 years per patient and the response was maintained even for 2 years. Initial reports on long-term adherence show that, while about 75% of patients achieve their treatment goals following the initial injection sessions, a considerable number discontinue therapy for various reasons.

Non – responsiveness to BoNT can occur as a result of insufficient injection accuracy, predominant muscle fibrosis or the formation of antibodies. In children undergoing BoNT treatment in the 1990s up to 30% were reported to develop antibodies. This problem was solved by reformulating the formula of the toxin itself, i.e. by decreasing antigenicity. In conclusion antibody formation does not seem to affect clinical decision and any "new" BoNT formulations that are introduced would have to prove their superiority to established preparations. [11,7]

CONCLUSION

We can finally conclude that Botulin toxin therapy of muscular spasms of children with cerebral palsy is a safe treatment. Botulin toxin decreases muscle tonus only in the active, non fibrotic and non contracted part of a muscle. The decrease of muscle tonus enables stretching which itself is a stimulus for muscle growth. Side effects after Botulin toxin treatment of children with cerebral palsy are rare. New consensus reached in 2009 is based on published works and works based on praxis in 9 European countries. Based on it, the authors have formed tables and graphs with measurements of basic motor functions of children with CP. They drew a new graph (CP graph Treatment Modalities Gross Motor Function) whose purpose is to ease communication between parents, therapists and doctor. It is important to stress that the doctor is the one on which rests responsibility to check and balance the dosage and to adjust it for every individual child, staying focused on the treatment's objectives.

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