Use of Intramuscular Botulinum Toxin in Malaysian Children With Cerebral Palsy

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SUMMARY
A study was carried out to determine the clinical effectiveness of intramuscular botulinum toxin type A (BTX) in the treatment of spasticity or dystonia in 58 consecutive children with cerebral palsy (CP). The effectiveness of the treatment was determined by the reduction of spasticity and global parental perception scale. The mean age of treatment was six years and the most frequent aim of treatment (91.1%) was functional improvement. The median reduction of spasticity as measured by modified Ashworth scale was 1. The short term outcome was graded as excellent or good by 44.6% and satisfactory by 38.4% of parents. Patients with dyskinetic Cerebral Palsy had the best response. Adverse effects were minimal. BTX treatment is modestly effective in the majority of our patients with spastic and dyskinetic cerebral palsy.

KEY WORDS: Botulinum toxin, Cerebral palsy, Effectiveness

INTRODUCTION
Botulinum toxin type A (BTX) when injected intramuscularly, binds tightly to the motor end plates, impairs the release of acetylcholine and causes chemical denervation. The use of intramuscular botulinum toxin type A (BTX) for children with cerebral palsy was started in 1990s1-3. Since then its efficacy has been demonstrated in improving gait following injection to the calf muscles in a few randomized double-blind placebo controlled trials4-6. However, the outcome of BTX injection in the upper limbs was more variable7, 8. The use of BTX in Malaysian children with cerebral palsy was started in 2000 at the Paediatric Institute, Hospital Kuala Lumpur. Our unpublished results were mixed in the early years. We report here our recent experience and clinical effectiveness with BTX on Malaysian children with various types of cerebral palsy.

MATERIALS AND METHODS
We analysed data collected prospectively using a standard proforma from all consecutive children with cerebral palsy treated with BTX, from January 2003 till December 2004. These children were treated at our multi-disciplinary cerebral palsy clinic, at the Paediatric Institute, Hospital Kuala Lumpur. Patients with neurodegenerative and neurometabolic disorders were excluded.

The indications and aims of the treatment were agreed upon by the team and patient's parents. They could be one or more of the following:-
1. To improve functional ability such as better sitting, standing or walking for the lower limb injections and to improve balance and hand skills for the upper limb injections.
2. To ease nursing care of the perineal area, dressing and hand hygiene for those with ‘thumb-in-palm’ deformity.
3. To prevent deformity / contracture or hip dislocation.
4. To relieve pain. This includes better tolerance to physiotherapy, ankle foot orthosis and standing frame as well as to relieve pain due to muscular spasm or following orthopaedic surgery.

The spasticity of the muscles targeted was determined by the modified Ashworth scale9. The dosage of the BTX (Dysport®) per injection in each session was determined by the degree of the spasticity, the number and size of the muscles injected and previous response to BTX. The dosage used ranged from 1 to 5 units/kg/muscle for smaller muscles and from 5 to 15 units/kg/muscle for bigger muscles. A maximum of 30 unit/kg/session and with an interval between injections of not less than three months were adhered to. Besides the BTX injection, the patients also received physiotherapy and / or occupational therapy and were prescribed ankle-foot-orthoses when appropriate. The patients were reviewed at six weeks post injection and three monthly thereafter to determine the response and adverse effects of the treatment. BTX injections were repeated whenever deemed necessary. The effectiveness of the treatment was determined by comparing the pre and post treatment modified Ashworth scale and global parental perception scale at follow up six weeks following the injection. Parents were requested to state whether the aim of the treatment or response was 1. Achieved / excellent, 2. Largely achieved / good, 3. Satisfactory, 4. Minimal response, 5. Not achieved / no response. (1 and 2 were considered as good responder, 3 as satisfactory responder, 4 and 5 were taken as poor responders).

The patients’ characteristics, dose of BTX, and types of cerebral palsy between the three treatment response groups were analysed. The likely contributing factors for poor treatment response were also examined.

The data were analysed using two tailed chi-squared analysis to compare differences between the categorical variables of treatment response groups.

This article was accepted: 25 November 2006

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RESULTS
The clinical characteristics of the patients are shown in Table I. A total of 58 children with cerebral palsy aged between 19 months to 15 years old (mean of 6 years) were treated during the study period. Of this number, 25 (43.1%) had spastic diplegia, 16 (27.6%) had spastic quadriplegia, 11 (19%) had spastic hemiplegia, 6 (10.3%) had dyskinetic cerebral palsy (2 choreoathetoid, 4 dystonic). The frequency of injections ranged from one to four, but most of them had received two injections. The interval between the injections ranged from 3 to 19 months with a median interval of seven months. The mean dose of BTX was 17.7 unit /kg/session for lower limbs and 6.5 unit /kg/session for the upper limbs treatment. Out of a total of 112 treatments for the 58 patients, most of the BTX treatments were aimed at improving the patients’ functional level (n=102, 91.1%). Twenty four (21.4%) treatment were to ease nursing care, 13 (11.6%) were to prevent deformity, contracture and hip dislocation, while 19 (17.0%) were for pain relief. For some of the treatment sessions, the aims were a combination of the above. The details on the treatment received according to the types of cerebral palsy are shown in Table I.

Treatment Outcome
The time to treatment response ranged from 1 to 14 days with a median of seven days. Maximal response was noted at one to nine weeks post-BTX. The median duration of response was four months (range: 1 to > 6 months). The median reduction of spasticity was 1 (range: 0.5 to 2) using the modified Ashworth scale. Short term outcome was graded as excellent or good by 44.6% and satisfactory by 38.4% of parents. More parents of patients with dyskinetic CP reported good or satisfactory response compared to the other groups although this was not statistically significant (p = 0.526) (Figure 1). Most of the improvements reported in the dyskinetic CP group were functional improvements such as better and longer sitting duration, better balance and postural control during sitting or walking.

Table II shows the important contributing factors leading to poor treatment response. Fixed contracture was the most important contributing factor (11 out of 19). Others include weak antagonist muscles (5), inadequate dose (5), poor compliance with post-BTX therapy (3), high parental expectation (2) and hip dislocation (1).

Adverse effects
No adverse effect was noted following 89.3% (100/112) of the BTX injections. Ten patients (8.9%) reported fever; mainly of low grade which lasted between one and four days. Five (4.5%) had transient weakness with more frequent falls which lasted between one and three days. Pain at the injection site, vomiting, anorexia and flu-like symptoms were reported in one patient each.

DISCUSSION
This study was carried out prospectively about two years after we started our Botulinum toxin injection programme for children with cerebral palsy. Although most studies on BTX for children with cerebral palsy were on children with spastic diplegia and hemiplegia, our study has shown that it can also be of benefit to other types of cerebral palsy. In fact, one
unexpected outcome of this study was that children with dyskinetic cerebral palsy benefited most, although this warrants more study.

Various researchers have used a number of outcome measures to determine the treatment effectiveness of BTX treatment such as modified Ashworth scale, video/observational gait analysis, gross motor function measure (GMFM), physician rating scale, parental global perception scale and goal attainment scaling. As our patients were rather heterogeneous, we decided to base our treatment effectiveness using modified Ashworth scale when appropriate and parental global perception scale. One of the advantages of parental global perception scale is that prior to the treatment, a realistic target of treatment is determined and agreed upon by the clinicians, therapists and parents. The disadvantage is its subjectivity and at times there may not be a complete agreement of the treatment response between parents and the clinicians as observed in two of our patients. As shown in the current study, over 90% of the treatment sessions were for functional improvement. However, successful reduction of focal spasticity or dystonia by the treatment did not always translate to functional gain as other determinants such as dose of BTX, strength of the antagonist muscles, amount of fixed contracture, selective motor control and motor retraining, age and cognition as other determinants such as dose of BTX, strength of the antagonist muscles, amount of fixed contracture, selective motor control and motor retraining, age and cognition are also important. Hence, the aim of treatment has to be realistic and meaningful to the child and his family.

One of the most common reasons why some of our patients did not benefit from BTX therapy was fixed contracture especially among the older patients. We are now more selective with regards to this group of patients and now routinely employ the modified Tardieu’s scale to determine the amount of fixed contracture among our patients. For the younger patients with mild to moderate fixed contracture, serial castings were employed together with BTX treatment. For some of the above cases that failed BTX treatment, we have convinced their parents to move from conservative approach to orthopaedic intervention.

Another reason for poor response to BTX treatment was weak antagonist muscles which were often only unmasked after the BTX injection. A few of our patients did not benefit from the treatment probably because of inadequate dose, poor compliance with post-BTX therapies like physiotherapy and use of ankle foot orthoses.

The commonest side effect following the treatment was fever but most of them may have been due to intercurrent childhood infections as this was not noted in randomised double-blind placebo controlled studies. Other side effects were transient, none were severe.

CONCLUSION
In conclusion, BTX treatment was modestly effective at least in the short term in the majority of our patients with spastic and dyskinetic cerebral palsy and had no serious adverse effects.

ACKNOWLEDGEMENTS
We would like to express our gratitude and appreciation to other members in our multidisciplinary assessment team including Puan Kamariah (Physiotherapist), Puan Masitah (Occupational therapist), Puan Rakyah and Puan Ruzniah (Neurodisability nurse coordinator), other colleagues at the Paediatric Neurology Unit, Head of Paediatric Department and Director General of Health, Ministry of Health for the permission to publish this paper.

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