The use of Botulinum toxin in Management of Spasticity and a review of injection techniques in relation to children with cerebral palsy.

Abstract
The use of Botulinum toxin type A (BTX-A) to manage focal spasticity in children with cerebral palsy has been rapid evolving since 1990. The success of BTX-A injections is very dependent on delivery of the toxin into the targeted muscle. The method of delivery however is not agreed upon and differs between patient populations. This paper reviews the different techniques for muscle localisation in relation to a paediatric patient population. As these children are likely to be quite young and receive more than one episode of BTX-A, the injection procedure and entire experience should be as stress-free as possible.

Introduction
Since 1993, Botulinum toxin type A (BTX-A) has steadily become the treatment of choice for children with cerebral palsy (Koman et al 1993). The fact that it acts locally at specifically targeted muscles, is reversible, has minimally adverse reaction and can be used repeatedly makes it an ideal choice (DePavia et al 1999, Naumann and Jankovic 2004). As BTX-A therapy has become more widely used for children with cerebral palsy, there has been an effort of produce guidance documents for the entire process (Graham et al 2000, Heinen et al 2006, Katchburian et al 2008, Koman et al 2003, Russman 1997). Recent papers have graded the quality of supporting papers according to guidelines such as Scottish Intercollegiate Guidelineline Network (SIGN) and gathered a wide base of experience from different countries/practioners with an ever growing number of children injected. These authors highlight that much of the use of BTX-A is “off-license” but concluded this is frequent practice in many areas of paediatrics (Heinen et al 2006, Katchburian et al 2008). Despite the increase of randomised control trials in the use of BTX-A, the attention to accuracy of injection technique is poor and procedures have not been standardised (Boyd et al 2001, Desloovere et al 2001, Koman et al 2000, Love et al 2001, Schroeder et al 2006, Sutherland et al 1999, and Ubhi et al 2000).

Botulinum toxin is produced by Clostridium botulinum and is the most potent biological toxin (Mooney et al 2003). There are seven distinct neurotoxins labelled A, B, C, D, E, F, and G. All have different potencies, duration of effect and target different intracellular proteins (Aoki and Guyer 2001). This paper will focus on the clinical use of BTX-A. BTX-A is marketed as Botox (Allergan, Irvine California) and Dysport (Ipsen Ltd.). Their doses are not interchangeable due to differences in the formulation process (Mooney et al 2003).

This paper will examine the different injection techniques for BTX-A in relation to the paediatric population and will therefore primarily focus on papers related to use of BTX-A in paediatrics. The case for BTX-A is well established in adults as recently published guidelines from the Royal College of Physicians indicate (RCP et al 2009). Children are not just small adults. Several well recognised authors concede this fact and highlight additional factors such as pain and tolerance that need to be taken into account when dealing with children (Heinen et al 2006, Schroeder et al 2006). In any patient population however, the effectiveness of BTX-A is dependent on delivery to the correct muscle through accurate needle placement (Koman et al 2003). Palpation, electromyographic guidance (EMG) and ultrasound-guided injections are the main methods of delivery discussed in the literature (Berweck et al 2002, Chin et al 2005, Koman et al 2003, Molloy et al 2002, O’Brien 1997) All of these methods have pros and cons in relation to need for additional training, availability of equipment and the specific patient population. Each method will be explained and examined in terms of benefits and disadvantages in relation to the paediatric population.

Botulinum toxin and Spasticity
Lance et al 1970, described spasticity as “a motor disorder characterized by velocity dependent increase in tonic stretch reflexes that exaggerate tendon jerks, resulting in hyperexcitability of the stretch reflex.” This primary disorder leads to a variety of well accepted secondary consequences such as muscle contracture and dynamic deformity which often lead to functional limitations (Farmer and James 2001, Koman et al 1993, Mooney et al 2003). Treatment interventions for spasticity were limited and tended to focus on the secondary consequences of muscle shortening and joint instability (Graham 2001). The typical progression to musculoskeletal pathology in cerebral palsy is illustrated in appendix 1.

Spasticity interferes with function, causes pain and may produce deformities over time in soft tissues, joints and bones. Growth and development may further affect combination of muscle imbalance and spasticity. Non-operative interventions were limited to therapies, casting and orthotics that focused on the consequences of spasticity, not spasticity itself (Mooney et al 2003). As the primary cause was
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unchanged, successful treatment was limited. These interventions focused on increasing function through normalising muscle tone based on the belief that abnormal muscle tone leads to abnormal patterns of movement that limited functional activity (Russman et al 1997).

Spasticity can be managed pharmacologically through oral or parenteral means. Oral medications have generalised effects that often produce undesirable side effects. Parenteral options include phenol, ethyl alcohol and BTX-A. Phenol and ethyl alcohol are non-selective, painful and have significant, sometimes permanent side effects such as peripheral nerve damage or muscle necrosis (Mooney et al 2003).

Graham et al 2000 provides a useful matrix for the management of spasticity in terms of general vs. focal and permanent vs. reversible. BTX-A is the only option given for focal/reversible treatment of spasticity. Other therapies frequently used in the management of spasticity are given but fall into the category combinations of general/reversible (Intrathecal baclofen or oral therapy), focal/permanent (surgery) or general/permanent (Selective dorsal rhizotomy). It is acknowledged that all therapy approaches may be appropriate depending on the specific needs of the patient but the ability for BTX-A to provide reversible, focal treatment of spasticity is of great benefit (Graham et al 2000).

Botulinum toxin selectively binds to the neuromuscular junction (NMJ) and blocks neuromuscular transmission by inhibiting the release of acetylcholine (Mooney et al 2003). This causes a temporary but reversible paralysis that is dose dependent (Aoki and Guyer 2001, Francisco 2004). The nerve endings gradually recover over 4-12 weeks, first by axonal sprouting and then by complete recovery of the neuromuscular junction (DePalva et al 1999). Despite complete recovery of the NMJ by 12 weeks, the clinical effects are recognised to be from 3-6 months or longer (Koman et al 1993, Mooney et al 2003). The use of BTX-A has shown to prevent the development of contractures in the spastic hereditary mouse (Cosgrove and Graham 1994). Although this is preclinical data, this paper is often referenced in support of the use of BTX-A in children with cerebral palsy. Contractures are a recognised secondary consequence of spasticity that result in adverse functional consequences such as limited joint mobility and muscle length, thus impacting lifestyle (Farmer and James 2001, Graham 2001, Mooney et al 2003).

Koman et al 1993 proposed that BTX-A was useful in the management of dynamic deformity in children with cerebral palsy. Despite having only a small number of patients and limited objective data on the non-ambulant patients, the study did show measurable improvement in foot deformities with ambulant patients. Several studies of increasing soundness (randomised, double-blinded, placebo-controlled) followed in relation to managing spasticity through the use of BTX-A (Boyd et al 2001, Cosgrove et al 1994, Ubhi et al 2000). A summary of uses for BTX-A in cerebral palsy are given in appendix 2. Since the introduction of BTX-A as a treatment intervention studies have shown a significant reduction in the number of children requiring complex orthopaedic surgery (Graham et al 2000, Molenears et al 2006).

In addition to the growing clinical efficacy of BTX-A in relation to children with cerebral palsy, it was and has been proven to be safe, even in high doses (Koman et al 1993, Cosgrove et al 1994, Goldstein et al 2006, Naumann et al 2006). Pain at injection site and temporary weakness continue to be the most common adverse effect (Naumann and Jankovic 2004).

Injection Technique

Of 4 conditions suggested to maximise the clinical effectiveness of BTX-A, accurate injection of the toxin inside the fascial compartment is the first - sufficient dosage, appropriate volume and minimisation of unwanted spread being the others (Ramachandran and Eastwood 2006). Although it BTX-A has been shown to diffuse and cross fascial planes (Shaari et al 1991), efficacy would assume correct injection into the intended muscle. This view is well supported in the literature and is seen as a prerequisite for safe and effective treatment with BTX-A (Chin et al 2005, Henien et al 2006, Kinnett 2004, O’Brien 1997 and Schroeder et al 2006) although additional factors that influence outcome do exist (appendix 3).

There is currently very limited robust evidence supporting one injection type over another (Chin et al 2005). Even expert opinion is divided (Barbano 2001, Jankovic 2001, Koman et al 1993, Lim and Seet 2008 and Schroeder et al 2006). To date only two papers attempt to compare standard injection techniques and only one fully addresses it from the paediatric perspective giving full consideration to the advantages/efficacy of ultrasound-guided injections (Lim and Seet 2008, Schroeder et al 2006). Palpation is the most commonly used method of muscle localisation (Kinnett 2004, Ramachandran and Eastwood 2006 and Schroeder et al 2006). Its benefits are simplicity, quickness and the ability to
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use smaller needles when compared to EMG (Berweck and Heinen 2003). Initial studies depended on anatomical knowledge, palpation and passive movement of the distal limb once the needle is inserted into the target muscle to confirm correct localisation (Barwood et al 2000, Cosgrove et al 1994, and Koman et al 1993).

It is often stated, without supporting evidence, that large superficial muscles are easily identified by manual palpation (Graham et al 2000, Koman et al 2000, and Cosgrove et al 1994). It is also frequently conceded that locating smaller deeper muscles may require guidance through electromyographic or electrical stimulation techniques but supporting evidence other than opinion is often absent (Graham et al 2000, O’Brien 1997, Preiss et al 2003).

Chin et al 2005 showed the need for additional guidance in all muscles other than the gastrocnemius. This independent study was done over 4 years with 226 children receiving 1,372 injections by experienced injectors (Chin et al 2005). The poor level of accuracy over such a long period negates the argument of skill acquisition and possibly casts doubts on all previous studies supporting the accuracy of palpation as a localisation technique (Barwood et al 2000, Cosgrove et al 1994, and Koman et al 1993). Inaccuracy of injection may be one reason why a study did not show statistically significant outcomes but is often not considered (Boyd et al 2001, Weigl et al 2007). Even well-designed studies that claim benefit from BTX-A assume accurate injection by palpation and do not include inaccuracy as a variable in their methodology (Desloovere et al 2001, Koman et al 2000, Love et al 2001, Sutherland et al 1999 and Ubhi et al 2000). Opinion may be changing as insufficient injection accuracy is becoming considered the main reason for nonresponsiveness to BTX-A (Chin et al 2005, Heinen et al 2006).

By highlighting the inaccuracy of palpation (appendix 4), some authors conclude that EMG/ES is therefore the superior method of muscle localisation. In actual fact, they have only proven the need for additional assistance in muscle localisation. None compare EMG/ES to ultrasound or credibly looks at the evidence supporting ultrasound and only one study involves children (Chin et al 2005, Haig et al 2003 and Molloy et al 2001).

Electromyographic guidance (EMG) to localise muscles can be done either actively or passively (Lim and Seet 2008). Passive EMG is done by recording motor unit potentials (MUPs) close to the needle tip inserted into a specific muscle. Active and passive range of movement confirms the correct needle placement (O’Brien 1997). MUPs are assessed acoustically and the examiner must have the training to distinguish between various sounds (O’Brien 1997, Schroeder et al 2006). Passive EMG is difficult with general anaesthetic due to the need for active muscle contraction and small muscles may be difficult to locate. Electrical stimulation (ES)/active EMG is beneficial for motor point stimulation in these cases (O’Brien 1997, Barbano 2001, Lim and Seet 2008).

Successful passive EMG can also be difficult for patients with spasticity who have poor selectivity (Lim and Seet 2008, O’Brien 1997). Active EMG/ES is associated with pain due to the need for high current intensity/repeated needle sticks and is relevant within the context of a paediatric population (Heinen et al 2006, Lim and Seet 2008, Koman et al 1993, Schroeder et al 2006). Due to this, muscle localisation with ES is usually associated with a general anaesthetic or oral sedation (Chin et al 2005, Schroeder et al 2006).

Reasons for increasing accuracy with EMG/ES are cost implication, prevention of neutralising antibodies and the ability to use less toxin and still get the same clinical effect (Barbano 2001, Childers 2003). No studies have specifically looked at the cost difference between injection models so the conclusion remains theoretical. The cost of EMG needles could be offset by the inaccurate injecting and “waste” of BTX-A (Barbano 2001). Since the reformulation of BTX-A in 1998, the risk of antibody formation is extremely low due to its lower protein load (Jankovic et al 2003).

Targeting the motor end-plates with low-dose/high concentration doses has some success but is based on “theoretical and preclinical data rather than on clinical studies with human subjects” (Childers 2003, Childers 2004, O’Brien 1997). Three studies looking specifically at targeting motor points and assuming proximity of motor-end plates found no significant difference in outcome in a single low-dose/high volume injection vs. multi-site low-dose/high volume injections (Childers et al 1996, Mayer et al 2008, Satila et al 2005). As these studies still gave the same overall dosage, the argument for use of less toxin is unclear.

A dual-localisation mode of EMG & ES was proposed to be effective for needle placement with low-dose/high-concentration injections having a “marked clinical and technical effect”. This paper only compares children that received botox vs. those that
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did not (Lowe et al 2006). It does not prove that EMG/ES localisation or low-dose/high-concentration injections are more effective than other localisation techniques or high-dose/low concentration injections. Further doubt to this paper is cast as their main reference supporting localisation with ES does not actually specify which localisation method is used (Love et al 2001).

It is worth noting that the main references for EMG/ES are expert opinion and technically considered a low level of evidence (Sackett et al 2000). There are no randomised control trials or cohort studies that specifically focus on the efficacy of using EMG with children. All authors are well published over several years in respect to the use of Botulinum toxin for adults and children. There are considerable differences of opinion between experts and all do state their papers are predominantly based on experience and opinion (Barbano 2001, Jankovic 2001, O’Brien 1997 and Schroeder et al 2006). It is interesting that some authors who chose not to use EMG due to the perceived pain of the larger needle do not use any form of analgesia when performing numerous intramuscular injections on children (Koman et al 1993, Koman et al 2000).

The use of sonography has been shown to be a safe, reliable, painless and non-invasive method to identify muscle anatomy that requires some additional training but not advanced technical expertise (Fisher et al 1988). Results are rapidly obtained and reproducible (Berweck et al 2004). The use of sonography has historically been popular in paediatrics as a non-invasive, painless procedure (Schroeder et al 2006). This equipment is often readily available in hospitals (Berweck and Heinen 2003, Westhoff et al 2003) although purchase-cost is suggested to be off-set by increased accuracy of injection and therefore better results (Berweck et al 2002).

Inaccuracy of palpation has previously been discussed. Sonography offers visually controlled injections as alternative to electrophysiological techniques which rely on acoustic feedback or muscle stimulation. (Lim and Seet 2008, Schroeder et al 2006) Cross sectional images clearly indentify anatomical structures and muscle fibres are easily located by changing the orientation of the transducer (Berweck et al 2002, Berweck et al 2004, Berweck and Heinen 2003, Westhoff et al 2003).

Inaccurate palpation has previously been discussed. Sonography offers visually controlled injections as alternative to electrophysiological techniques which rely on acoustic feedback or muscle stimulation. Limited numbers, proven 100% accuracy is significant although there are only a few studies with small numbers, proven 100% accuracy is significant (Berweck et al 2002, Westhoff et al 2003, Willenborg et al 2002). Improved accuracy would suggest improved efficacy (Heinen et al 2006, Schroeder et al 2006). Numbers are increasing with recognised experts claiming rapidly increasing experience with 6000-9800 sonography-guided injections in children between 2000 – 2005 (Berweck et al 2004, Schroeder et al 2006).

The use of sedation with sonography-guided injections varies from topical anaesthetic to oral sedation or general anaesthetic depending on the patient, location of muscles and number of muscles to be injected (Berweck et al 2002, Westhoff et al 2003, and Willenborg et al 2002). This is not significantly different from injections utilising EMG/ES (Chin et al 2005, Schroeder et al 2006).

In an attempt to offer clear comparison between EMG/ES and ultrasound, Schroeder et al 2006 looks at 18 different areas of the injection procedure (appendix 5). Ultrasound is clearly their method of choice. Although the information is a summary of their paper, the points are not well referenced on the table (Schroeder et al 2006). The authors of this paper are however clinicians with extensive experience and have been very strong advocates of the use of sonography through several published works (Berweck et al 2002, Berweck et al 2004, Berweck and Heinen 2003 and Schroeder et al 2006).

Conclusion

Although recent reviews state that there no evidence to support or refute the efficacy of BTX-A in improving functional outcomes for children with cerebral palsy, the amount of clinical evidence is overwhelming. It is well recognised that lack of evidence of efficacy does not constitute lack of efficacy (Ade-Hall and Moore 2000, Lannin et al 2006).

Several papers, in addition to those previously listed, review and support the use of BTX-A giving clear guidance on mechanism of action, indications, its tolerability and lack of adverse effects, need for
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multidisciplinary team, goals/outcome measures, dosage and dilution but are quite vague on the method of localisation (Boyd and Hays 2001, Criswell et al 2006, Jefferson 2004, Koman et al 2003, Preiss et al 2003). Opinion is evolving that a greater attention needs to be given to accuracy of technique but there is no clear consensus (Chin et al 2005, Heinen et al 2006, Kinnett 2004). Chin clearly states that “accurate delivery of BTX-A is inherently important to good treatment outcomes, given that the objective is focal reduction of spasticity of the selected muscles (Chin et al 2005).


Appendix 1
The pathway to progressive musculoskeletal pathology in cerebral palsy
- CNS lesion (e.g. periventricular leucomalacia)
- Upper Motor Neuron syndrome
- Spasticity plus weakness/reduced activity
- Failure on longitudinal growth in skeletal muscle
- Fixed contracture
- Bony torsion
- Joint instability
- Joint dislocation or degenerative changes


Appendix 2
Frequently suggested uses for BTX-A in children with cerebral palsy:
- Equinus gait
- Crouched gait
- Knee flexion deformity
- Scissoring
- Varus hindfoot

- Knee extension during swing phase
- Shoulder deformity
- Elbow flexion deformity
- Wrist flexion deformity
- Finger flexion deformity
- Thumb-in-palm
- Excessive pronation
- Painful spasticity
- Movement disorders
- Enhancement of neuromuscular stimulation
- Facilitation and/or reduction of specific caregiver functions
- Decreased post-operative pain
- Improvement of self-esteem due to decreased associated reactions


Appendix 3
Factors that affect outcome of BTX-A therapy (Also related to dosage selection)
1. Patient related factors
   a. Severity of spastic Hypertonia
   b. Number of muscles involved
   c. Chronicity of spastic Hypertonia
   d. Age and body mass
   e. Previous response to BTX-A
   f. Concurrent therapy for spastic Hypertonia

2. Clinician-related factors
   a. Expertise and experience
   b. Second-hand experience

3. Other factors
   a. Cost of therapy

4. Availability of adjunctive therapy

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Appendix 4
Accuracy of palpation

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Injectors</th>
<th>Time frame</th>
<th>Accuracy</th>
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| Chin et al 2005 | 226 children (age 1-18), 502 muscles | 3 experienced injectors of BTX-A in children | Over 4 years | Gastoc-soleus = 78%
|                |                    |           |            | Hamstrings = 46%
|                |                    |           |            | Hip adductors = 67%
|                |                    |           |            | Tibialis posterior = 11%
|                |                    |           |            | Biceps brachii = 62%
|                |                    |           |            | Adductor pollicis = 35%
|                |                    |           |            | Pronator teres = 22%
|                |                    |           |            | FCR = 13%
|                |                    |           |            | FCU = 16%
| Haig et al 2003 | 10 cadaver lower limbs 36 muscles | 3 experienced electromyographers | Not given | Gastoc-soleus = 60-90%
|                |                    |           |            | Hamstrings = 75%
|                |                    |           |            | Hip adductors = 20-30%
|                |                    |           |            | Tibialis posterior = 10%
| *see below     |                    |           |            | Total of 263 injections
| Molloy et al 2002 | 14 patients with focal hand dystonia 38 muscles | 4 neurologists with minimum 2 years experience, 2 EMG fellowship trained | Not given | 14/38 accurate injections
|                |                    |           |            | = 37%
|                |                    |           |            | Extensor compartment
|                |                    |           |            | = 37%
|                |                    |           |            | Flexor compartment
|                |                    |           |            | = 38%

* Haig et al 2003 looked at additional muscles, have listed same muscles to allow comparison

Appendix 5

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<th>EMG</th>
<th>Muscle stimulation</th>
<th>Ultrasound</th>
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Key: “+” = Advantage, “0” = acceptable, “-” = unfavourable

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Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of
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