J Neural Transm (2009) 116:319–331
DOI 10.1007/s00702-008-0175-8

BASIC NEUROSCIENCES, GENETICS AND IMMUNOLOGY - REVIEW ARTICLE

Effectiveness of botulinum toxin A for upper and lower limb spasticity in children with cerebral palsy: a summary of evidence

Marissa Barlaan Lukban · Raymond L. Rosales · Dirk Dressler

Received: 14 September 2008 / Accepted: 11 December 2008 / Published online: 14 January 2009

Abstract Botulinum toxin type A (BoNT-A) therapy has gained wide acceptance in the management of spasticity in cerebral palsy (CP). Clinical experience from numerous case reports and series, retrospective and prospective open label cohort studies, and randomized controlled trials (RCT) has grown over the past 10 years. Several independent systematic reviews on the role of BoNT-A for upper and lower limb spasticity have been written by various authors. The objective of this paper is to summarize past systematic reviews and recent RCT not yet included in the systematic reviews that assess the effectiveness of BoNT-A in upper and lower limb spasticity in children with CP. We reviewed four Class II RCT discussed in five independent systematic reviews and two new Class II trials on the use of BoNT-A alone or with occupational therapy compared to placebo or occupational therapy alone in children with upper limb spasticity. There were 229 children recruited in these six trials and of those, 115 children received BoNT-A in the upper limbs. Five of six RCT showed a time limited decrease in muscle tone most especially at the wrist. Four of six trials showed improvement of hand function on a few specific functional tests. Four systematic reviews concluded that there is insufficient and inconsistent evidence to support or refute the effectiveness of BoNT-A in upper limb spasticity but one recent review recommended that BoNT-A should be considered as a treatment option in upper limb spasticity. For lower limb spasticity, we reviewed 13 RCT discussed in six systematic reviews and two new trials comparing BoNT-A with placebo or other rehabilitation modalities such as physiotherapy, occupational therapy, casting or electrical stimulation. In these studies, 617 children were recruited and of those, 360 children received BoNT-A in the lower limbs. There were six Class I and nine Class II trials. Three Class I trials documented significant improvement in gait pattern in children with gastrocnemius spasticity and one Class I study showed significant reduction in tone in the hip adductors. The most recent review establishes BoNT-A as an effective treatment for equinovarus deformity. Adverse events in these trials were mild and self-limited. The most common complaints were pain in the injection sites and transient weakness. BoNT-A is considered safe for use in children. In conclusion, there is now growing convincing evidence for the time limited beneficial effect of BoNT-A in decreasing muscle tone in children with upper and lower limbs spasticity associated with CP. Decrease muscle tone in the lower limbs translates to improved gait in CP children with spastic equinovarus however more systematic studies are necessary to show sufficient evidence for improved hand function from BoNT-A injection in the upper limbs.

Keywords Botulinum toxin · Spasticity · Cerebral palsy · Review

M. B. Lukban (✉)
Departments of Pediatrics and Neurosciences,
University of the Philippines College of Medicine,
Manila, Philippines
e-mail: mblukban@yahoo.com

R. L. Rosales
Department of Neurology and Psychiatry,
Santo Tomas University Hospital, Manila, Philippines

D. Dressler
Department of Neurology, Hannover Medical School,
Hannover, Germany

Introduction

Cerebral palsy (CP) is a static encephalopathy characterized by aberrant control of movement or posture

appearing early in life secondary to a central nervous system lesion, damage or dysfunction and not as a result of a progressive or degenerative brain disease (Russman et al. 1997). CP is due to a variety of conditions that may occur during the prenatal, perinatal and postnatal life of the newborn infant. The hallmarks of the damage to the developing brain's motor system include increased or decreased muscle tone, spasticity, muscle weakness, involuntary movements and loss of control of muscle coordination (Goldstein 2004). Impairment in movement and tone and other associated central nervous system dysfunction may lead to motor, verbal, visual, hearing and learning disabilities.

The management of CP, therefore, involves two issues: the treatment of injured brain areas that control muscle coordination and movement and the management of impaired muscle coordination and its resulting disabilities (Goldstein 2004). Depending on the injury mechanism, the manifestations may vary, with spasticity as the most common symptom. Pharmacologic treatment with antispasmodics and nonpharmacologic modalities such as physiotherapy (PT) and occupational therapy (OT) have been mainstays in spasticity management. In 1988, the first clinical trials using botulinum neurotoxin (BoNT) for spasticity in children with CP were started by Andrew Koman and co-workers. Results of these trials were first reported in 1993 (Koman et al. 1993).

BoNT is a potent neurotoxin produced by the anaerobic bacterium *Clostridium botulinum* with serotypes A (BoNT-A) and B (BoNT-B) used for therapeutic purposes. BoNT causes chemodenervation and muscle relaxation by disrupting acetylcholine release into the synaptic cleft thus blocking the neuromuscular junction (Pidcock 2004). The different formulations available in the market, BoNT-A as Botox® (100 units/vial, Allergan), Dysport® (500 units/vial, Ipsen), or Xeomin® (100 units, free of complexing proteins/vial, Merz) and BoNT-B as Myobloc® or Neurobloc® (5,000 and 10,000 units/vial, Solstice) are not generically bioequivalent and have different recommended dosing, efficacy and side effects profile.

After its first application in strabismus, BoNT-A was introduced for the treatment of blepharospasm and cervical dystonia. Currently, its use has been extended for other neurologic conditions such as post-stroke spasticity, hemifacial spasms, strabismus and eye movement disorders, urinary bladder dysfunction, exocrine gland hyperactivity, hyperkinetic movement disorders and pain syndromes (Panicker and Muthane 2003). It has gained acceptance as an adjunct therapy for spasticity for children with CP. For the past 10 years, clinical experience from numerous case reports, retrospective and prospective open label cohort studies and randomized controlled trials (RCT) have described the potency of BoNT-A to treat upper and lower limb spasticity in children with CP. Additionally, several independent systematic reviews, meta analysis and consensus statements from various groups have been published. We are unaware of published trials in CP, using Xeomin® for spasticity. The clinical trials with BoNT-B for CP are limited, mostly open label pilot studies and include patients who were secondary non-responders to BoNT-A therapy (Schwerin et al. 2004; Sanger et al. 2007). The regional and systemic anticholinergic adverse side effects of BoNT-B limit its clinical use.

The objective of this review is to summarize the independent systematic reviews and recent (RCT) which are not yet included in the past systematic reviews. We hope to present the evidence on the effectiveness of BoNT-A for reducing upper and lower limb spasticity in children with CP and to show whether these studies reduce muscle tone and translate into an improved functional outcome.

Methods

A literature search using the electronic databases MEDLINE, PUBMED, DARE, BMJ updates, and TRIP database for published articles in English from 1990 to May 2008 was conducted using botulinum toxin, CP, spasticity and treatment as search terms. Systematic reviews and recent RCT that were not included in previous systematic reviews are included in this review. Studies must compare BoNT-A with placebo, other pharmacotherapies, or a combination of BoNT-A with non pharmacological therapies. Only studies in children with CP were included. Only class I and class II studies were retrieved, reviewed and tabulated. Clinical trials on the arm and the legs were separately reviewed. The RCT were graded according to the American Academy of Neurology Classification of Evidence for Therapeutic Articles (Edlund et al. 2004).

In 2005, the Philippine Society of Neurorehabilitation (PSNR) formed a technical review panel composed of pediatric neurologists and rehabilitation specialists whose aim was to appraise all available studies on BoNT-A from 1994 to 2004 to make consensus statements for Filipino practitioners on the use of BoNT-A for children with CP. The members of the technical review panel which was headed by the primary author (M. L.) independently reviewed and graded the class I and class II RCT, which are included in this review. Each trial was appraised independently by two reviewers. Any disagreements were settled by the whole group (Lukban et al. 2006). Recent RCT from 2005 to 2008 and the newly published systematic reviews were appraised and summarized by the primary author, then concurred with the coauthors (R. R. and D. D.).

Results

Upper limbs spasticity

There are only six RCT on BoNT-A involving 229 children with upper limb spasticity due to CP (Corry et al. 1997; Fehlings et al. 2000; Speth et al. 2005; Lowe et al. 2006; Wallen et al. 2007; Russo et al. 2007) and all are class II studies (Table 1). BoNT-A injections were administered to 115 children. Five independent systematic reviews published from 2004 to 2008 evaluated these studies (Table 2) (Wasiak et al. 2004; Garces et al. 2005; Reeuwijk et al. 2006; Park and Rha 2006; Simpson et al. 2008). The recent trials by Wallen et al. (2007) and Russo et al. (2007) have not been reviewed.

Two groups independently produced systematic reviews on BoNT-A for upper limb spasticity in CP and both appraised the two RCT available at that time. Wasiak et al. (2004) with the Cochrane Movement Disorders Group from Australia (Wasiak et al. 2004) and Garces et al. (2005)with the Canadian Coordinating Office for Health Technology Assessment (Garces et al. 2005) both selected and appraised the studies of Corry et al. (1997) and Fehlings et al. (2000). Corry et al. (1997) performed a randomized double-blind, placebo-controlled trial comparing Botox® (Allergan) and Dysport® (Ipsen) to placebo in 14 children with CP. The trial lasted for 12 weeks and evaluated muscle tone by the Ashworth scale (Ashworth 1964), active range of motion (AROM), patients' and parents' assessment of disability and function by a five scale questionnaire as well as occurrence of adverse events (AE) (Corry et al. 1997). The study by Fehlings et al. (2000) was a randomized, single-blind study comparing Botox® with OT to OT alone. The trial involved 29 patients, lasted for 24 weeks and assessed muscle tone using the modified Ashworth scale (MAS) (Bohannon and Smith 1987), functional outcome using Quality of Upper Extremity Skills Test (QUEST) (DeMatteo et al. 1992) and Pediatric Evaluation Disability Inventory (PEDI) (Haley et al. 1992) as well as AE (Fehlings et al. 2000).

Corry et al. (1997) reported a significant improvement in elbow muscle tone at 2 weeks but not at 12 weeks after BoNT injection and significant improvement of wrist muscle tone 2 and 12 weeks after BoNT injections. Thumb muscle tone was not improved by BoNT. There was also a significantly greater median change in the AROM of the elbow and thumb extension 2 weeks, but not 12 weeks after BoNT injections. Wrist extension, thumb abduction or metacarpophalangeal extension was not improved. However, in a five category scale questionnaire, the patients and their parents reported improvement in function at 2 and 12 weeks after BoNT injection.

Fehlings et al. (2000) showed a decline in spasticity in both the children treated with BoNT-A plus OT and those managed with OT alone. Although the BoNT-A group showed greater reduction in muscle tone (MAS), the overall differences between BoNT-A and the control group were not statistically significant. Despite the lack of significant difference in MAS between the two groups, in the QUEST and PEDI assessments for functional outcomes, those who received BoNT-A significantly performed better compared to occupational therapy alone.

Both studies reported transient excessive weakness but no other AE. Because of the small sample size in these studies and their conflicting results, the use of BoNT-A for upper limb spasticity was initially not recommended as standard care.

More recently, two additional single-blind RCT were published by Speth et al. (2005) and Lowe et al. (2006). Speth et al. (2005) enrolled 20 children with spastic hemiplegia aged 4–16 years. Half of the children were randomly assigned to receive BoNT-A injections after 6 months of PT and OT. Increase in active dorsal flexion and reduced tone in the wrist was observed in the BoNT-A group compared to the control group. However, functional outcomes as measured by the Melbourne assessment of unilateral upper limb function (Johnson et al. 1994; Randall et al. 1999), PEDI, and nine hole peg test (Mathrowitz et al. 1985) were not significantly different between the BoNT-A and control group.

Lowe et al. (2006) enrolled 42 children aged 2–8 years who previously received OT and the intervention group were randomly assigned to receive BoNT-A. Muscle tone was described by the Ashworth scale, functional improvement by QUEST, Canadian Outcome Performance Measure (COPM) (Law et al. 1998), parent and therapist Goal Attainment Scaling (GAS) (Kiresuk et al. 1994) and PEDI. Differences in mean QUEST total scores between treatment and control groups were significant at 1 and 3 months ($p < 0.001$) but not at 6 months ($p = 0.318$). A significantly larger proportion of children in the BT group showed a greater than 20% change above baseline QUEST scores at 1 and 3 months. Although both treatment and control groups showed improvement in functional skills and attainment of treatment goals from baseline scores as measured by COPM, GAS and PEDI, there was greater improvement seen in the BoNT-A group which was statistically significant.

The RCT studies of Corry et al., Fehlings et al. and Speth et al. (class II) and nine other uncontrolled trials (class IV) were reviewed by Reeuwijk et al. (2006). They analyzed the overall effect of BoNT-A on short (less than 12 weeks) and long-term (more than 12 weeks) change in tone, active and passive range of motion (PROM) and upper limb function based on the level of activity. Only the

Table 1 Randomized controlled trials on botulinum toxin use alone or in combination with other treatment modalities for upper limb spasticity in cerebral palsy

Author (year)	Study design	Intervention studied	Number of patients Tx:Control (Age)	AAN class of evidence	Outcome measures	Result
Corry et al. (1997)	RCT DB PC	BoNT-A vs. Placebo	14 7:7 (4–19 years)	II	Ashworth AROM Questionnaire	Significant decrease in muscle tone and active range of motion at the elbow with BoNT-A compared to placebo at 2 weeks but not at 12 weeks after injection
Fehlings et al. (2000)	RCT Single blind	BoNT-A with OT vs. OT alone	30 15:15 (2.5–10 years)	II	MAS PEDI QUEST	No significant difference in reduction of muscle tone in both groups, but significant difference in functional outcome with BoNT-A plus OT
Speth et al. (2005)	RCT Single blind	BoNT-A with PT/OT vs. PT/OT alone	20 10:10 (4–16 years)	II	Ashworth Melbourne. PEDI Nine hole peg test	Significant increase in AROM and decrease in muscle tone at the wrist with BoNT-A, but no significant difference in functional outcome
Lowe et al. (2006)	RCT Single blind	BoNT-A low dose/high concentration vs. OT alone	42 21:21 (2–8 years)	II	Ashworth QUEST COPM GAS PEDI	BoNT-A group had significantly greater improvement in tone and function compared to placebo at 1, 3, 6 months except for QUEST scores at 6 months
Wallen et al. (2007)	RCT Single blind	BoNT-A with OT vs. BoNT-A alone vs. OT alone vs. no treatment	80 20:21:20:19 41 patients received BoNT-A (2–14 years)	II	COPM GAS QUEST PEDI Melbourne ass. AROM PROM CHQ	BoNT-A plus OT showed significant short-term decrease in tone and improved hand function (but in only two functional tests) compared with BoNT-A alone, OT alone or no treatment
Russo et al. (2007)	RCT Single blind	BoNT-A with OT vs. OT alone	43 21:22 (3–16 years)	II	MAS Tardieu Scale GAS PEDI PedsQL AMPS	BoNT-A plus OT had significantly decreased tone and improved hand function at 3 months compared with OT alone

RCT randomized controlled trials, *DB* double blind, *PC* placebo controlled, *BoNT-A* botulinum toxin type A, *Tx:Control* number of patients in intervention group vs. control group, *OT* occupational therapy, *PT* physiotherapy, *AAN* American Academy of Neurology, *MAS* modified Ashworth Score, *PEDI* Pediatric Evaluation Disability Inventory, *QUEST* Quality of Upper Extremity Skills Test, *Melbourne* Melbourne assessment of unilateral upper limb function, *COPM* Canadian Outcome Performance Measure, *GAS* Goal Attainment Scale, *CHQ* Child Health Questionnaire, *PedsQL* Pediatric Quality of Life Inventory, *AMPS* Assessment of Motor and Process Skills

Table 2 Systematic reviews on botulinum toxin use alone or in combination with other modalities for upper limb spasticity in cerebral palsy

Author (year)	Study design	Included trials	AAN class of evidence	Conclusion AAN level of recommendation
Wasiak et al. (2004)	Systematic review	2 RCT (Corry et al. 1997; Fehlings et al. 2000)	Class II	Data inadequate treatment unproven (U)
Garces et al. (2005)	Systematic review	2 RCT (Corry et al. 1997; Fehlings et al. 2000)	Class II	Data inadequate treatment unproven (U)
Reeuwijk et al. (2006)	Systematic review	3 RCT (Corry et al. 1997; Fehlings et al. 2000; Speth et al. 2005) 9 uncontrolled studies	Class II Class III Class IV	Data inadequate Insufficient evidence for short or long-term effects in decreasing tone, range of motion and improved function (U)
Park and Rha (2006)	Systematic review	4 RCT (Corry et al. 1997; Fehlings et al. 2000; Speth et al. 2005; Lowe et al. 2006) 8 case series 4 case reports	Class II Class III Class IV	Data inadequate treatment possibly effective in improving muscle tone, but unproven in improving function (U)
Simpson et al. (2008)	Systematic review	3 RCT (Corry et al. 1997; Fehlings et al. 2000; Speth et al. 2005)	Class II	BoNT-A should be considered as a treatment option (B)

RCT randomized controlled trials, *BoNT-A* botulinum toxin type A, *AAN* American Academy of Neurology, *U* unproven, *B* treatment probably useful/effective

small RCT study of Corry and four of seven uncontrolled studies showed short-term significant difference in tone in the BoNT-A group. For long-term reduction of spasticity, none of the RCT and only one out of five uncontrolled studies reported significant difference in measurements of tone compared with the baseline values. Short-term increase in AROM was observed by both Corry and Speth but none in five uncontrolled trials. The improvement in AROM extended until 9 months in the trial by Speth. No trial showed significant change in short-term PROM. No trial consistently showed improvement in most functional measures. They concluded that for the time being, the evidence is still neither sufficient nor consistent to support or refute the clinical use of BoNT-A in upper limb spasticity in children with CP.

Park and Rha (2006) reviewed the three previous RCT of Corry, Fehlings and Speth and added the RCT of Lowe (class II), eight uncontrolled case series and four case reports (class III, IV). Different assessment tools were used in the four RCT trials thus a pooled risk difference between groups was not possible. This group also arrived at the same conclusion: that the use of BoNT-A for upper limb spasticity is still inconclusive.

Recently, Wallen et al. (2007) extended his case series and prospectively and randomly assigned 80 children with spastic quadriplegia, triplegia and hemiplegia into four groups: BoNT-A plus OT, BoNT-A alone, OT alone and no treatment (class II). The objective was to assess whether BoNT-A with OT improves spasticity and function compared to BoNT-A alone, OT alone or neither treatment. By concealed allocation, each group randomly enrolled 17–20 patients in each group. In those children treated with BoNT-A plus OT, muscle tone (MAS) was significantly reduced 2 weeks after BoNT-A injection compared to the three other groups. Six months after BoNT-A injection, the tone had returned to baseline evaluation. However, despite the time limited improvement in muscle tone, primary functional outcomes measured by COPM and GAS showed that with the combination of BoNT-A and OT the children reached their functional goals earlier. Secondary outcome assessment tools such as the Melbourne Assessment of Unilateral Upper Limb Function, QUEST, PEDI, and Child Health Questionnaire (Waters et al. 1999) did not show differences between both groups. The active and PROM was not different as well (Wallen et al. 2007).

To further emphasize functional measurements and quality of life, Russo et al. (2007) in a single-blind RCT, studied 43 hemiplegic children aged 3–16 years comparing BoNT-A plus OT with OT alone. Outcome measures included domains on body structure by the MAS and

Tardieu Scale (Tardieu et al. 1954) and activities participation domains using the Assessment of Motor and Process Skills (Fisher 2003), GAS, PEDI, and Pediatric Quality of Life Inventory (Varni et al. 2001). Self-perception was also measured 3 months after BT injections. Children who received BoNT-A and OT performed significantly better in terms of body structure and activities participation compared to the children who received OT alone. The authors reported improvements in self-perception for the global self-worth domain. Six months after BoNT-A injection the differences between the intervention and the control groups persisted for the measures of body structure, but not for activities participation or self-perception (Russo et al. 2007).

Only the studies of Corry, Fehlings and Speth were included in the review by Simpson et al. (2008)with the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Based on these three class II studies, they recommended that BoNT-A injection should be considered as a treatment option in children with upper limb spasticity in children with CP.

Thus, based on the systematic reviews of earlier studies and the two recent single-blind RCT studies of Russo et al. (2007) and Wallen et al. (2007) five of six class II RCT show that there is a greater decrease in tone among children who received BoNT-A therapy compared to placebo or OT alone. In addition, in four of six RCT, a reduction in spasticity led to a time limited improvement in hand function.

Lower limbs spasticity

There are 15 RCT on BoNT-A involving 617 children with lower limb spasticity due to CP (Koman et al. 1994; Corry et al. 1998; Flett et al. 1999; Sutherland et al. 1999; Ubhi et al. 2000; Koman et al. 2000; Baker et al. 2002; Love et al. 2001; Boyd et al. 2001; Bjornson et al. 2007; Scholtes et al. 2007; Detrembleur et al. 2002; Bottos et al. 2003; Ackman et al. 2005; Mall et al. 2006), eight of which are class I trials (Table 3). Two of these studies are recent and have not been reviewed. Six independent systematic reviews were published from 2000 to 2008 to evaluate these studies (Garces et al. 2005; Simpson et al. 2008; Ade-Hall and Moore 2000; Boyd and Hays 2001) (Table 4). BoNT-A was administered to 360 children.

Ade-Hall and Moore (2000) were the first to summarize RCT on BoNT-A for lower limb spasticity in a systematic review. They combined three RCT from the groups of Koman et al. (1994), Corry et al. (1998) and Flett et al. (1999). Koman et al. (1994) compared BoNT-A with injection of a placebo in 12 ambulatory children with spastic diplegia and found statistically non-significant improvements in gait in the BoNT-A group. Corry et al. (1998) and Flett et al. (1999) compared BoNT-A with the use of casts. Each included 20 children and found that compared to baseline scores, there were improvements in gait, range of ankle movement and muscle tone in both the BoNT-A and the cast groups. However, there were no statistically significant differences between the two groups in either trial.

Flett et al. (1999) also assessed motor function using the gross motor function measure (GMFM) (Russell et al. 1989) and found statistically significant improvements in each group compared to baseline but no statistically significant differences between the groups. Corry et al. (1998) performed 3D gait analysis on those children able to co-operate. Maximal plantar flexion and maximal dorsiflexion during walking were both found to be significantly greater in the BoNT-A group compared to the cast group. In all other dimensions there were no statistically significant differences between both groups.

Increased availability of published studies allowed Boyd et al. (2001) to include 10 RCT with a total of 407 patients and seven prospective non-randomized studies with a total of 193 patients in her systematic review. The RCT trials were considered of moderate to high methodological quality. Nine of 10 trials had concealed allocation. Because the selected studies were designed differently and had varying outcome measures, the investigators were unable to pool the results of all or most of the studies together. Nevertheless, four trials comparing BoNT-A with placebo showed a pooled risk difference of 0.25 (95% CI 0.13, 0.37) using the Physicians Rating Scale (PRS) (Maathuis et al. 2005). Two trials (Corry et al. 1998; Flett et al. 1999) comparing BoNT-A with casting yielded a pooled risk difference of 0.23 (95% CI 0.06, 0.53) in the PRS. Thus these early studies concluded that moderate dose-dependent treatment effects of botulinum toxin in the lower extremities can be assumed (Boyd and Hays 2001).

The Canadian group led by (Garces et al. 2005) also evaluated BoNT-A for lower limb spasticity in CP children and included 13 RCT in their review. We did not retrieve and review two clinical abstracts, one crossover trial and one trial on hip adductor spasticity which was designed to study the effect of BoNT-A on pain. These studies were assessed as poor quality studies with unclear concealments. Of the remaining studies reviewed, five trials were randomized, double-blind and placebo controlled (Koman et al. 1994; Sutherland et al. 1999; Ubhi et al. 2000; Koman et al. 2000; Baker et al. 2002). Two trials compared BoNT-A with serial casting (Corry et al. 1998; Flett et al. 1999) and two trials compared BoNT-A with physiotherapy (Love et al. 2001; Boyd et al. 2001). Outcome measures were not similar in all studies: two reported on muscle tone, six assessed PROM, three reported on AROM, five studied motion and gait analysis, seven used caregivers'

Table 3 Randomized controlled trials (Class I and Class II) on botulinum use alone or in combination with other treatment modalities for lower limb spasticitiy in cerebral palsy

Author (year)	Study design	Intervention studied	Number of patients Tx:Control (age)	AAN level of evidence	Outcome measures	Result
Koman et al. (1994)	RCT DB PC	BoNT-A vs. placebo	12 6:6	II	PRS dynamometry physiotherapy eval. parent/guardian ass.	Uncertain significant difference in improved gait function between groups
Corry et al. (1998)	RCT Single blind	BoNT-A vs. fixed cast stretching	20 10:10	II	PRS Ashworth PROM Gait analysis	Significant difference in improved gait function, range of motion and tone from baseline in both groups but no significant difference between groups
Flett et al. (1999)	RCT Single blind	BoNT-A vs. fixed cast stretching	20 10:10 (2–8 years)	II	PRS MAS GMFM Goniometry	No significant difference in tone, range of motion and gait
Sutherland et al. (1999)	RCT DB PC	BoNT-A vs. placebo	20 10:10 (2–16 years)	I	PROM Gait analysis	Significant difference in improved range of motion and gait favoring BoNT-A
Ubhi et al. (2000)	RCT DB PC	BoNT-A vs. placebo	40 22:18 (2–16 years)	I	Gait analysis GMFM PCI Goniometry	No significant difference in PROM but significant difference in improved gait favoring BoNT-A
Koman et al. (2000)	RCT DB PC	BoNT-A vs. placebo	114 56:58 (2–16 years)	I	Gait analysis PRS goniometry NCV	Significant difference in AROM and improved gait favoring BoNT-A No significant difference in PROM
Baker et al. (2002)	RCT DB PC	BoNT-A dose ranging vs. placebo	126 95/31 (2–9 years)	I	Goniometry GMFM	Significant difference in PROM at 4 weeks only, no significant difference in GMFM at week 4 and 16 Best dose with 20 MU/kg
Love et al. (2001)	RCT matched pair	BoNT-A vs. placebo	24 12:12 (3–13 years)	II	GMFM MAS	Significant difference in tone and gross motor function favoring BoNT-A
Boyd et al. (2001)	RCT Single blind	BoNT-A with hip abduction brace vs. current practice	39 19:20 (1–4 years)	II	MAS GMFN	No significant difference in gross motor function

Table 3 continued

Author (year)	Study design	Intervention studied	Number of patients Tx:Control (age)	AAN level of evidence	Outcome measures	Result
Bjornson et al. (2007)	RCT DB PC	BoNT-A vs. placebo	33 17:16 (3–12 years)	I	GMFM Ashworth EMG COPM GAS	Significant improvement in tone, range of motion and gross motor function favoring BoNT-A
Scholtes et al. (2007)	RCT Single blind	BoNT-A with comprehensive rehab (PT, orthoses, casting) vs. usual care	47 23:24 (4–11 years)	II	Goniometry Muscle length Gait analysis	Significant difference in tone, muscle length and improved gait in favor of BoNT-A with comprehensive rehab
Detrembleur et al. (2002)	RCT Single blind	TES post BoNT-A vs. BoNT-A alone	12 6:6 all patients received BoNT-A (4.75–6 years)	II	Gait analysis goniometry PRS MAS	BoNT-A with TES is not superior to BoNT-A alone
Bottos et al. (2003)	RCT Single blind	Casting post BoNT-A vs. BoNT-A alone	10 5:5 all patients received BoNT-A (4–11 years)	II	Ashworth Range of motion GMFM Gait analysis	Casting post BoNT-A is superior to BoNT-A alone in decreasing tone and improving gait
Ackman et al. (2005)	RCT Single blind	BoNT-A with casting vs. casting and placebo vs. BoNT-A alone	39 12:14:13 25 patients received BoNT-A (4–14 years)	II	Ashworth GMFM	Casting post BoNT-A is superior to casting and placebo in decreasing tone and improving gait. BoNT-A alone did not improve outcome measures
Mall et al. (2006)	RCT DB PC	BoNT-A vs. placebo (adductors)	61 33:28 (2–10 years)	I	Knee–knee distance Ashworth GAS	Significant difference in improvement in all outcome measures favoring BoNT-A

RCT randomized controlled trial, *DB* double blind, *PC* placebo controlled, *BoNT-A* botulinum toxin type A, *Tx:Control* number of patients in intervention group vs. control group, *AAN* American Academy of Neurology, *TES* short-term electrical stimulation, *GMFM* gross motor function measure, *PCI* physiological cost index, *PRS* physician rating scale, *MAS* modified Ashworth score, *EMG* electromyogram, *COPM* Canadian outcome performance measure, *GAS* Goal Attainment Scale

Table 4 Systematic reviews on botulinum toxin use alone or in combination with other treatment modalities for lower limb spasticity in cerebral palsy

Author (year)	Study design	Included trials	AAN level of evidence	Conclusion AAN level of recommendation
Ade-Hall and Moore (2000)	Systematic review	3 RCT	II	Weak evidence favoring treatment however, statistically insignificant (B)
Boyd and Hays (2001)	Systematic review Meta-analysis	10 RCT 7 prospective cohort	I, II, III	Significant improvement favoring BoNT-A (B)
Garces et al. (2005)	Systematic review	13 RCT	I, II, III	Significant improvement favoring BoNT-A (B)
Cardoso et al. (2006)	Systematic review Meta-analysis	6 Class I RCT	I, II	Significant improvement favoring BoNT-A (A)
Lannin et al. (2006)	Systematic review (compares addition of other therapies post BT-A)	9 RCT	II, III	Inconsistent benefit of combination therapies vs. BoNT-A alone (U)
Simpson et al. (2008)	Systematic review	14 RCT (4 Class I for gastrocnemius spasticity) (2 class I for adductor spasticity and pain)	I, II	BoNT-A is an effective treatment for equivarus deformity (A), BoNT-A should be considered for adductor spasticity (B)

RCT randomized controlled trials, *BT-A* botulinum toxin A, *AAN* American Academy of Neurology, *U* unproven, *B* treatment probably useful/effective, *A* treatment effective

and physicians' assessment of function and disability, two reported on pain and five noted AE.

BoNT-A treatment resulted in decreased muscle tone across most trials. Compared to baseline values, increased range of motion and improved gait are shown in many studies but statistical significant difference between the treatment and control group is not always reached (Garces et al. 2005). Parents and caregivers however rate greater satisfaction in those treated with BoNT-A. Pain in the injection site and transient weakness were the AE most commonly reported. However, none of the AE led to the withdrawal of patients from the study. Pooled data on three trials on AE showed a risk difference of 0.16 (95% CI 0.07, 0.25) suggesting a significant difference in the treatment group (Ubhi et al. 2000; Koman et al. 2000; Baker et al. 2002).

Cardoso et al. (2006) limited his review to class I studies that evaluate functional outcome using PRS and video gait analysis for children with equinovarus. His meta-analysis of double-blind RCT with placebo control included six studies with a total of 335 patients (Koman et al. 1994; Sutherland et al. 1999; Ubhi et al. 2000; Koman et al. 2000; Baker et al. 2002; Love et al. 2001). Four studies with a total of 183 patients were pooled together to assess gait improvement using the Physician Rating Scale and video gait analysis (Koman et al. 1994; Sutherland et al. 1999; Ubhi et al. 2000; Koman et al. 2000). His analyses showed statistically significant gait improvement in CP children with spastic equinus foot (Peto odds ratio 3.49, 95% CI 2.20–7.22) (Cardoso et al. 2006). In subjective assessment of disability and function using questionnaires administered to 136 parents or guardians, two studies reported significant improvement in the BoNT-A group (Peto odds ratio 3.99, 95% CI 1.50–8.12) (Koman et al. 1994; Baker et al. 2002) AE were reported in four studies with a total of 332 patients. AE which were mild and self-limited were significantly higher with BoNT-A (Peto odds ratio 2.62, 95% CI 1.47–4.67) (Koman et al. 1994; Sutherland et al. 1999; Ubhi et al. 2000; Koman et al. 2000; Baker et al. 2002).

In the American Academy of Neurology (AAN), Simpson et al. (2008) reviewed four class I double-blind, placebo-controlled RCT which were also reviewed by Cardoso et al., but the group excluded the small trial of 12 children by Koman et al. (2000) and the trial of Love et al. which had unclear concealment (Sutherland et al. 1999; Ubhi et al. 2000; Baker et al. 2002). The video gait analysis, which is a clinically relevant outcome measure was reported in two studies and showed statistically significant difference between the treatment and placebo group (Ubhi et al. 2000; Koman et al. 2000) In summary, these two Class I studies establishes that BoNT-A is an effective treatment in the management of spastic equinus in children with CP.

The most recent studies which were not yet reviewed in the systematic reviews from Bjornson (Bjornson et al. 2007) and Scholtes (Scholtes et al. 2007). Bjornson et al. (2007) attempted to evaluate the effect of BoNT-A injections in 33 children in five domains of medical rehabilitation: pathophysiology, impairment, functional

limitation, disability and societal or contextual factors. The study is a randomized, double-blind, placebo-controlled trial comparing BoNT-A with saline injections into the gastrocnemius of children with spastic diplegia. They showed a significant improvement in tone, range of motion and some functional outcome measures (GMFM) but no significant difference between the two groups in satisfaction with performance goals (COPM, GAS), energy expenditure, Ashworth and AE.

The study by Scholtes et al. (2007) is a randomized single-blind trial on the effect of BoNT-A and comprehensive rehabilitation vs. usual care in 46 children with spastic CP who walk on flexed knees. Multilevel injections and comprehensive rehabilitation (intensive physiotherapy, orthoses and/or serial casting) which were given to the treatment group demonstrated significant improvements in knee extension during gait, increased muscle length and decreased spasticity compared to control.

The American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) systematic reviews provide biomedical researchers and clinical practitioners with current analyses of various interventions for the management of developmental disabilities. In 2006, Lannin et al. (2006) specifically reviewed published articles on children and adolescents with CP who had received BoNT-A injections in either upper or lower limbs in combination with other therapies such as physiotherapy, electrical stimulation and serial casting. Aside from the effect of BoNT-A, they wanted to study the additional benefits of other non medical interventions on the outcome of children who had prior BoNT-A therapy. Eight trials on lower limb spasticity were identified. One was a retrospective chart review and four were case series. Two class III cohort studies with a concurrent control group studied the effect of serial casting after BoNT-A. One small RCT studied the effect of electrical stimulation post BONT-A. This single RCT by (Detrembleur et al. 2002) enrolled 12 CP children and showed that electrical stimulation for 30 min, six times a day for 3 days after lower limb BoNT-A had no significant effect on gait parameters.

The before and after BoNT-A study of Boyd et al. (2000) compared the 3D gait analysis of 15 diplegic and 10 hemiplegic children. Subanalysis of the cohort of 10 children who underwent post BoNT-A casting 3 weeks after injection revealed that all children were reported to show improvement in ankle kinematics from baseline to 12 and 24 weeks, irregardless of whether they received post BoNT-A casting or not. There was an additional improvement of PROM in the subgroup of children who received casting post BoNT-A. The cohort study of Desloovere et al. (2001) randomly assigned children to be put on serial stretching casts either before or immediately after BoNT-A. None of the studies showed a significant benefit to the addition of casting post BoNT injection.

The recent small RCT by Bottos et al. (2003) and Ackman et al. (2005) have not been included in the systematic review by Lannin et al. Ten children who were injected with BoNT-A were randomly assigned by Bottos and coworkers to either the treatment group who immediately were placed on a 3-week period of casting or the control group who were fitted with ankle-foot orthosis and physiotherapy after the injections. Both groups showed reduction of spasticity on Ashworth scale, improved gross motor activities on GMFM and increased walking speed from baseline values. In addition, there was statistically significant difference in the outcome measures between the two groups, with greater improvement seen in those who had post BoNT casting which was maximally observed at 4 months post injections (Bottos et al. 2003).

Ackman et al. (2005) randomly assigned children into three groups: BoNT-A alone, placebo and casting, or BoNT-A plus casting. Outcome measures include gait analysis, change in tone using Ashworth and Tardieu scales and ranges of motion. Contrary to previous studies, he did not show any improvement in any of the outcome measures among those treated with BoNT-A alone. There were improvements in the outcome measures among those who received casting and placebo but the greatest improvement was seen in those who received both BoNT-A and casting.

Based on these single blinded studies, Simpson et al. (2008) concluded that there is still insufficient and consistent evidence to support or refute the benefit of additional casting to BoNT injection.

Lastly, there is a recent single class I study by Mall et al. (2006) that evaluated the effect of BoNT-A injection into the adductors and medial hamstrings which showed significant improvement in knee-to-knee distance of about 9 cm ($p < 0.002$) and decrease in adductor spasticity on MAS ($p < 0.001$). This was included in the review by Simpson and they concluded that based on this single class I study, botulinum toxin injection is probably effective in improving adductor spasticity and range of motion (Simpson et al. 2008).

AE in the upper and lower limb studies

Parallel to that of upper and lower limb post-stroke spasticity (Rosales 2008), most of the trials considered BoNT-A to be safe for use in children. The AE reported were mild to moderate, self-limited, and were not sufficient to cause withdrawals from the studies. The most common complaints were pain in the injection sites as well as transient local weakness.

In the upper limb trials, Corry et al. (1997) and Fehlings et al. (2000) reported upper limb weakness resulting in

temporary decrease in grip strength and worsening in performance of certain functional tests. Wallen and co-workers (2007) report transient soreness at the wrist, nausea and vomiting, flu-like symptoms, and fever. No child or family reported excessive weakness, however; Lowe et al. (2006) showed no significant difference in the AE between groups. The most severe AE was reported by Russo in two patients with previous history of epileptic attacks who had prolonged seizures, one coming from the intervention group and the other patient from the control group. Five children in his intervention group also had excessive weakness (Russo et al. 2007).

In the lower limb trials, other AE include increased frequency of falls, dysphagia, and incontinence (Sutherland et al. 1999; Ubhi et al. 2000; Koman et al. 2000; Baker et al. 2002). One child in the study by Sholtes et al. (2007) had increased micturition and fecal soiling for 1 month. The meta-analysis of Cardoso et al. 2006) which pooled the AE of four trials reported 69 AE in the BoNT group compared to 17 AE in the placebo group giving a Peto odds ratio of 2.63 (Koman et al. 1994; Ubhi et al. 2000; Koman et al. 2000; Baker et al. 2002.

Discussion

Although the United States Food and Drug Administration have approved BoNT-A in the management of strabismus, blepharospasm, hemifacial spasms and cervical dystonia, its use for spasticity in children with CP remains off label. However, since botulinum toxin therapy for CP children was introduced in 1999 there is growing evidence that for a limited period of time, it can decrease muscle tone and improve range in joints served by injected muscles. Various independent systematic reviews further supported these findings thus reinforcing the conclusions of different groups and strengthening recommendations to consider botulinum toxin therapy as one of the most important therapeutic options to treat CP children with spasticity, both in the upper and lower limbs.

The clamor to establish that a decreased muscle tone and an improved joint range of motion leads to improvements of function, patient satisfaction and quality of life has been emphasized in all the systematic reviews that has been done so far. The recent RCT completed last year for both upper and lower limb spasticity addressed this issue. There is now clinical evidence establishing the role of botulinum toxin to improve function in the upper and lower limb. Further trials will most likely address functionality in more detail with the establishment of a combination of validated instruments with respect to the dimensions of the international classification of functioning, disability and health (Rosenbaum and Stewart 2004). This is echoed by the 2006 European consensus table panelists who outlined in detail the best practice and current understanding regarding botulinum toxin treatment options in children with CP (Heinen et al. 2006).

Most of the previous trials cover short observation periods ranging from 6 to 24 weeks only. They are, therefore, insufficient to capture long-term effects of repeated botulinum toxin injection such as the prevention of contractures and secondary pain. Attempts to document the ability of early intervention with botulinum toxin to decrease or delay the need for orthopedic surgery have been started thru the retrospective evaluation of the experience with BoNT-A for the past 10 years (Hagglund et al. 2005; Ruiz et al. 2004). Early interventions may be especially important in a growing organism. This trend of early intervention with BoNT-A in the management of spasticity has also been alluded to in post-stroke intervention (Rosales 2008). What may spell the difference between spasticity states would be the growing nature of the muscles in a child and the unitary concept of separating chronicity (and hence even contracture) from those, where so much of neuroplasticity factors (and hence disease modification) may still play roles at early stages.

Since botulinum toxin injection has been part of standard treatment on some medical units, a prospective study will later best answer how BoNT-A will affect the future need for surgery and its associated outcomes including the cost effectiveness of botulinum toxin injection in the comprehensive management of CP (Ruiz et al. 2004).

Future consensus statements on botulinum toxin and CP should include injection schemes, i.e., target muscle selection for best responders, BoNT-A dosages, use of anesthesia during injections and use of electromyography/ultrasound for injection guidance. Target muscle selection and dosaging may be influenced by numerous considerations including (1) the specific aim of the injection (e.g., complementary to rehabilitation care and orthopedic care, hygienic considerations, prevention of fixed contracture, cosmesis, etc.); (2) the degree of muscle hyperactivity and (3) maturity of muscle fascial planes influencing diffusion (Rosales and Dressler 2006). The factors of muscle hyperactivity and diffusion along fascial planes may impact on certain AE that occur following BoNT-A injection in CP. Thus, one should exercise extreme caution in injecting BoNT-A in the very young and sick children who are malnourished with atrophic muscles.

Conclusion and recommendation

This review which summarized the class I and class II trials involving 115 children with upper limb spasticity and 360 children with lower limb spasticity shows the growing

evidence that BoNT-A is effective in reducing spasticity and provides a time limited improvement in function in the upper and lower limbs for children with CP. The management of CP is multidisciplinary as the central nervous system dysfunction in CP leads to various disabilities. BoNT-A is a major breakthrough in the treatment of spasticity. Combined with surgical and nonpharmacological interventions by an interdisciplinary team is the best treatment approach for children with CP. The goals of BoNT-A therapy in CP spasticity go beyond decrease in muscle tone leading towards pain relief, prevention of contractures, psychosocial integration and—finally—functional improvement. Future discussion should focus on optimized injection schemes. Pharmacoeconomic issues will eventually also have to be addressed.

Acknowledgments We thank the members of the technical panel of the Philippine Society of Neurorehabilitation who appraised the early studies on BoNT-A: Dr. Myrna S. Fojas, Dr. Ermenilda L. Avendano, Dr. Fe A. de los Reyes and Dr. Sharon D. Ignacio.

Conflict of interest statement None.

References

Ackman JD, Russman BS, Thomas SS et al (2005) Comparing botulinum toxin A with casting for treatment of dynamic equinus in children with cerebral palsy. Dev Med Child Neurol 47:620–627

Ade-Hall RA, Moore AP (2000) Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. The Cochrane Database of Systematic Reviews. The Cochrane Library

Ashworth B (1964) Preliminary trial of carisoprodol in multiple sclerosis. Practitioner 192:540–542

Baker R, Jasinski M, Maciag-Tymecka I, Michalowska-Mrozek J, Bonikowski M, Carr L et al (2002) Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose ranging study. Dev Med Child Neurol 44:666–675

Bjornson K, Hays R, Graubert C et al (2007) Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. Pediatrics 120:49–58

Bohannon RW, Smith MB (1987) Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 67:206–207

Bottos M, Benedetti MG, Salucci P (2003) Botulinum toxin with and without casting in ambulant children with spastic diplegia: a clinical and functional assessment. Dev Med Child Neurol 45:758–762

Boyd RN, Hays RM (2001) Current evidence for the use of botulinum toxin type A in the management of children with cerebral palsy: a systematic review. Eur J Neurol 8(Suppl 5):1–20

Boyd RN, Pliatsios V, Starr R, Wolfe R, Graham HK (2000) Biomechanical transformation of the gastroc-soleus muscle with botulinum toxin A in children with cerebral palsy. Dev Med Child Neurol 42:32–41

Boyd RN, Dobson F, Parrott J, Love S, Oates J, Larson A et al (2001) The effect of botulinum toxin type A and a variable hip abduction orthosis on gross motor function: a randomized controlled trial. Eur J Neurol 8(Suppl 5):109–119

Cardoso ES, Rodriguez MD, Barroso M et al (2006) Botulinum toxin type A for the treatment of spastic equines foot in cerebral palsy. Pediatr Neurol 34:106–109

Corry IS, Cosgrove AP, Walsh EG, McClean D, Graham HK (1997) Botulinum toxin A in the hemiplegic upper limb: a double blind trial. Dev Med Child Neurol 39:185–193

Corry IS, Cosgrove AP, Duffy CM (1998) Botulinum toxin A compared with stretching casts in the treatment of spastic equines: a randomized prospective trial. J Pedia Orthop 18:304–311

DeMatteo C, Law M, Russell D, Pollock N, Rosenbaum P, Walter S (1992) QUEST: quality of upper extremity skills test. McMaster University, Neurodevelopmental Clinical Research Unit, Hamilton

Desloovere K, Molenaers G, Jonkers I, De Cat J, De Borre L, Nijs J, Eyssen M, Pauwels P, De Cock P (2001) A randomized study of combined botulinum toxin type A and casting in the ambulant child with cerebral palsy using objective outcome measures. Eur J Neurol 8(Suppl 5):75–87

Detrembleur C, Lejeune TM, Renders A (2002) Botulinum toxin and short term electrical stimulation in the treatment of equinus in cerebral palsy. Mov Disord 17:162–169

Edlund W, Gronceth G, SoY, Franklin G (2004) American Academy of Neurology Clinical Practice Guideline Process Manual

Fehlings D, Rang M, Glazier J, Steele C (2000) An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. J Pediatr 137:331–337

Fisher AG (2003) AMPS: assessment of motor and process skills volume 1: development, standardization, and administration manual, 5th edn. Three Star Press Inc, Fort Collins

Flett PJ, Stern LM, Waddy H (1999) Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. J Paediat Child Health 35:71–77

Garces K, McCormick A, McGahan L, Skidmore B (2005) Botulinum toxin A for upper and lower limb spasticity: a systematic review. Can Coordin Off Health Technol Assess 51:1–70

Goldstein M (2004) The treatment of cerebral palsy: what we know, what we don't know. J Pediatr 145:S42–S45

Hagglund G, Andersson S, Duppe H, Pedertsen HL, Nordmark E, Westbo L (2005) Prevention of severe contractures might replace multilevel surgery in cerebral palsy: results of a population-based health care programme and new techniques to reduce spasticity. J Pediatr Orthop 14:269–273

Haley SM, Coster SJ, Ludlow LH, Haltiwanger JT, Andrellos PJ (1992) Pediatric evaluation of disability inventory (PEDI): development, standardization, and administration manual. New England Medical Center and PEDI Research Group, Boston

Heinen F, Molenaers G, Fairhurst C, Carr LJ, Desloovere K, Valayer EC, Morel E, Papavassiliou AS, Tedroff K, Pascual-Pascual SI, Bernert G, Berweck S, Di Rosa G, Kolanowski E, Krageloh-Mann I (2006) European consensus table 2006 on botulinum toxin for children with cerebral palsy. Eur J Paediatr Neurol 15:215–225

Johnson LM, Randall MJ, Reddihough DS, Oke LE, Byrt TA, Bach TM (1994) Development of a clinical assessment of quality of movement for unilateral upper-limb function. Dev Med Child Neurol 36:965–973

Kiresuk TJ, Smith A, Cardillo JE (1994) Goal attainment scaling: applications, theory, and measurement. Lawrence Erlbaum Associates, Hillsdale

Koman LA, Mooney JP, Smith BP et al (1993) Management of spasticity in cerebral palsy with botulinum toxin A: preliminary investigation. J Pediatr Orthop 13:489–495

Koman LA, Mooney JF, Smith BP (1994) Management of spasticity in cerebral palsy with Botulinum A toxin: report of a

preliminary, randomized, double blind trial. J Pediatr Orthop 14:299–303

Koman LA, Mooney JF, Smith BP, Walker F, Leon JM, BOTOX Study Group (2000) Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. J Pediatr Orthop 20:108–115

Lannin N, Scheinberg A, Clark K (2006) AACPDM systematic review of the effectiveness of therapy for children with cerebral palsy after botulinum toxin A injections. Dev Med Child Neurol 48:533–539

Law M, Baptiste S, Carswell A, McColl MA, Polatajko H, Pollock N (1998) Canadian occupational performance measure, 2nd edn. Canadian Association of Occupational Therapists, Toronto

Love SC, Valentine JP, Blair EM, Price CJ, Cole JH, Chauvel PJ (2001) The effect of botulinum toxin type A on the functional ability of the child with spastic hemiplegia a randomized controlled trial. Eur J Neurol 8(Suppl 5):50–58

Lowe K, Novak I, Cusick A (2006) Low dose/high concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy. Dev Med Child Neurol 48:170–175

Lukban MB, Fojas MS, Avendano EL, delos Reyes FA, Ignacio SD, Rosales RL (2006) The management of spasticity in children with cerebral palsy: Consensus Statement of the Philippine Society of Neurorehabilitation. Neurorehabil Neural Repair 20:198–199 (abstract)

Maathuis KG, van der Schans CP, van Iperen A, Rietman HS, Geertzen JH (2005) Gait in children with cerebral palsy: observer reliability of Physician Rating Scale and Edinburgh Visual Gait Analysis Interval Testing scale. J Pediatr Orthop 25:268–272

Mall V, Heinen F, Siebel A et al (2006) Treatment of adductor spasticity with BTX-A in children with CP: a randomized, double-blind, placebo-controlled study. Dev Med Child Neurol 48:10–13

Mathrowitz V, Weber K, Kashman N, Volland G (1985) Adult norms for the nine hole peg test of finger dexterity. Occup Ther J Res 5:24–38

Panicker JN, Muthane UB (2003) Botulinum toxins: pharmacology and its current therapeutic evidence for use. Neurology India 51:455–460

Park ES, Rha D (2006) Botulinum toxin type A injection for management of upper limb spasticity in children with cerebral palsy: a literature review. Yonsei Med J 47:589–603

Pidcock FS (2004) The emerging role of the therapeutic botulinum toxin in the treatment of cerebral palsy. J Pediatr 145:S33–S35

Randall MJ, Johnson LM, Reddihough DS (1999) The Melbourne assessment of unilateral upper limb function. Royal Children's Hospital Melbourne, Melbourne

Reeuwijk A, van Schei PEM, Becher JG, Kwakkei G (2006) Effects of botulinum toxin type A on upper limb function in children with cerebral palsy: a systematic review. Clin Rehabil 20:375–387

Rosales RL (2008) Chua-Yap A: evidence-based systematic review on the efficacy and safety of botulinum toxin therapy in post-stroke spasticity. J Neural Transm 115:617–623

Rosales RL, Dressler D, Bigalke H (2006) Pharmacologic differences between botulinum toxins. Eur J Neurol 13:2–10

Rosenbaum P, Stewart D (2004) The World Health Organization International Classification of Functioning, Disability, and Health: a model to guide clinical thinking, practice and research in the field of cerebral palsy. Semin Pediatric Neurol 11:5–10

Ruiz FJ, Guest JF, Lehmann A, Davie AM, Guttler K, Schluter O, Dreiss G (2004) Costs and consequences of botulinum toxin type A use management of children with cerebral palsy in Germany. Eur J Health Econ 5:227–235

Russell DJ, Rosenbaum PL, Cadman DT, Gowland C, Hardy S, Jarvis S (1989) The gross motor function measure: a means to evaluate the effects of physical therapy. Dev Med Child Neurol 31:341–352

Russman BS, Tilton A, Gormley ME (1997) Cerebral palsy: a rational approach to a treatment protocol and the role of botulinum toxin in treatment. Muscle Nerve 20(Suppl 6):S1–S11

Russo RN, Crotty M, Miller MD et al (2007) Upper-limb botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial. Pediatrics 119:1149–1158

Sanger TD, Kukke SN, Sherman-Levine S (2007) Botulinum toxin improves the speed of reaching in children with cerebral palsy and arm dystonia: an open-label, dose escalation pilot study. J Child Neurology 22:116–122

Scholtes VA, Dallmeijer AJ, Knol DL, Speth LA, Maathuis CG, Jongerius PH, Becher JG (2007) Effect of multilevel botulinum toxin A and comprehensive rehabilitation on gait in cerebral palsy. Pediatr Neurol 36:30–39

Schwerin A, Berweck S, Fletzek IM, Helnen F (2004) Botulinum toxin B treatment in children with spastic movement disorders: a pilot study. Pediatr Neurol 31:109–113

Simpson DM, Gracies JM, Graham HK, Miyasaki JM, Naumann M, Russman B, Simpson LL, So Y (2008) Assessment: botulinum neurotoxin for the treatment of spasticity (an evidenced based review). Neurology 70:1691–1698

Speth LA, Leffers P, Janssen-Potten YJ (2005) Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: a randomized trial in children receiving intensive therapy. Dev Med Child Neurol 47:468–473

Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG, Mubarak SJ (1999) Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. Gait Posture 10:1–9

Tardieu G, Shentoub S, Delarue R (1954) A la recherche d'une technique de mesure de la spasticite imprime avec le periodique. Neurologique 91:143–144

Ubhi T, Bhakta BB, Ives HL, Allgar V, Roussounis SH (2000) Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. Arch Dis Child 83:481–487

Varni JW, Seid M, Kurtin PS (2001) PedsQL4.0: reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. Med Care 39:800–812

Wallen M, O'Flaherty SJ, Waugh MC (2007) Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: a randomized controlled trial. Arch Phys Med Rehabil 88:1–10

Wasiak J, Hoare B, Wallen M (2004) Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy. Cochrane Database Syst Rev (4): 1–25 (CD003469)

Waters E, Salmon L, Wake M, Wright M, Hesketh K (1999) Australian authorised adaptation of the child health questionnaire. Centre for Community Child Health, Royal Children's Hospital Melbourne, Melbourne