Analgesic effects of botulinum toxin A: a randomized, placebo-controlled clinical trial

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Postoperative pain in children with spastic cerebral palsy (CP) is often attributed to muscle spasm and is difficult to manage using opiates and benzodiazepines. Adductor-release surgery to treat or prevent hip dislocation in children with spastic CP is frequently performed and is often accompanied by severe postoperative pain and spasm. A double-blinded, randomized, placebo-controlled clinical trial of 16 patients (mean age 4.7 years) with a mainly spastic type of CP (either diplegic or quadriplegic in distribution) was used to test the hypothesis that a significant proportion of postoperative pain is secondary to muscle spasm and, therefore, might be reduced by a preoperative chemodenervation of the target surgical muscle by intramuscular injection of botulinum toxin A (BTX/A). Compared with the placebo, BTX/A was found to be associated with a reduction in mean pain scores of 74% ($P<0.003$), a reduction in mean analgesic requirements of approximately 50% ($P<0.005$), and a reduction in mean length of hospital admission of 33% ($P<0.003$). It was concluded that an important component of postoperative pain in the patient population is due to muscle spasm and this can be managed effectively by preoperative injection with BTX/A. These findings may have implications for the management of pain secondary to muscle spasm in other clinical settings.

Hip displacement is a common deformity experienced by children with spastic cerebral palsy (CP) (Bleck 1987, 1990; Rang 1990). The incidence varies closely with severity of involvement and with ambulatory status. In children with hemiplegia, it is less than 1% but in children with spastic quadriplegia it may rise to 75% (Lonstein and Bleck 1986). Hip displacement is a major cause of morbidity because of pain and fixed deformity (Sharrard et al. 1975; Cooperman et al. 1986; Bleck 1987, 1990; Rang 1990).

The orthopaedic management of hip displacement in spastic CP can be conveniently considered in three stages: (1) early diagnosis and preventive surgery; (2) reconstructive surgery; (3) salvage or palliative surgery (Miller et al. 1995).

It has been stated that efforts should be concentrated on early diagnosis and prevention of hip displacement (Miller et al. 1995, Scrutton and Baird 1997). Preventive surgery consists of lengthening the adductor muscles of the hip sometimes in combination with lengthening the psoas tendon and division of the anterior branch of the obturator nerve (Banks and Green 1960, Reimers 1980, Wheeler and Weinstein 1984).

The reported complications of adductor surgery include infection, heterotopic bone formation, abduction contractures, and recurrent adduction contractures (Miller et al. 1995). However, in our experience, the most important and common complication is excessive postoperative pain and those of associated analgesic use.

In children with CP, it is unlikely that incisional pain alone is responsible for the postoperative course experienced by many, and it is considered that muscle spasms play a major role (Miller et al. 1995, Graham 1997). After surgery or injury, children with normal innervation suppress all movement in a largely unconscious effort to relieve pain (Yates and Smith 1994). This normal, pain-relieving manoeuvre seems to be denied to children with spastic CP (Graham 1997). In such children the stretch reflex is excitable and the threshold below which the reflex will fire appears to be reduced still further by the anxiety and pain which accompanies surgery. We feel that this spasm is further exacerbated by splinting the hips in abduction after adductor release surgery, which is essential for a successful outcome (Houkom 1986).

The management of postoperative pain in children with spastic quadriplegia is a therapeutic dilemma. Regional anaesthetic techniques are effective and indicated in this patient population. In the hands of paediatric anaesthetists, the complication rate associated with these techniques is low. However, their availability is not universal. Analgesic regimens after adductor surgery, therefore, commonly include opiates (for incisional pain), yet the response to standard doses is frequently inadequate, unpredictable, and requires supplementation with benzodiazepenes (for muscle spasm). The combination of these potent analgesics, especially in the child with 'total-body' involvement, poses the risk of excessive sedation, respiratory depression, aspiration, and pulmonary infections. This is an example of the dilemma recognized by Gabrielle Fabricius as early as 1742 when he stated that, 'If soporifics are too weak, they do not help, but if they are too strong, they are dangerous' (Duncan 1947). Inadequate pain control may also undermine confidence in surgical management and lead to a refusal to consider further intervention. There is ample evidence to

suggest that uncontrolled or poorly controlled postoperative pain may also lead to longer hospitalization and to increased complications (Cullen et al. 1985; Cousins 1989, 1994).

For these reasons, we wished to improve the postoperative management of these children and specifically to investigate the possible role for botulinum toxin A (BTX/A) as an adjunctive agent in relieving pain, presumed to be the result of muscle spasms.

Therefore we hypothesized that muscle spasms after adductor release might be controlled by preoperative intramuscular injection of BTX/A and that this may reduce postoperative pain, analgesic requirements, and complications, as well as facilitate an earlier and safer discharge from hospital. We tested this hypothesis in a double-blinded, randomized, placebo-controlled clinical trial.

BTX/A has been used for many years in the management of a wide variety of clinical conditions characterized by focal muscle overactivity. The main applications in CP management are short-term control of muscle overactivity and increasing joint range of motion in an effort to improve functional skills such as walking (Koman et al. 1993, 1994; Cosgrove et al. 1994; Boyd and Graham 1997). The effects of BTX/A in skeletal muscle have been appropriately described as a 'chemodenervation' (Wall et al. 1993). The toxin binds to postsynaptic nerve terminals, blocking release of acetylcholine, interrupting neuromuscular conduction and producing a reversible partial flaccid paralysis (Dolly et al. 1984, 1990). Recovery is by proximal axonal sprouting and muscle reinnervation takes place by the formation of new neuromuscular junctions (Duchen and Strich 1968), and eventually regeneration of the original neuromuscular junction (De Paiva et al. 1999).

Method

PATIENTS

Entry criteria were children with spastic type CP (severe diplegia or quadriplegia), aged 2 to 10 years, who had clinical and radiological evidence of 'hips at risk', and who had been independently scheduled for isolated adductor release surgery by one of two orthopaedic surgeons. All children were attending the multidisciplinary CP service at the Royal Children's Hospital, Melbourne which is a paediatric tertiary care institution.

Hips considered 'at risk of dislocation' were defined as having reduced abduction (less than 40° combined range) with a migration percentage in excess of 40% on one or both hips or an increase in migration percentage of more than 10% in 1 year (Reimers 1980; Cornell 1995, 1997; Scrutton and Baird 1997). Informed written consent was a prerequisite for entry into the trial, which received ethical approval from our institutional review board.

Exclusion criteria were children outside the age range, lack of informed consent, previous hip surgery, medication for spasticity, and injections of BTX/A in the previous year.

Randomization was performed after the date for surgery had been scheduled, informed consent had been given, and the child entered into the trial. A clinician allocated each child to the treatment or control group by opening a sealed envelope containing the instruction 'BTX/A' or 'normal saline'. These envelopes had been prepared in advance in blocks of eight with equal numbers of each instruction in each group (restricted randomization). The trial was double blind by restricting the information 'BTX/A' or 'normal saline' to a single clinician experienced in injecting BTX/A. Children, parents, carers, and other investigators were unaware of the agent drawn by envelope and subsequently administered.

Before the injection, a standardized physical examination was performed by the same physiotherapist with emphasis on the hip range of movement. Spasticity of the hip adductor muscles was also assessed using the modified Ashworth scale (Bohannon and Smith 1986) and modified Tardieu scale (Tardieu et al. 1954, Held and Pierrot-Deseilligny 1969, Boyd et al. 1998a).

INJECTION TECHNIQUE

Five to 10 days before the scheduled date of surgery, the child was examined in the outpatient clinic. Injections of BTX/A or placebo were performed as follows. Injection sites were marked on both hips using a marker pen. The site was covered with local anaesthetic cream (EMLA, Astra pharmaceuticals, Herts, UK) and an occlusive dressing applied for 30 minutes before injection. The injection sites were identified by palpating the pubic tubercle and adductor longus tendon with both hips held in abduction and flexion by an assistant (Fig. 1). These landmarks are reliable and easily found in children with CP. Injections were performed at two sites on each lower limb, approximately 2 cm and 4 cm from the pubic tubercle, 1 cm posterior to the adductor longus tendon, and into the palpable adductor muscle mass. No attempt was made to inject specific adductor muscles, as the toxin is known to diffuse readily across fascial barriers (Shaari et al. 1991). All four injections were performed quickly using a 23 gauge needle and caused minimum distress.

The total dose of BTX/A was 8 units/kg/child, using 'BOTOX' preparation (Allergan Inc., Irvine, CA, USA). As there were two injection sites per lower limb, each site received 2 units/kg. This dose was chosen as being in a therapeutic range for large skeletal muscle groups and within recognized safe dose limits (Brin 1997). BTX/A was prepared by adding 1 mL of normal saline to 100 units of freeze-dried BTX/A giving a standard dilution of 10 units per 0.1 mL.

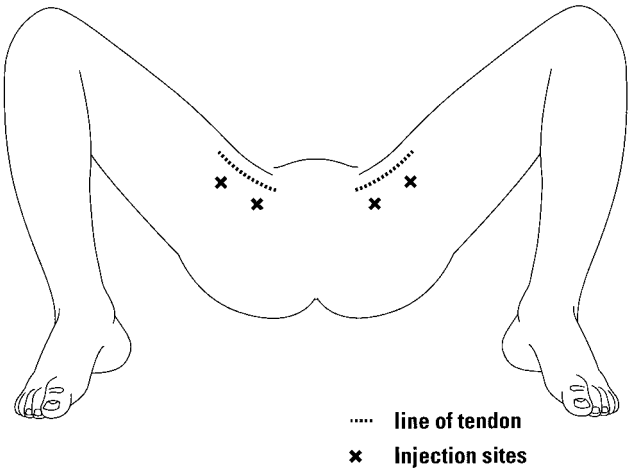

Figure 1: *Site of botulinum toxin A injection to the hip adductor muscles.*

Equal volumes of normal saline were used for placebo injections. Injections were prepared out of sight of the parents and child and drawn up in an unmarked 1 mL graduated syringe. On the date of surgery, the child was reexamined and parents questioned regarding possible side effects of BTX/A.

SURGICAL PROCEDURE

All aspects of the perioperative care were standardized, including the anaesthetic, surgery, and postoperative pain management. Surgery was standardized to include routine lengthening of adductor longus and gracilis, lengthening of adductor brevis partially or completely until 30 to 40° of hip abduction in flexion was obtained to a combined abduction range of 60 to 80°. Hips with asymmetric abduction range preoperatively, were managed by asymmetric surgery to obtain a symmetrical range of abduction. Tenotomy of psoas at the lesser trochanter was performed selectively when examination under anaesthesia indicated a hip flexion contracture in excess of 20° and the child was non-ambulant. After surgery, the child's lower limbs were immobilized in abduction plasters with the hips extended and abducted to a combined measured angle of 50° abduction. These plaster casts remained for 4 weeks, after which a fixed hip abduction brace was fitted and used for 3 to 6 months.

Surgery was performed under inhalational general anaesthesia, supplemented by a single caudal regional block

Table I: Demographic, type of cerebral palsy, preoperative mobility level, physical examination, and radiologic data of the botulinum toxin A (BTX/A) and placebo groups before treatment

	BTX/A Mean (± 2SE)	*Placebo Mean (± 2SE)*	*Mean difference (95% CI)*	*P value*
Age (y)	4.3 (± 1.3)	5.0 (± 1.6)	–0.7 (–2.9, 1.5)	<0.50
Sex (M, F)	3 M, 5 F	3 M, 5 F		
Weight (kg)	12.9 (± 1.9)	15.9 (± 4.9)	–3.0 (–9.0, 3.0)	<0.29
Type of CP	2 severe diplegia 6 quadriplegia	1 severe diplegia 7 quadriplegia		
Mobility level (Palisano 1997)	2 level IV 6 level V	2 level IV 6 level V		
Hip migration percentage (Reimers 1980)	38.7 (±10.4)	37.3 (± 9.3)	1.4 (–13.8, 16.8)	<0.84
Range of abduction (°)	40.9 (± 7.3)	35.6 (± 4.9)	5.3 (–4.2, 14.8)	<0.25
Ashworth scale (adductors)	2.03 (± 0.24)	2.37 (± 0.49)	–0.34 (–0.95, 0.26)	<0.23
Femoral neck-shaft angle (°)	38.4 (± 4.5)	45.0 (± 6.1)	–6.6 (–15.0, 1.9)	<0.11
Hip flexion contracture (°)	5.9 (±11.8)	17.2 (± 11.9)	–11.3 (–29.2, 6.7)	<0.20

Table II: Results of variables that follow statistically normal distributions for the botulinum toxin A (BTX/A) and placebo group (S) (Shapiro–Wilks test <0.05)

	BTX/A Mean (± 2SE)	*Placebo Mean (± 2SE)*	*Mean difference (95% CI for difference)*	*P value (Student's t)*
Combined narcotic dose				
24 h (mg/kg)	0.53 (± 0.19)	0.74 (± 0.15)	0.21 (–0.06, 0.47)	< 0.12
48 h (mg/kg)	0.59 (± 0.20)	1.17 (± 0.32)	0.58 (0.17, 1.00)	< 0.009[a]
Total admission (mg/kg)	0.59 (± 0.20)	1.33 (± 0.43)	0.74 (0.21, 1.26)	< 0.005[a]
Morphine requirement				
24 h (mg/kg)	0.52 (± 0.21)	0.73 (± 0.16)	0.21 (–0.07, 0.49)	< 0.13
48 h (mg/kg)	0.56 (± 0.21)	1.10 (± 0.36)	0.54 (0.07, 0.99)	< 0.03[a]
Total admission (mg/kg)	0.56 (± 0.21)	1.16 (± 0.46)	0.60 (0.03, 1.17)	< 0.04[a]
Codeine requirement				
48 h (mg/kg)	0.47 (± 0.41)	1.54 (± 1.12)	1.07 (–0.28, 2.43)	< 0.10
Total admission (mg/kg)	0.59 (± 0.41)	3.39 (± 2.08)	2.8 (0.33, 5.27)	< 0.03[a]
Duration morphine infusion (h)	26.1 (± 9.5)	43.8 (± 11.3)	17.7 (1.7, 33.6)	< 0.03[a]
Pain score 24 h (score out of 9)	1.2 (± 0.6)	3.4 (± 0.9)	2.2 (1.0, 3.4)	< 0.002[a]
Pain score 48 h (score out of 18)	1.6 (± 0.7)	5.3 (± 1.5)	3.7 (1.9, 5.5)	< 0.001[a]
Pain score				
Total admission	1.7 (± 0.7)	6.5 (± 2.3)	4.8 (2.1, 7.5)	< 0.003[a]
Diazepam requirements				
Total admission (mg/kg)	0.5 (± 0.17)	1.2 (± 0.6)	0.7 (0.6, 1.5)	< 0.04[a]
Paracetamol requirements				
Total admission (mg/kg)	107 (± 21)	240 (± 68)	133 (52, 215)	<0.002[a]
Length of hospital admission (h)	54.4 (± 4.9)	81.1 (± 14.2)	26.7 (9.6, 43.9)	< 0.003[a]

[a] Significant difference between the two groups using Student's *t* test.

(bupivicaine 0.25% with adrenaline 1:400000, in a volume of 1 mL/kg). Postoperative analgesia was strictly standardized with doses on sliding scales 'on demand' as required by the patient, including: morphine by intravenous infusion (0.01 to 0.04 mg/kg/hour); diazepam, orally or per rectum (0.1 to 0.3 mg/kg every 8 hours); paracetamol, orally or per rectum (20 mg/kg every 4 to 6 hours); codeine, orally (1 mg/kg every 4 to 6 hours) once the morphine infusion had ceased.

The aim of this regimen was to commence with intravenous analgesia and to wean the child to oral medication in preparation for discharge from hospital. Laxatives and antiemetics (metoclopramide) were prescribed as required and regular medications were continued.

Postoperative assessment consisted of regular scoring of pain, nausea, vomiting, and sedation. Vital signs, analgesic requirements, complications, length of admission, and readmission rate in the first 3 months were also documented. Due to the similar effects of morphine and codeine, doses were combined to give a 'total narcotic dose', apart from when the individual analgesic requirements were recorded. Solomon (1994) suggests using a conversion factor of 20:1 when comparing the effects, therefore the codeine dose (mg) was divided by 20 and added to the morphine dose (mg) to devise the 'total narcotic dose' (mg). As no child was able to self-report, three observers (nurse, parent, and trial coordinator) reported independently to allow correlation and internal validation. The pain scoring system used a validated observational paediatric category rating scale (0 = no pain, up to 3 = severe pain) (McGrath and Unruh 1994). Pain scores were assessed hourly by nursing staff (to account for roster changes), and 8 hourly by the other two observers. The pain scores from the nursing staff were then averaged over each 8-hour period. This score was then averaged with the parent and trial coordinator score to give a total pain score from 0 to 3 for each 8-hour period. The same technique was employed to devise sedation and nausea scores for each 8-hour period.

Children were considered suitable for discharge when they were able to maintain adequate oral intake of fluids and diet, their pain was controlled with oral analgesia, and there were no other complications.

STATISTICAL ANALYSIS

There were no previous data to guide in sample size calculations. It was decided to conduct the trial as a pilot for 1 calendar year and to conduct an interim analysis to calculate sample size for the definitive trial. The distribution of each outcome measure was analysed using the Shapiro–Wilks test. Those found to follow normal distributions were analysed using the unpaired Student's *t* test while non-parametric data were analysed using the Mann–Whitney *U* test. P values of less than 0.05 were regarded as significant.

Results

Sixteen of 17 eligible patients were successfully recruited into the trial over a 12-month period. Eight patients received BTX/A and eight patients received normal saline.

All children underwent bilateral adductor tenotomies as described. Ten children also required iliopsoas tenotomy (four in the BTX/A group, six in the placebo group).

The demographic, type of CP, preoperative mobility level (Palisano et al. 1997), physical examination, and radiologic data of the two groups are given in Table I and show no significant difference between these groups. No child had the ability to self-report their pain scores mainly because of limited cognitive abilities, very limited speech, and their young age. Most results were found to follow a normal distribution (see Table II). Results for those variables that did not follow normal distributions are given in Table III.

There were no side effects from the BTX/A therapy or injection technique in this trial.

ANALGESIC REQUIREMENTS

All eight children in the placebo group were considered to require a morphine infusion postoperatively, compared to seven in the BTX/A group.

During the first postoperative 24 hours, in the BTX/A group, there was a trend towards reduced morphine requirements ($P<0.13$) and combined narcotic dose ($P<0.12$), but these did not reach statistical significance (see Table II). After the first postoperative 48 hours, the reduction in morphine requirements ($P<0.03$) and combined narcotic dose ($P<0.009$) were both significant, and there was a trend towards reduced codeine requirements ($P<0.1$) (see Table II). Over the entire admission, the reduction of both morphine and codeine requirements was significant, giving a combined narcotic dose of the BTX/A group of approximately half that of the placebo group ($P<0.005$) (see Table II). There was also a significant difference between the groups in the mean duration of morphine infusion ($P< 0.03$) (see Table II).

PAIN SCORES

Despite requiring significantly less postoperative analgesia,

Table III: Results of variables that do not follow statistically normal distributions for the botulinum toxin A (BTX/A) and placebo group (S) (Shapiro–Wilks test > 0.05)

	BTX/A Median (range)	*Placebo Median (range)*	*P value (Mann–Whitney U)*
Codeine requirement 24 h (mg/kg)	0.00 (0.00 – 1.59)	0.00 (0.00 – 0.93)	< 0.93
Sedation score Total admission	4.27 (0.0 – 6.21)	4.71 (2.60 – 9.54)	< 0.29
Nausea score Total admission	0.5 (0.0 – 3.0)	2.5 (0.0 – 6.0)	< 0.16
Metaclopramide requirements Total admission (mg/kg)	0.015 (0.0 – 0.20)	0.0 (0.0 – 0.28)	< 0.91

the BTX/A group also had a significant reduction in postoperative pain during their admission (see Table II). This reduction in pain was evident and significant within the first 24 hours in which the placebo group reported nearly three times the mean level of pain scores than the BTX/A group (see Table II). This difference in accumulated postoperative pain scores remained significant throughout the entire admission, being 3.3 times greater in the placebo group at 48 hours and on discharge, the mean total pain scores of the placebo group were nearly four times greater than those of the BTX/A group (see Table II).

The reduction in mean diazepam requirements during admission was also significant (see Table II). The BTX/A group required less than half the diazepam dose of the placebo group. All children requiring antiepileptic medication used non-benzodiazepine medications and were, therefore, not expected to have any 'tolerance' to the diazepam. Mean paracetamol requirements were also significantly reduced in the BTX/A group and were again less than half the mean requirements of the placebo group (see Table II). Despite the reduction in narcotic analgesic requirements in the BTX/A group, the differences in metaclopramide requirements, nausea score, and sedation were not significant (see Table III).

There was a significant reduction in the mean length of hospital admission for the BTX/A group of 26 hours or 33% when compared with the placebo group (see Table II). No child had complications unrelated to their surgery, which prolonged their hospital admission.

There were no readmissions in the BTX/A group in the 3 months after discharge, but there were three readmissions in the placebo group, two of which were due to difficulties with pain management at home. One child required codeine over a 7-day period after discharge which led to prolonged nausea, vomiting, and eventual dehydration with mild renal impairment. The other child required readmission 4 weeks after surgery when the abduction plasters were replaced by an abduction brace. The additional duration of these readmissions and subsequent analgesic requirements were not included with those of the initial admission. One child from the placebo group required readmission for the treatment of a superficial wound infection.

Discussion

The first 16 patients entered into the study were recruited within 1 year and were to serve as a pilot study from which sample size calculations were to be made for a definitive study. However, there was a highly significant difference in outcome between the two study groups and a full trial was judged both unnecessary and unethical.

The differences in pain scores and analgesic consumption were less marked in the first 24 postoperative hours than in the second and subsequent periods. This may be the result of a number of factors which might tend to equalize pain and analgesic requirements in both groups, including the routine use of a bupivicaine caudal block, the perception by nursing staff of a 'standard' analgesia requirement, and for 'normal incisional pain'. The differences in pain scores and analgesic requirements became increasingly marked and statistically significant after 24 hours when persistent muscle spasms are often most severe.

Improved pain control was followed by faster resumption of normal oral fluid intake and diet. It was not surprising, therefore, that improved analgesia led to earlier discharge from hospital with both social and financial advantages. The earlier discharge from hospital more than recouped the cost of using BTX/A. There was both a humanitarian as well as a financial benefit in using BTX/A in this specific context.

The effects of BTX/A in reducing the need for analgesics appeared to persist long after discharge from hospital in that there were two readmissions because of inadequate pain control in the placebo group but none in the toxin-treated group. This is consistent with the reported clinical duration of action of BTX/A of at least 3 to 6 months (Boyd and Graham 1997). We do not consider the duration of action of type-A toxin to be a disadvantage in this context. On the contrary it appears to help subsequent management, especially the cast removal and application of abduction brace at 4 weeks after surgery and the reintroduction of a physiotherapy programme.

It is probable that BTX/A may have a useful analgesic role in other postoperative situations in the management of children with CP. We have used BTX/A with apparent benefit after reconstructive hip surgery to control the severe spasms associated with excision of a deformed femoral head, and to protect tendon transfers in the upper limb from uncontrolled spasms in the immediate postoperative period. Although the effects of toxin were convincing in these individual case studies, none was suitable for study within a clinical trial framework. As a general principle, acute pain which appears to be wholly or partially caused by muscle spasms may respond favourably to BTX/A chemodenervation.

We conclude that there may be an important clinical role for BTX/A in reducing postoperative pain and analgesic requirements after hip adductor release surgery in children with CP. It may be useful in other clinical situations.

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