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Botulinum toxin type A injections can be an effective treatment for pain in children with hip spasms and cerebral palsy

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AIM Botulinum toxin type A (BoNT-A) injections were used in the treatment of lower-limb spasticity in children with cerebral palsy (CP). Anecdotal evidence suggests a reduction in pain after this treatment in children who had pain localized to a displaced hip joint. We report on our current clinical practice.
METHOD Twenty-six children with non-ambulant quadriplegic CP (Gross Motor Function Classification System level V) were assessed as having significant spasticity and pain at the hip level. Twelve were males and 14 females, with an age range of 2 to 19 years (mean age 11y 6mo, SD 4y 9mo). Ten had functional difficulties secondary to predominant spasticity and 16 had a mix of a high-background peripheral tone with superimposed dystonia. Of the 26 children assessed, 10 had at least one hip which was dislocated and three had at least one hip which was subluxed. As part of their spasticity management programme they received targeted BoNT-A injections to the adductor magnus, medial hamstrings and iliopsoas muscle groups. The Paediatric Pain Profile was used as the primary outcome measure.
RESULTS All had highly significant improvement in their recorded pain profile scores measured at 3 months after treatment ($p<0.001$). There was equal efficacy in response to treatment in the children with subluxed or dislocated hips. In addition, families commented on improved quality of life for the children across several areas, including sleep, postural management, and activities of daily living.
INTERPRETATION This report demonstrates that targeted BoNT-A injections reduced pain in children with significant spasticity and pain at the hip level. They may also improve quality of life of non-ambulant children with CP and a hip problem.

Cerebral palsy (CP) is the most common cause of physical disability in childhood. It affects up to three children per 1000 throughout Europe.[1] Studies suggest that more than 25% of children with CP fall in the more severely affected group, Gross Motor Function Classification System (GMFCS) levels IV and V. These children are not independently ambulant and are more likely to have cognitive and communication difficulties. They are at high risk of developing displacement of the femoral head due to spasticity in the muscles around the hip.[2–7] Previous studies suggested that up to half of these hips were painful. Uncontrolled muscle spasticity and pain in the hip joint may cause difficulties with activities of daily living such as upright sitting, sleep, dressing, and changing. Prevention of painful hip displacement has been advocated through screening programmes.[7,8] However, a large number of children continue to present to paediatric neurodisability and orthopaedic services with troublesome lower-limb muscle spasms and a displaced hip. These involuntary and sustained muscle contractions are thought to contribute significantly to pain in children with CP and a hip problem.[9–11]

Throughout the developed world a variety of strategies are used in the management of spasticity. Early

multidisciplinary assessment and intervention assist with diagnosis and minimizing the impact of functional difficulties and prevention of future deformity. These include assessment of postural difficulties and provision of appropriately supportive equipment, which may assist in maintaining hip integrity.[5] Adequate 24-hour postural management may also be beneficial in terms of comfort and reduction of spasms. There is increasing awareness that early input from expert orthopaedic services can help prevent serious joint deformity in later years.[7,8,12] Specific medical interventions, including tone-modifying medications, can be used to manage generalized spasticity causing functional problems, particularly in the more severely affected non-ambulant group. Movement-modifying medicines such as trihexyphenidyl hydrochloride, also known as Benzhexol, can be a useful adjunct given orally in children with dystonia and dyskinesis. Muscle relaxants such as oral or intrathecal baclofen can help reduce high muscle tone.[13]

Botulinum toxin type A (BoNT-A) is a well-established, clinically effective and safe treatment for the management of focal spasticity in CP.[14–19] It is licensed for use in the treatment of lower-limb spasticity in children with CP by injection of the gastocnemius and tibialis posterior muscles, although it is also widely used off-licence to inject the muscles around the hip and knee joints, as well as in the upper limb. Anecdotal evidence suggests a reduction in pain after this treatment in children who had pain localized to a displaced hip joint. Research suggests that it may have a beneficial effect in reducing pain due to spasticity.[20] Barwood et al. established that BoNT-A was safe in the perioperative period for children with CP undergoing preventive soft tissue surgery for management of a displaced hip joint.[9] Their work demonstrated that if BoNT-A was given preoperatively to the adductor magnus muscle group then children had reduced analgesia requirements during their in-patient stay.

The pattern of muscles injected has changed as our clinical experience using BoNT-A for spasticity management in the lower limb has increased. We initially injected the adductor magnus muscle groups alone to reduce spasticity in the hip region. Subsequently we moved to combinations of injections to the adductors, medial hamstrings, and rectus femoris muscles, more recently including ultrasound-guided injection of the iliopsoas, dictated by the needs of the individuals.[9,14,15,18] Carers reported improvement in the functional activities of daily living after treatment but also a reduction in pain when they were mobilizing the hip joint in those children who were known to have a painful displaced hip.

Describing pain in children with cognitive impairment is challenging as research has shown that self-reporting in this group may be unreliable.[10,11,21,22] Hunt et al. provided a validated pain profile questionnaire which enabled researchers to measure pain objectively in the more severely neurologically affected group of children with communication difficulties by assessing different patterns of pain-related behaviour.[23] This pain profile ranks pain on a composite ordinal scale. The values are then grouped as mild, moderate, severe, or very severe.

METHOD

Children were referred for treatment of spasticity in the lower limb that was causing functional difficulties in activities of daily living. Referrals were either from community paediatric or from paediatric orthopaedic services if the child was awaiting surgery for a displaced hip. All children had a non-progressive but not unchanging disorder of movement and/or posture, due to an insult or anomaly of the developing brain. All were non-ambulant and were in GMFCS level V. The children were seen at the Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK. The ethics committee and the Lead for Paediatric Research and Development approved the anonymous reporting of the clinical findings in this cohort.

A standard assessment was carried out in all children. The clinical history focused on the functional difficulties for each child and family. A standardized format for history taking was used to cover antenatal, perinatal and developmental history, neuroimaging, current medical factors, sleep, positioning and posture, equipment and multidisciplinary input, as well as activities of daily living and quality of life. As part of this, a standardized physical examination and the validated Paediatric Pain Profile questionnaire were used to identify and assess potential causes of discomfort and pain. This questionnaire, which looks at 20 different pain-related behaviour patterns in non-communicating children, provides scores out of 60 which can subsequently be grouped into various levels of severity: mild (10–19), moderate (20–29), severe (30–39), and very severe (>40).[23] The examination included static and dynamic lower-limb joint ranges, assessment of tone and physical identification of the causes of discomfort and the limitations that this imposed on their activities of daily living. At the end of each assessment individual treatment goals were set, based on the areas of specific functional difficulty identified by parents and carers. Hip radiographs were performed if no local hip-screening programme was in place or if there was obvious discomfort on examination or an asymmetric range of hip abduction in flexion. Hips were considered subluxed if the migration percentage was greater than 30% and dislocated if the migration percentage was greater than 50%.[7]

In children and young people where muscle spasm and spasticity was felt to be playing a major role in discomfort around the hip region, the use of targeted BoNT-A injections was discussed as an appropriate treatment. Potential local and systemic side effects were explained to the child and their carers. Written consent was obtained for treatment. The injections were given approximately 2 months after the initial clinic assessment on the hospital day-care unit. The injections were administered with the use of ultrasound guidance according to Heinen et al.'s recommendation.[15] Younger children were given oral midazolam as analgeso-sedation for the procedure. All children had a topical anaesthetic. The muscles injected included unilateral or bilateral iliopsoas, adductores magni, and medial hamstrings (semimembranosus and semitendinosus). Injection sites were dependent on the source of hip discomfort, spasm, and functional problems. Dose ranges for Dysport (Ipsen Limited, Slough, UK) and Botox (Allergan Limited, Buckinghamshire, UK) were guided by the European Consensus Statement (total: 30 IU/kg Dysport and 12 IU/kg Botox).[19] Choice of preparation used in each first course of injections was guided by hospital pharmacy availability of BoNT-A or what type of BoNT-A had previously been used in an individual, i.e. either Dysport or Botox.

Follow-up was standardized at 1, 3, and 6 months after the injections. At these appointments possible side effects were discussed. The individual's discomfort was reappraised using the Paediatric Pain Profile questionnaire 3 months after the injections. The efficacy of treatment was also assessed by discussing outcome with respect to the functional treatment goals that were set at the initial consultation, such as improving ease of dressing and toileting, and tolerance of postural systems.

Statistical calculations were performed on the results of the pain profile scores using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). Data were examined for normality using measures of skewness, kurtosis, and the Shapiro–Wilk test. A paired *t*-test was used to compare pain scores before and after treatment. A *p*-value of less than 0.05 was assumed to be significant. Analysis of covariance (ANCOVA) was used to examine whether response to treatment was influenced by age, sex, plans for surgery, or the preparation of BoNT-A used. Comparison of the initial pain score between various subgroups was performed using Mann–Whitney *U* and Kruskal–Wallis tests and by multiple linear regression.

RESULTS

Forty-two children and young people with a main functional difficulty of spasticity and pain in the hip region were referred over a 1-year period to regional neurodisability services. All had a quadriplegic movement disorder at GMFCS level V. We reported the Paediatric Pain Profile scores of 26 children who were felt to be suitable candidates for injections of BoNT-A (12 males, 14 females; mean age 11y 6mo SD 4y 9mo, range 2–19y) in order to improve comfort. Of the 26 patients, 10 had at least one hip which was dislocated and three had at least one hip which was subluxed. The predominant pattern of movement disorder was of high peripheral tone in 10 of the children and of high peripheral tone with superimposed dystonia in 16 children.

Seventeen children received Dysport using a maximum dose of 30IU/kg, total maximum dose of 1000IU (range 400–1000IU). Nine children received Botox with a maximum dose of 12IU/kg, total maximum dose 300IU (range 100–300IU). No child had significant side effects reported after treatment with either preparation at 1, 3, or 6-month follow-up. Dose range used was within accepted international practice for multilevel injections and guided by the European Consensus Statement. No individual had had BoNT-A injections in the preceding 6 months.

At the time of initial referral all children were experiencing troublesome pain in their hip region, rated as at least moderate, with the majority having frequent severe painful episodes by day and night. These were most frequently observed when they had been in one posture for more than an hour, e.g. in their seating system. Pain at initial assessment was not related to any factor on paired testing or in a multiple linear regression model (age, sex, previous surgery or BoNT-A injection, need for surgery, or presence of subluxation or dislocation). The pain scores before and after treatments were distributed normally. The pain scores before and after treatment in the various subgroups are shown in Table I.

All pain scores fell when measured at 3 months after treatment (Fig. 1). The mean pain score before treatment was 42.2 (SD 8.6, range 20–59). The mean pain score after treatment was 9.5 (SD 5.2, range 1–23). The mean reduction in pain score was, therefore, 32.7 (95% confidence interval [CI] 29.1–36.4), with a minimum reduction of 12 points and a maximum reduction of 58 points. A paired *t*-test demonstrated that this reduction in pain was highly statistically significant ($p<0.001$).

ANCOVA was used to confirm that the reduction in pain score with injection of BoNT-A did not depend on the preparation used (Botox vs Dysport), sex, or whether the child was awaiting surgery. The model used the pain score after treatment as the dependent variable, the pain score before treatment as a covariate, and the drug preparation used (Botox vs Dysport) as a fixed factor. The analysis was also repeated with 'sex' and 'plans for surgery' as fixed factors.

Table I: Demographic factors and pretreatment and posttreatment pain scores

Sex	Male	Female	
Number	12	14	
Median pain score (pretreatment)	43.5	43.5	
Median pain score (posttreatment)	9	8	
Previous BoNT-A	No	Yes	
Number	18	8	
Median pain score (pretreatment)	43	46.5	
Median pain score (posttreatment)	8.5	10	
Previous surgery	No	Yes	
Number	22	4	
Median pain score (pretreatment)	43.5	41	
Median pain score (posttreatment)	9	7.5	
Awaiting surgery	No	Yes	
Number	16	10	
Median pain score (pretreatment)	44	43	
Median pain score (posttreatment)	8.5	9	
Hip position	In place	Subluxed	Dislocated
Number	13	3	10
Median pain score (pretreatment)	44	30	43.5
Median pain score (posttreatment)	9	7	9

BoNT-A, botulinum toxin type A.

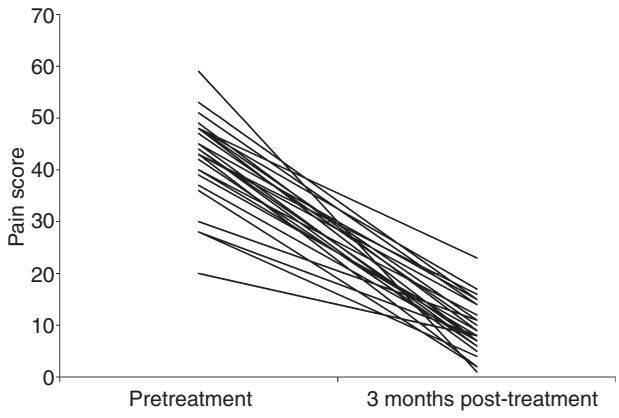

Figure 1: Individual pain profile scores before and 3 months after treatment with botulinum toxin type A.

None of these factors appeared to influence the efficacy of treatment. Nine patients were treated with Botox and 17 were treated with Dysport. The median dose of Dysport used was 750IU (range 250–1000IU) and the median dose of Botox was 200IU (range 100–300IU). Dysport produced a mean reduction in pain score of 32 points (95% CI 27.4–36.6) and Botox produced a mean reduction in pain score of 34.1 points (95% CI 26.7–41.5). The reduction in pain score was not correlated with dose for either preparation.

Many children that we see are considered to be at too high an anaesthetic risk for surgery, have declined a surgical option, are in discomfort while on the waiting list, or have considerable pain secondary to spasticity in the muscles of the hip region. In this group of 26 children, 10 were awaiting hip surgery. The remainder did not require surgery, had already undergone surgery, or had declined surgery. All groups showed equal efficacy in response. The mean reduction in pain score after BoNT-A injections in those children awaiting surgery was 29.2 (95% CI 22.4–36.0) with a mean reduction in pain score of 34.9 (95% CI 30.5–39.3) in the remaining children. Pain scores before or after treatment did not appear to correlate with age. Age was not a significant factor when included as a covariate in an ANCOVA. Males and females did not differ in their pain scores either before or after treatment.

We did not formally quantify the achievement of specific functional goals beyond a goal attainment scale, these were rated at least eight out of 10 for efficacy by parents/carers. However, as part of the structured follow-up assessment, individual families commented on an improved sleep pattern for the child such as settling more easily to sleep, having a reduction in the frequency of night-time waking secondary to pain, and need for turning because of hip discomfort. This had an advantage in improved sleep for carers. Some families stated that this had the most significant impact on the whole family's quality of life in comparison to any other previous intervention.

Other reported functional benefits reported were the following: improved tolerance of seating systems; increasing the length of time between the need for changes of positioning; and less pain on moving and handling, leading to tolerance of hoisting and easier dressing, toileting, and changing. Individual feedback from teachers, carers, and therapists also reported improved developmental achievements, especially concentration and learning and gross and fine motor skills. Interestingly, four families reported improvements in feeding and swallowing skills after administration of BoNT-A in the hip region. In these children there was

considerable reduction in lower-limb spasticity and discomfort after treatment.

DISCUSSION

It is our routine practice to screen children for hip problems in accordance with the recommendations by Scrutton and Baird and to refer those with significant hip migration for an early specialist paediatric orthopaedic consultation.[7] It has previously been shown that BoNT-A injections to the lower-limb muscle groups can improve spasticity management in children at the time of soft-tissue orthopaedic surgery for hip subluxation. However, in the non-ambulant population with CP, hip spasticity and discomfort are not solely seen in this group. Others without subluxation, awaiting surgery, or considered too high an operative risk can experience pain in the hip region. Focal spasticity can cause direct pain and also a number of other functional difficulties for the child and parent. There have been a considerable number of studies into the efficacy of BoNT-A injections in the management of children with CP.[9,16–19] Many of these have focused on its unlicensed or off-label use in improving gait and upper-limb function in ambulant children with a mild to moderate disability.

The benefits for non-ambulant children with a more severe movement disorder have been less extensively reported. Often this group of children have a very complex medical and developmental pattern of disability. Many different medical problems lead to a situation where a range of professional teams are involved in assessing and managing the needs of the individual child. It can, therefore, be difficult for the children and their carers to remain focused on managing their holistic care rather than looking at life as solving a series of specific interrelated problems.

When carers are dealing with issues of pain in children with a moderate to severe neurological disability, not only can it be difficult for children to communicate their specific needs but, because of intrinsic insensitivity, indifference, or acceptance of pain, it can also be hard for those around them to recognize reliably their levels of discomfort.[10,24] The development of pain profiles that use symptom clues to help quantify pain has helped considerably. Over the past decade non-communicating pain assessment tools using prompts such as motor pattern activity, protection and guarding, expressions, vocalizations and physical and behavioural patterns by day and night have helped us focus more on what causes the discomfort for this group of children and what we can do to intervene.[21,23] This has further led to the vast expansion recently of work assessing quality of life for the individual.

Musculoskeletal discomfort at or around the hip level was a common problem for this group. Painful spasms were frequently reported by families and we recorded their severity with the help of individual pain profiles. Management of musculoskeletal pain led us to review our clinical practice with BoNT-A. The possible analgesic effects of such injections are not limited to their direct block of acetylcholine release at the level of the motor end plate, thereby causing a reduction in muscle tone in the injected muscles. As well as this direct effect of reducing mechanical stimulus to the pain afferent system in the soft tissues surrounding the hip joint, a number of other ways that BoNT-A injections can reduce pain in muscles have also been put forward. These include the effect of directly reducing the increased compression on the blood vessels and nerves, causing a reduction in nociceptive stimulus. There is also some evidence of direct peripheral analgesic and anti-inflammatory activity.[9,20,25–27]

BoNT-A injections to the hip adductor muscles can result in functional improvements, such as increased length of time that a child can spend sitting, or ease of access for toileting and dressing. Quantification of these functional benefits is an area for future study.

Over recent years the pattern of muscles injected at our centre has altered for two reasons. First, it became easier to access individual muscle groups with the aid of ultrasound guidance and second, we developed greater clinical experience of which muscles were causing the greatest degree of pain for this group of individuals. While recognizing that individuals vary, we now routinely inject the iliopsoas, adductor magnus and medial hamstring muscle groups. It was on the basis of this that we decided to formally review our interventions using a specific validated pain tool.

Our treatment dose range was universally in the middle of accepted peer practice guided by the European Consensus Statement. Recent reported cases of fatalities secondary to the use of BoNT-A were reported to have used considerably higher total body doses, much closer to the LD50 for the preparations. We recommend keeping to accepted reported peer practice when using BoNT-A off-licence.

The recognition and assessment of pain can be a challenge in a population of children who often have limited communication skills. However, our work shows that, with careful holistic assessment and selection of patients, BoNT-A can be safe and effective in pain relief for children with CP.

The conclusions from this study could be limited because of a number of factors. This is a report of our current clinical practice rather than a controlled trial. Blinding was not possible in a routine clinical situation as the parents and carers who assessed the child's pain were obviously aware that the child had been treated. However, the magnitude of the reduction in pain scores and the consistency of this effect were unlikely to be explained entirely

by a placebo effect. Also, the global improvement in the demeanour of the children was reported by a number of other interdisciplinary professionals with access to the children who were not specifically aware of the timing of injections, such as teachers, therapists, and referring doctors.

CONCLUSION

The results suggested that using targeted BoNT-A injections in the treatment of hip pain in children with CP was beneficial, both in children awaiting hip surgery and in those who are not. Areas for future study might include quality of life issues which we did not formally assess, such as improved sleep and ease of carrying out activities of daily living, as well as duration of effect of treatment and possible benefits or adverse effects of serial injections. However, this study showed that targeted administration of BoNT-A in non-ambulant children with CP significantly reduced pain and could improve quality of life for both the child and family.

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