The impact of botulinum toxin A and abduction bracing on long-term hip development in children with cerebral palsy

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ABBREVIATIONS

MCPHCS Melbourne Cerebral Palsy Hip Classification System
RCT Randomized controlled trial
SWASH Sitting, Walking And Standing Hip orthosis

AIM To study the long-term impact of 3 years of botulinum toxin A (BoNT-A) injections and abduction bracing on hip development in children with bilateral spastic cerebral palsy (CP). We wanted to know if early treatment improved hip development and reduced the need for surgery.
METHOD A long-term review of hip morphology and surgery requirements in children who participated in a multicentre, randomized controlled trial. The trial investigated short-term effects of BoNT-A injections combined with an abduction brace, compared with usual care, on hip displacement in children with bilateral spastic CP.
RESULTS Forty-six children with bilateral spastic CP (31 males, 15 females; 10 with diplegia, 36 with quadriplegia; mean age at enrolment of 3y 2mo, mean age at most recent clinical review 13y 11mo [range 10y 6mo–16y 8mo]; three children in Gross Motor Function Classification System level II, 11 in level III, 20 in level IV, 12 in level V) were followed for a mean of 10 years 10 months from recruitment to the trial. Mean migration percentage was 15.9% in the BoNT-A group and 15.2% in the comparison group (t=0.26, p=0.79). Eighty-nine percent of hips in the treatment group and 91% hips in the comparison group had satisfactory development, using a valid scale (Mann–Whitney U test=867.50, z=−1.59, p=0.11). Forty children had preventive surgery (21 treatment group, 19 comparison group) and 18 children had reconstructive surgery (10 treatment, 8 comparison).
INTERPRETATION In children with bilateral spastic CP, early treatment with BoNT-A and hip abduction bracing does not reduce the need for surgery or improve hip development at skeletal maturity.

Cerebral palsy (CP) is the most common cause of childhood disability in Australia.[1] Secondary musculoskeletal pathology is common and 35% of children with CP in Australia will develop hip displacement.[2,3] Hip displacement may be painful and lead to difficulties with walking, transfers, sitting, bathing, and dressing.[4–6] Without early detection and treatment, silent hip displacement can progress to painful dislocation.[2,7] Population-based studies have demonstrated that the incidence of hip displacement is directly related to walking ability, as described by the Gross Motor Function Classification System (GMFCS).[3,7–9] This information has led to the development of Australian Hip Surveillance Guidelines for children with CP.[10,11] Hip surveillance programmes are effective in preventing hip dislocation and reducing the need for salvage surgery.[12–14]

Efforts have been made to characterize the natural history of hip displacement in children with CP and to design interventions to reduce displacement before it becomes severe or symptomatic.[8–10] Non-operative interventions to reduce or prevent hip displacement may include postural sleeping systems, seating modifications, abduction bracing, and injection of neurolytic agents such as botulinum toxin A (BoNT-A) and phenol.[4,6] The level of evidence for many of these interventions is limited. Surgery for hip displacement in children with CP has been classified as preventive (adductor releases), reconstructive (combinations of femoral osteotomy), or salvage surgery.[6]

Non-operative interventions may be sought by the parents and carers of children with CP and some physiotherapists.[12] Injections of BoNT-A are effective in reducing spasticity in the hip adductor muscles and can result in increased hip abduction range.[15,16] It has been suggested that the use of an abduction brace to stretch the hip adductor muscles after BoNT-A injection may increase the effectiveness of the injections.[17]

This combination of BoNT-A and abduction bracing was investigated in a randomized controlled trial (RCT) conducted in four Australian centres, between 1997 and 2004.[18] The study included 91 children with CP and investigated the effectiveness of BoNT-A injections to the hip adductor and hamstring muscles, combined with hip abduction bracing, in the prevention of hip displacement, measured by migration percentage.[19,20] Six-monthly injections of BoNT-A over 3 years, combined with use of the SWASH (Sitting, Walking

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And Standing Hip orthosis; CAMP, Helsingborg, Sweden),[18] was compared with a group receiving standard care and surveillance, but no bracing or injections of BoNT-A.[10,11] The positive findings of the RCT were that fewer children in the treatment group required surgery (11 treatment vs 22 control) and the rate of hip displacement was lower in the treatment group than in the comparison group (2.6% per annum vs 5.7%).[18] The negative finding was that hips in both groups continued to displace. Although the rate of displacement was lower in the treatment group, this was of borderline statistical significance. The clinical significance was unclear because of the short follow-up. The trial was designed to have a good chance of detecting a treatment effect by the recruitment of younger children with early hip displacement and combining injections of botulinum toxin to the hip adductors and hamstrings, in therapeutic doses, with abduction bracing for 3 years.[18] Given the highly significant reduction in surgery required in the treatment group during the trial, the questions to be answered in long-term follow-up were as follows: (1) Did 3 years of 6-monthly injections of BoNT-A plus SWASH bracing reduce the number of hip operations? (2) Was hip development enhanced by the 3 years of treatment with BoNT-A and SWASH bracing?

METHOD

Participants

Children enrolled in the RCT had bilateral spastic CP, were between 1 and 5 years of corrected age at study entry, had clinical evidence of adductor spasticity and scissoring postures, and were recruited from four Australian centres (Fig. 1). They had radiological evidence of 'hips at risk', defined as a migration percentage of between 10% and 40%.[19,21] Management was standardized between the four centres during the 3-year RCT but surgical management of hip displacement varied in the four centres according to local protocols. Children who were followed at The Royal Children's Hospital in Melbourne were offered preventive and reconstructive surgery according to defined indications and standardized protocols. Preventive (adductor release) surgery was advised when the migration percentage of one or both hips exceeded 40% and hip abduction was less than 40°.[6] Reconstructive (bony) surgery was advised when the migration percentage of one or both hips remained greater than 40% more than 24 months after adductor releases. For additional details about the surgical protocol, see Appendix SI (supporting information published online). To exclude selection bias, the aim of this study was to review all children, from both treatment and comparison groups, from this one centre.

Ethical approval was granted under the audit provisions of The Royal Children's Hospital Human Research Ethics Committee, approval number 31052A.

Procedure

The migration percentage was measured from the most recent radiograph of the hips using a reliable protocol.[20] Hip morphology was classified from the same radiograph according to the Melbourne Cerebral Palsy Hip Classification System (MCPHCS) which is a valid and reliable classification of hip morphology for individuals with CP (Appendix SII, supporting information published online).[22,23] The number and type of preventive and reconstructive operations required by each child was recorded from a chart review of both hip surveillance and orthopaedic department records. Progress of children through the RCT and open follow-up is summarized in Figure 1.

What this paper adds

- Keeping the hips of children with CP in joint is difficult, and studies with short-term follow-up may not predict long-term outcomes.
- Three years of BoNT-A injections and bracing does not reduce the need for surgery nor improve hip development.
- Preventive and reconstructive surgery is successful for most hips at 10-year follow-up.

Statistical analysis

To determine if there was any significant difference between the groups in migration percentage, results were analysed using an independent t-test. Difference in MCPHCS between the groups was analysed using the Mann–Whitney U test appropriate for managing ordinal data. We analysed frequencies of (1) 'preventive surgery', (2) 'bony surgery', or (3) 'both' to investigate differences in requirements for surgery between the groups. Differences between the groups in children's age at surgery was analysed using an independent t-test. All analyses were performed using SPSS software (version 14.0SPSS Inc., Chicago, IL USA).

RESULTS

A detailed description of the children enrolled in the RCT has been published previously and is summarized in Figure 1.[18] Fifty-nine males and 32 females participated in the study with a mean age at enrolment of 3 years 2 months. Twenty-nine children had diplegia and 62 had quadriplegia. Clinical and radiographic records were reviewed for 46 of 47 surviving children who were followed at one centre, The Royal Children's Hospital, Melbourne. One participant was lost to follow-up as he moved between states soon after completion of the RCT. The long-term study group included 31 males and 15 females, 10 with diplegia and 36 with quadriplegia. Mean age at most recent clinical review was 13 years 11 months (range 10y 6mo–16y 8mo). Mean follow-up was 10 years 10 months (range 7y 10mo–13y 1mo) from enrolment in the RCT. Three children were in GMFCS level II, 11 were GMFCS III, 20 were GMFCS IV, and 12 were GMFCS V.

There was no difference between the groups in mean migration percentage at most recent follow-up. Mean migration percentage was 15.9% in the children who had been in the treatment group and 15.2% in those who had been in the comparison group (t=0.26, p=0.79; 95% CI −4.58 to 5.976). There was no difference between the groups in hip morphology as described by the MCPHCS (Mann–Whitney U test=867.50, z=1.59, p=0.11; Fig. 2 and Appendix SII). Most hips in both groups were satisfactory, MCPHCS grades I to III (near normal to mildly dysplastic). There were more hips at grade IV (subluxated) in the treatment group than the comparison group (5 vs 2; Fig. 2).

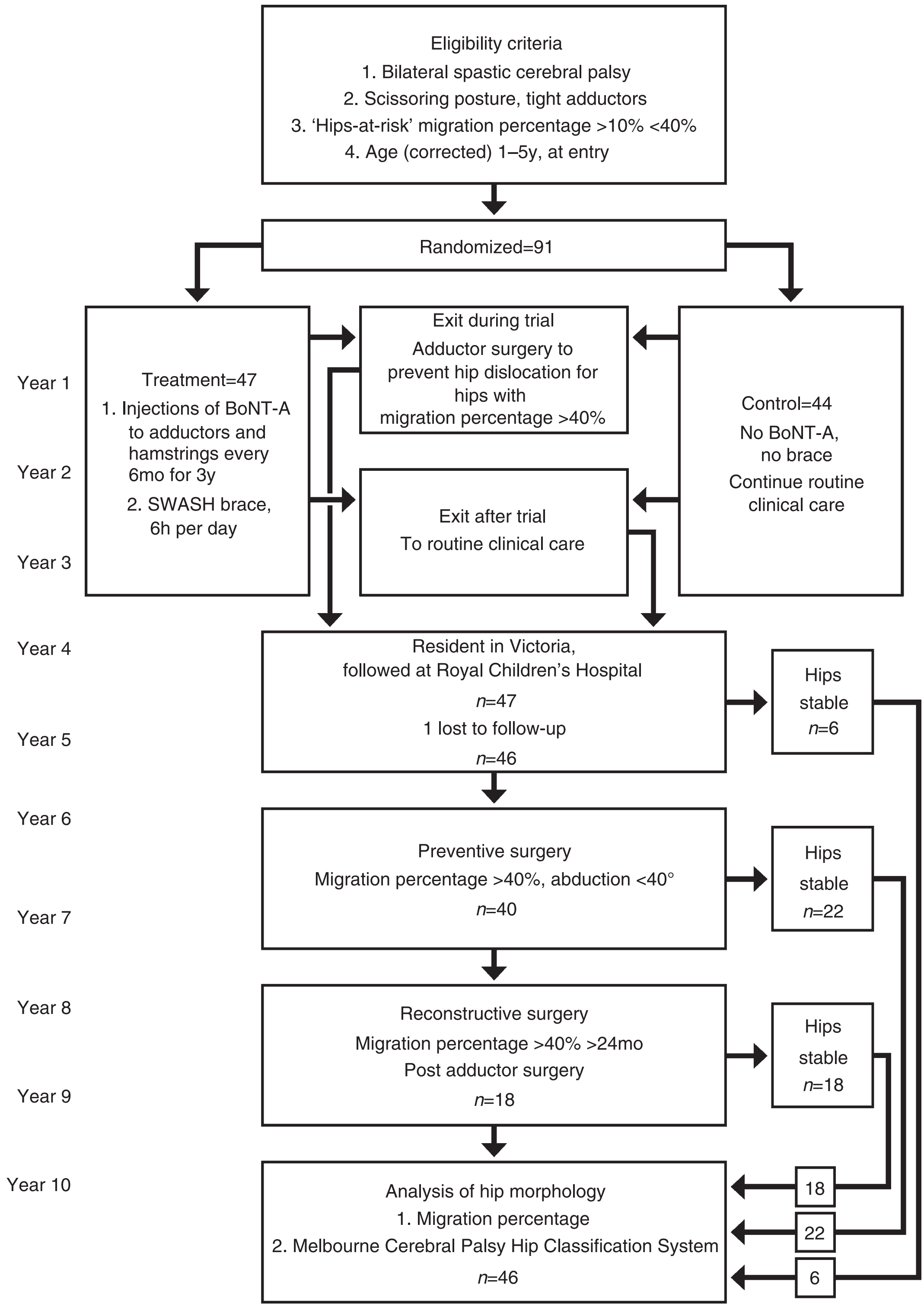

Figure 1: Summary of randomized controlled trial and follow-up.

The need for preventive surgery was high and similar in both groups, with 21 out of 23 children from the treatment group and 19 out of 23 from the comparison group requiring surgery (Fig. 3). The requirement for reconstructive surgery was also similar between the groups (10 vs 8; Fig. 3). At long-term follow-up, 40 out of 46 children had undergone preventive or reconstructive surgery, or both. Of the children who required surgery, there was no statistically significant difference between the groups in mean age at either preventive or reconstructive surgery. The mean age at preventive surgery for the treatment group was 6 years 7 months compared with a mean age of 5 years 1 month for the comparison group

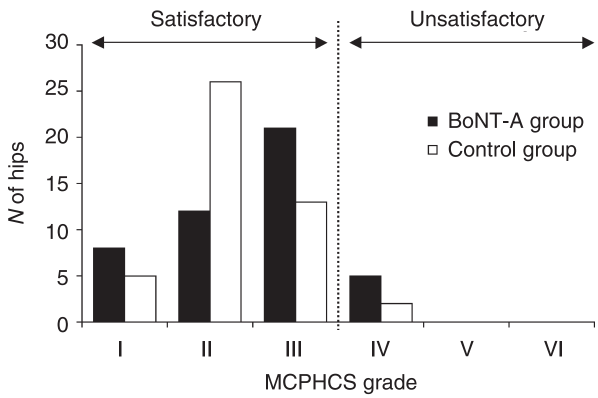

Figure 2: Comparison of hip morphology between the groups. MCPHCS, Melbourne Cerebral Palsy Hip Classification System.

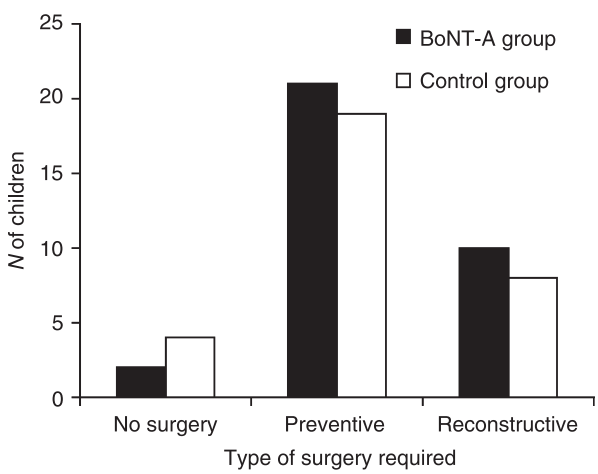

Figure 3: Comparison of the need for surgery between the groups.

(t=2.04, p=0.05). The mean age at reconstructive surgery for the comparison group was 9 years 2 months compared with a mean age of 8 years 10 months for the treatment group (t=−0.39, p=0.698).

DISCUSSION

Historically, emphasis has been given to adductor spasticity as a key cause of hip displacement in children with CP.[4–6] In turn, this has led to a focus on the need to reduce adductor spasticity and contracture and to improve the range of hip abduction. More recent work suggests that lack of functional ambulation affects the growth and development of the proximal femur.[24] It may be the excessive anteversion and coxa valga that is partly responsible for the very high rates of hip displacement in children in GMFCS levels IV and V, rather than adductor spasticity. This theory also goes a long way to explaining the high failure rate of interventions designed to reduce spasticity in the hip adductors as well as the high failure rate of adductor release surgery in non-ambulant children (GMFCS levels IV and V). A recently published study has shown that the success rate of adductor surgery is predicted by GMFCS level and the type of adductor surgery is relatively unimportant.[25] The success rate of adductor surgery in ambulant children was high, 94% in GMFCS level II, dropping to 49% in GMFCS level III. However, adductor surgery had a very high failure rate in non-ambulant children, with a success rate of only 27% in GMFCS level IV and 14% in GMFCS level V. It is thought that this is because of secondary changes in the hip joint that occur owing to lack of weight bearing and ambulation.

In the randomized clinical trial, of which this study is a subset, the reduction in hip displacement in the treatment group was small and disappointing. However, fewer children from the treatment group exited the study and progressed to surgery during the study period than from the comparison group. It was not clear if these decisions were based entirely on differences in migration percentage or whether perceived differences in adductor spasticity and passive hip abduction may have contributed.[18] A legitimate question in this long-term study was, therefore, what the subsequent need for surgery would be for these children, as well as the long-term status of their hips.

This study has shown no long-term benefit from 3 years of non-operative treatment, including 6-monthly injections of BoNT-A and abduction bracing in reducing the need for surgery or enhancing hip development. The requirement for both preventive and reconstructive surgery in both groups was very high (Fig. 3).

The differences in age between the groups at both preventive and reconstructive surgery were not significant. Children in the treatment group were, on average, 18 months older than those in the comparison group when they had preventive surgery. The literature on the effects of age at preventive surgery is not conclusive but some studies suggest that preventive surgery may be more successful at earlier ages. Therefore, age at preventive surgery, if anything, favours the outcome for the comparison group. However, children in the comparison group were a mean of 5 months older than those in the treatment group at the time of reconstructive surgery. Literature on the effects of age at reconstructive surgery is even more inconclusive. Some authorities have suggested that older age at reconstructive surgery is advantageous to outcome.[26]

Hip morphology at long-term follow-up was satisfactory in most hips in both groups. Satisfactory hip morphology, defined as MCPHCS grades I to III, was found in 41 of 46 hips in the treatment group and 44 out of 46 hips in the comparison group (Fig. 2 and Appendix SII).[22] However, there were 'failures' in both groups, with five grade IV hips in the treatment group and two grade IV hips in the comparison group. The failures were the result of scoliosis and pelvic obliquity in three children, windswept hip deformity in one child, and refusal to proceed with reconstructive surgery in another child.[6,27] No hips from either group are currently painful or have required salvage surgery.

The strengths of this study were adherence to a standardized management protocol during the RCT and open follow-up, and the use of valid and reliable measures of hip morphology. Weaknesses of the study include the lack of a comparison group during long-term follow-up and the lack of functional outcome measures, activity, and participation. Although the sample size of this study may be considered small, it represents a complete subset of participants in a well-designed RCT who subsequently had hip displacement managed by a standardized surveillance and surgical protocol. Although a larger sample may have decreased the confidence interval around our finding of 0.7% difference in migration percentage between the groups, it was not possible in a long-term outcome study of this nature.

The conclusion from this study is that in children with bilateral spastic CP, satisfactory hip development can be obtained in most hips at skeletal maturity by careful hip surveillance, followed by preventive and reconstructive surgery.[6,10,12,27] A previous period of preventive treatment with BoNT-A and bracing neither reduces the requirement for surgery, nor the complexity of the surgery, nor does it enhance the morphology of hip development at long-term follow-up. It remains to be seen if other non-operative treatments can reduce hip displacement in children with CP. Long-term follow-up to skeletal maturity is required to ascertain the true impact of early management.

SUPPORTING INFORMATION

The following additional material may be found in the online version on this article.

Appendix SI: Surgical protocols for adductor release and bony reconstruction.

Appendix SII: Melbourne Cerebral Palsy Hip Classification Scale (MCPHCS).

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