Safety of Botulinum Toxin Type A for Children With Nonambulatory Cerebral Palsy

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OBJECTIVE: To determine safety of intramuscular botulinum toxin A (BoNT-A) injections to reduce spasticity and improve care and comfort of nonambulatory children with cerebral palsy (CP).

METHODS: Nonambulatory children with CP were randomly allocated to receive either BoNT-A (n = 23) or sham procedure (n = 18) in Cycle 1. In Cycle 2, the BoNT-A group received a second episode of BoNT-A (n = 20) and sham group received their first episode of BoNT-A (n = 17). A pediatric rehabilitation specialist masked to group allocation graded each adverse event (AE) according to system, severity (mild, moderate, serious, sentinel) and causality (unlikely/unrelated; possible; probable/definite).

RESULTS: There was no difference for all moderate/serious AEs between the BoNT-A and sham/control groups in either Cycle 1 (incident rate ratio = 1.30, 95% confidence interval = 0.43–4.00; \( P = .64 \)) or Cycle 2 (incident rate ratio = 0.72, 95% confidence interval = 0.30–1.75; \( P = .47 \)). In Cycle 2, 1 serious, 3 moderate (single-episode group), and 24 mild (single-episode group n = 10; 2 episode group n = 14) AEs were probably/definitely related to BoNT-A.

CONCLUSIONS: Children receiving BoNT-A were at no greater risk of moderate/serious AEs compared with a sham control procedure. There was no increased risk of moderate/serious AEs between one and two episodes of BoNT-A.

WHAT’S KNOWN ON THIS SUBJECT: Children with marked cerebral palsy (CP) are considered at greater risk of adverse events (AEs) after intramuscular injections of BoNT-A. To date there has been no randomized controlled trial examining safety of intramuscular BoNT-A injections in children with marked CP.

WHAT THIS STUDY ADDS: Children with nonambulatory CP had no greater risk of moderate or serious AEs after intramuscular injections of BoNT-A compared with a sham/control group. There was no greater risk of AEs for children receiving 2 compared with 1 episode of BoNT-A.
Botulinum toxin A (BoNT-A) is regularly used for goal-directed focal management of spasticity and dystonia for children with cerebral palsy (CP). Intramuscular BoNT-A injections decrease spasticity locally by interfering with cholinergic transmission at the neuromuscular junction. In a double-blind randomized controlled trial (RCT), BoNT-A has been shown to reduce pain and improve care and comfort goals for nonambulatory children with CP. In 2008, the safety of BoNT-A for children with CP was called into question by the US Consumer Advocacy Group Public Citizen, which petitioned the US Federal Drug Administration to increase label warnings for commercially available BoNT-A products. At this time, 9 deaths had been reported in children with CP under 16 years of age after intramuscular injections of BoNT-A. Concerns had been raised after BoNT-A injections in children with neuromuscular conditions and subsequent adverse events (AEs). The temporal association resulted in a black box warning appearing on labels of BoNT-A (Dysport and Myobloc [Botox Allergan PLC, Dublin, Ireland]) of the risk of spread of BoNT-A beyond the injection site, with associated risks of dysphagia, aspiration, pneumonia, and death.

Gaining a clear understanding of the incidence of AEs in children with CP after BoNT-A is complex. Because of the heterogenous nature of CP, consideration must be given to comorbidities and level of impairment. A population-based study demonstrated a 10-fold increase in comorbidities for children classified as Gross Motor Function Classification System (GMFCS) Level V compared with Level I. Seventy-three percent of total reported comorbidities occurred in the GMFCS V group despite representing only 34% of the population. A retrospective audit of AEs after BoNT-A showed an increase in the number of AEs according to GMFCS level. The authors articulated concerns about administration of BoNT-A to children with preexisting respiratory and swallowing difficulties. Two systematic safety reviews highlighted variability in reporting of AEs secondary to a lack of consistent definitions, reporting methodology, indications, preparations, dosing, dilution, sedation, and injection techniques. Our recent randomized, double-blinded sham-controlled trial supported efficacy of intramuscular injections of BoNT-A for nonambulatory children with CP (GMFCS IV and V) to improve comfort and reduce carer burden. Children who received BoNT-A compared with the sham procedure had significantly and clinically greater gains in performance of and satisfaction with care and comfort goals (Canadian Occupational Performance Measure; mean difference of 2.2, 95% confidence interval [CI] 0.8–3.5; P = .02). Children receiving BoNT-A had significantly less pain compared with baseline and improved reported quality of life. This study now investigates whether intramuscular injections of BoNT-A increased the risk of AEs for children with CP classified as GMFCS IV or V compared with a sham/control group and whether there was an increase in AEs with repeated BoNT-A injections.

METHODS
Design and Procedure
This study was conducted at a pediatric tertiary referral center for children with CP in Brisbane, Australia, between March 2009 and August 2011. This study was undertaken in 2 cycles. Cycle 1 was a double-blind, randomized sham/control trial. Children were randomized using concealed allocation to either receive intramuscular BoNT-A injections or sham procedure. In Cycle 2, all children received BoNT-A treatment. Participants, parents and assessors were blinded to group allocation which was not revealed until after completion of Cycle 2. Full ethical approval and trial registration were obtained and study methodology is reported in detail elsewhere.

Participants
Recruitment was undertaken through a statewide tertiary referral service. Eligibility was confirmed by a pediatric rehabilitation specialist. Children were eligible for inclusion if they had (1) a confirmed diagnosis of CP and were aged 2 to 16 years, (2) were GMFCS IV or V, (3) had spasticity affecting comfort or carer burden. Children were ineligible if they had (1) body weight <10 kg, (2) received intramuscular BoNT-A injections or orthopedic surgery within 6 months of study entry, or (3) change to spasticity medication within 2 months of study entry.

Interventions
Assessment of hypertonicity and parent/caregiver care and comfort goals were performed to determine muscle groups for BoNT-A injection before randomization in Cycle 1. On entry to the trial, a comorbidity assessment was completed by 1 of 3 rehabilitation specialists (P.E., K.M., T.C.; Supplemental Appendix 1). On the date of injections, an assessment of health status was completed by study nurses (Supplemental Appendix 1).

Injection Procedure
Topical analgesia (EMLA cream) was applied 1 hour before and intranasal fentanyl (1.5 mcg/kg of 300 mcg/mL solution) was administered 10 minutes before the procedure. Dose range of BoNT-A was 0.5 U to 4 U Botox (Allergan PLC) per muscle with a maximum mean dose of 12 U Botox per kg/body weight (maximum total dose 400 U). Dilution of Botox was 100 U per mL for all injections. Blinding was maintained by the use of a screen blocking view of the procedure from the monitoring nurse, parent, and child. Families were not required to pay for any medication...
associated with the trial. All trial medications were funded through the Queensland Pediatric Rehabilitation Service, Royal Children’s Hospital, Brisbane, Australia.

Sham Procedure

Topical analgesia (EMLA cream) was applied 1 hour before and intranasal saline was administered 10 minutes before the sham procedure. A screen was used to obscure vision from the sham injecting procedure. The sham group did not receive any BoNT-A injections in Cycle 1. All sites were covered with adhesive dressings and tincture of iodine to mask the sham injection site.

Reporting of AEs

An AE is defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medication, whether or not considered related to the medication. In this study, AEs were recorded during the injection procedure and at 2, 4, and 16 weeks after each procedure on a standardized questionnaire by a nurse (V.W., J.L.) masked to group allocation (Supplemental Appendix 2). A pediatric rehabilitation specialist (P.E.) experienced in use of BoNT-A and masked to group allocation independently graded each AE according to system, severity, and causality. For causality, events were graded as unrelated or unlikely/possibly, or as probably/definitely related to the intervention procedure (defined in Fig 1). These were attributed on the basis of patient history, onset or duration of symptoms, contact history of similar symptoms, and consistency with previous literature of common AEs thought to be related to intramuscular BoNT-A injections. For severity, events were graded as mild, moderate, serious, or sentinel (defined in Fig 1). An external safety officer was notified of any serious or sentinel events within 72 hours. In the case of a sentinel event, the study would be suspended until reviewed by the independent safety officer with expedited reporting to the ethics committee.

Sample Size

The sample size of 40 participants was initially calculated for the parent trial considering efficacy of intramuscular injections of BoNT-A for nonambulatory children with CP to improve comfort and reduce carer burden. When considering the size of the between-group difference detectable for the primary outcome for this study (moderate/serious AEs), it was assumed that 10% of BoNT-A participants would have a serious AE. With \( \alpha = 0.05 \), there was 80% power to detect a fivefold difference in moderate/serious AE rates between groups (ie, to detect a 10% rate in the control group of \( \leq 2\% \)).

Statistical Analysis

Outcome variables were summarized as means and SD if continuous and as frequency (percentage) if categorical. The association between treatment group and number of events in Cycles 1 and 2 was investigated using Poisson regression with robust standard errors. Group (BoNT-A/control) was entered as the main effect. The association between health status risk factors (epilepsy, gastrostomy, hydrocephalus) and the incidence of total and related AEs was investigated using Poisson regression with robust standard errors. Model assumptions were tested with the deviance goodness-of-fit statistic. Results are presented as incident rate ratio (IRR) and 95% CI. Analysis was undertaken using Stata statistical software V12.0 (StataCorp, College Station, TX).

RESULTS

Study recruitment and follow-up for both cycles of the study are reported in Fig 2. Seventy-seven children were eligible for inclusion. Forty-one were randomized in Cycle 1 to the sham/control (n = 18) or BoNT-A group (n = 23). Thirty-seven children completed Cycle 2 including 20 children (87%) who received BoNT-A in Cycle 1 with a repeat episode of BoNT-A in Cycle 2. In the BoNT-A group, 1 child in Cycle 1 did not proceed to Cycle 2 because of concerns with AEs (patient identification no. [ID5] floppy, no vocalization, increased drooling: Supplemental Table 5), and 2 exited the study because of progression to orthopedic surgery (ID30, 38, Supplemental Table 5). In the sham group, 1 child exited the study before Cycle 2 because of progression to orthopedic surgery (ID3, Supplemental Table 6). Seventeen children (94%) received their first intratrial episode of BoNT-A in Cycle 2. Efficacy of clinical outcomes in Cycle 1 have been reported elsewhere.

Safety Results in Cycle 1

All children in both groups completed follow-up for Cycle 1. Patient...
demographics, baseline characteristics, and comorbidities for each group are reported in Table 1. Groups were demographically similar at baseline; however, the sham group had a greater proportion of children with epilepsy and using oral medications for spasticity (Table 1). In Cycle 1, the mean total dose of BoNT-A was 10.5 U Botox per kilogram body weight (SD ± 2.5 U/kg) and the dilution was standardized at 100 U Botox per 1 mL normal saline (Table 1).

Adverse events are summarized in Table 2 and reported individually in Supplemental Tables 5 and 6. Adverse events by severity are displayed in Fig 3.

The overall incidence of moderate/severe AEs was similar between groups (IRR = 1.30, 95% CI: 0.43–4.00; P = .64). There was little difference between groups in incidence of moderate/severe events that were related to the BoNT-A/fentanyl procedure (IRR = 0.78, 95% CI: 0.12–5.15; P = .80). There were a small number of serious AEs, 2 in 1 child (<1%) in the sham group and 3 in 3 children (13%) in the BoNT-A group. No serious AE was independently classified as being either definitely or probably related to the BoNT-A/fentanyl intervention. For moderate events, 4 AEs were reported in 3 children (17%) in the sham group and 7 in 5 children (22%) in the BoNT-A group.

Moderate/severe events were similar between groups. Events classified as having a definite/probable relationship to the intervention included 1 in the sham group (ID21: focal seizures on night of procedure) and 2 in the BoNT-A group (ID30: weakness, gagging, vomiting, constipation, temperature, seizure; ID41: increased saliva at 1 week and increased seizures at 2 weeks, see Supplemental Tables 5 and 6).

Overall, in Cycle 1, there were a total of 33 mild, moderate, or serious AEs reported for 23 children (56% of children) across both groups. Of these, 8 AEs occurred in 5 children (27%) in the sham/control group and 25 AEs in 18 children (78%) in the BoNT-A group. Although children receiving BoNT-A did not have a statistically significantly greater incidence of mild, moderate, or serious AEs, they were 2.45 times as likely to have any AE as a child in the sham group (IRR = 2.45, 95% CI: 0.96–6.20; P = .06) (Table 3). Most of this difference is attributable to a large number of bruises related to the injection procedure in the BoNT-A group that were classified as mild events. There were 2 mild AEs reported in 2 children (11%) in the sham group and 15 mild AEs in 13 children in the BoNT-A group (57%).
In Cycle 2, the mean total dose of BoNT-A was 10.8 Botox per kilogram body weight (SD ± 2.4 U/kg) for the 2 BoNT-A episode group and 10.5 U/kg (SD ± 1.9U/kg) for the single-episode BoNT-A group with the dilution standardized at 100 U Botox per 1 mL normal saline (Table 1). One child received a maximum dose of 14 U/kg, exceeding trial protocol.

The incidence of moderate/serious AEs was similar between groups (IRR = 0.72, 95% CI: 0.30–1.75; P = .47). There were 2 serious AEs in 2 children (12%) in the single-episode BoNT-A group and 4 serious AEs in 2 children (10%) receiving repeat injections. One serious AE (ID10) was thought to be definitely/probably related to the BoNT-A/ fentanyl intervention from the single-episode group. There were 11 moderate AEs in 8 children (47%) in the single BoNT-A group and 7 moderate AEs in 6 children (30%) in the repeat BoNT-A group. Of these events, 3 were considered to be definitely/probably related, all of which occurred in the single-injection group (ID7 hallucinating, teary, upset within timing of fentanyl; ID25 increased drooling 1–4 weeks; ID29 decreased head control, increased saliva, urinary incontinence at 2–10 days; see Supplemental Tables 5 and 6).

There were a total of 49 AEs in 27 children (73%) across both groups. Of these, 23 AEs occurred in 12 children (71%) in the single-episode BoNT-A group (n = 17) and 26 AEs in 15 children (75%) in the repeat-BoNT-A group (n = 20; IRR = 0.96, 95% CI: 0.52–1.79; P = .90).

There were 10 mild AEs in 7 children (41%) in the single BoNT-A injection group and 15 mild AEs in 13 children (65%) in the repeat-injection group. Eighteen mild AEs from both groups (75%) were definitely related to the intervention (bruising).

There was 1 child from the repeat BoNT-A episode group who had repeated serious AEs, 1 in Cycle 1 and 3 in Cycle 2 (ID31). These AEs were classified as unlikely/unrelated to the intervention. One child from the single-injection group had repeated moderate AEs, 2 in Cycle 1 (sham/control group) and 1 in Cycle 2 (ID32). These events were repeated lower respiratory tract infections classified as unlikely related to the intervention.

Association Between Health Status Risk Factors and Incidence of AEs

Children with simple or complex epilepsy did not have significantly greater risk of moderate/serious AEs compared with no epilepsy after either 1 or 2 injections of BoNT-A (Table 4). Similarly, the presence of hydrocephalus posed no significantly greater risk of moderate/serious AEs after either 1 or 2 injections of BoNT-A. Children with a gastrostomy were
1.9 and 5.4 times more likely to have a moderate/serious AE after 1 and 2 injections of BoNT-A, respectively.

**Longer-term Follow-up**

No child died while participating in the study. All children who participated in the trial have subsequently been followed up posttrial through our clinical service. Since study completion in August 2011 to November 2014, 7 of the 41 children have died. Two children were in the single-episode group and 4 were in the 2-episode group. These deaths were all reviewed for any relationship to BoNT-A treatment and comorbidities. One death had a temporal association with BoNT-A. This child received sham treatment in Cycle 1. After Cycle 1, BoNT-A injections were administered at 6 months post-follow-up with orthopedic surgery. Subsequent BoNT-A injections occurred at 20 months after surgery and then another episode 7 months thereafter. This child (ID3) died 15 days after the third posttrial episode of BoNT-A. The death was associated with prolonged status epilepticus. The child was known to have epilepsy. The medical team treating this child postulated subtherapeutic dosing of anticonvulsants as causal. This death was reported to and reviewed by the study external safety committee. For the 6 other children who died poststudy, causes of death included respiratory complications (n = 3); gastrointestinal tract hemorrhage.

![Figure 3](image-url)

**TABLE 2** AEs for Group Allocation, AE by System and Patient ID Number

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>AE Type</th>
<th>Sham/Control (n = 18)</th>
<th>BoNT-A (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 wk</td>
<td>Serious 0</td>
<td>R = ID32, 35; N = ID21</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>Moderate 3/3</td>
<td>S = ID16; G = ID28</td>
<td>5/4</td>
</tr>
<tr>
<td></td>
<td>Mild 2/2</td>
<td>S = ID36; G = ID29</td>
<td>15/13</td>
</tr>
<tr>
<td>≤4 mo</td>
<td>Serious 2/1</td>
<td>R = ID36; G = ID36</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate 1</td>
<td>R = ID32</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>Mild 0</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle 2</th>
<th>AE Type</th>
<th>Sham/Control BoNT-A ×1 (n = 17)</th>
<th>BoNT-A ×2 (BoNT-A Group) (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 wk</td>
<td>Serious 2/2</td>
<td>N = ID10, 12</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate 8/8</td>
<td>G = ID21</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>Mild 10/7</td>
<td>G = ID25; G = ID16; B = ID2, 7, 12, 16, 20, 25, 42</td>
<td>14/12</td>
</tr>
<tr>
<td>≤4 mo</td>
<td>Serious 0</td>
<td></td>
<td>3/2</td>
</tr>
<tr>
<td></td>
<td>Moderate 3/2</td>
<td>R = ID7, 25; N = ID7</td>
<td>3/3</td>
</tr>
<tr>
<td></td>
<td>Mild 0</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

B, bruising; E, renal; G, gastroenterological; N, neurologic; R, respiratory; S, systemic.
(n = 1); complex cyanotic congenital heart disease (n = 1), and renal failure (n = 1). There were no formal autopsies, and these were based on clinical judgment by their pediatric rehabilitation specialist and neurologist.

**DISCUSSION**

In the first cycle of this double-blind RCT of intramuscular injections of BoNT-A compared with a sham/control group with independent evaluation of AE severity and causality, there were no statistically significant differences between groups in the rate of moderate/severe AEs for nonambulatory children with CP. Children in the BoNT-A group were almost 2.5 times more likely to have any AE; however, this difference is due to a greater number of mild AEs in the BoNT-A group. Furthermore, in Cycle 2 when comparing 1 to 2 episodes of BoNT-A treatment in trial conditions with the same unbiased, blinded evaluation of AE severity and causality, there was a greater incidence of moderate/severe AEs in the single-injection group considered to be related to the intervention. Results indicate that there was no added risk of having a second episode of BoNT-A after a 6-month period (the mean number of related moderate/severe AEs per child was 0.13 after 1 injection and 0.10 after 2 injections).

To our knowledge, this is the first double-blind sham/controlled trial of BoNT-A injections with independent evaluation of AE severity and attribution of causality in nonambulatory children with CP. Verbal probability expressions have been reported extensively in the literature and are often used in discussions with patients because they are easily understood in terms of risk. Independent evaluation of pretrial comorbidities for both treatment and control groups has not previously been undertaken prospectively in a double-blind trial of BoNT-A in CP. Prospective evaluation of AEs has been reported using clinical audits with similar reporting of significant comorbidities in children with CP classified GMFCS IV and V. In a retrospective safety review study, O’Flaherty reported a higher incidence of health issues in a 1-month period preceding BoNT-A injections compared with 1 month after BoNT-A in children classified GMFCS IV and V (95/316 (30%) and 56 of 255 children (22%)). Although our sham/control group had a slightly greater proportion of children with epilepsy and regular use of spasticity medication at baseline, this difference was not statistically different.

Consistent with other RCTs of BoNT-A, further follow-up of the sample postrtrial identified some children who died. Significant morbidity and mortality are associated with nonambulatory CP and comorbid epilepsy; however, overall life expectancy, particularly for children with severe disabilities, has improved over a 20-year period. In a prospective cohort of 6277 children with CP, those with severe CP represented 18% of the person-years but 69% of deaths. Another cross-sectional survey of the health status of children with CP classified GMFCS V (n = 122) who had a feeding tube found that the group that used the most health care resources had the highest rate of respiratory problems and poorest Global Health scores. A retrospective review of CP data from California (513 children) reported reduced mobility and feeding ability as factors associated with increased risk for death. When reviewing the children who participated in this study, clinicians believe that selection of eligible patients with pain and comfort goals identified the most frail and medically complex children. The present study was a carefully conducted RCT that studied a high-risk population and identified no additional risk with BoNT-A and fentanyl compared with a control group and no additional risk from a second episode of BoNT-A injections. A potential limitation for interpretation of the study is that AEs were related to the combination of BoNT-A and fentanyl, and it was not possible to differentiate the relative contribution of each on AEs. Fentanyl is considered to be a safe and effective analgesic; however, it cannot be discounted that fentanyl may have contributed to AEs in the study.

One potential limitation of our study is that it was powered to evaluate efficacy of BoNT-A to improve care and comfort goals in nonambulatory children with CP and may have been underpowered to determine differences in incidence of moderate/severe AEs between groups. However, the rate difference between groups was not large, with a point estimate of between-group difference...
Sham only (n = 18)

<table>
<thead>
<tr>
<th>No. of Injections</th>
<th>All Events</th>
<th>Moderate/Serious Events</th>
<th>Related Moderate/Serious Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>IRR (95% CI); P</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Sham only (n = 18)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex (n = 10)</td>
<td>0.20 (0.42)</td>
<td>1.00</td>
<td>0.20 (0.42)</td>
</tr>
<tr>
<td>Simple (n = 5)</td>
<td>0.40 (0.89)</td>
<td>2.00 (0.22–18.22)</td>
<td>0.40 (0.89)</td>
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<tr>
<td>Absent (n = 3)</td>
<td>1.33 (1.53)</td>
<td>6.67 (1.25–35.67)</td>
<td>0.67 (1.15)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Absent (n = 15)</td>
<td>0.40 (0.91)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Present (n = 3)</td>
<td>0.67 (0.58)</td>
<td>1.67 (0.41–6.63)</td>
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<tr>
<td>Gastronomy</td>
<td>Absent (n = 6)</td>
<td>0.67 (1.21)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Present (n = 12)</td>
<td>0.33 (0.65)</td>
<td>0.50 (0.09–2.87)</td>
</tr>
<tr>
<td>1 injection (n = 40)</td>
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<tr>
<td>Epilepsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex (n = 21)</td>
<td>1.38 (1.32)</td>
<td>1.00</td>
<td>0.67 (0.91)</td>
</tr>
<tr>
<td>Simple (n = 8)</td>
<td>0.88 (0.64)</td>
<td>0.63 (0.34–1.19)</td>
<td>0.38 (0.52)</td>
</tr>
<tr>
<td>Absent (n = 11)</td>
<td>1.09 (0.83)</td>
<td>0.79 (0.44–1.43)</td>
<td>0.55 (0.69)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Absent (n = 31)</td>
<td>1.26 (1.12)</td>
<td>1.00</td>
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<tr>
<td></td>
<td>Present (n = 9)</td>
<td>1.00 (1.00)</td>
<td>0.79 (0.38–1.80)</td>
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<tr>
<td>Gastronomy</td>
<td>Absent (n = 14)</td>
<td>0.71 (0.61)</td>
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</tr>
<tr>
<td></td>
<td>Present (n = 26)</td>
<td>1.46 (1.2)</td>
<td>2.05 (1.19–3.51)</td>
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<tr>
<td>2 injections (n = 20)</td>
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<td>Epilepsy</td>
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<tr>
<td>Complex (n = 11)</td>
<td>1.18 (0.75)</td>
<td>1.00</td>
<td>0.55 (0.82)</td>
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<tr>
<td>Simple (n = 3)</td>
<td>2.00 (2.65)</td>
<td>1.69 (0.46–6.25)</td>
<td>1.00 (1.73)</td>
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<td>Absent (n = 8)</td>
<td>1.17 (1.17)</td>
<td>0.99 (0.43–2.28)</td>
<td>0.33 (0.52)</td>
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<tr>
<td>Hydrocephalus</td>
<td>Absent (n = 16)</td>
<td>1.44 (1.31)</td>
<td>1.00</td>
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<tr>
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<td>Present (n = 4)</td>
<td>0.75 (0.50)</td>
<td>0.52 (0.25–1.08)</td>
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<tr>
<td>Gastronomy</td>
<td>Absent (n = 7)</td>
<td>1.14 (0.90)</td>
<td>1.00</td>
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<tr>
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<td>Present (n = 13)</td>
<td>1.38 (1.39)</td>
<td>1.21 (0.56–2.62)</td>
</tr>
</tbody>
</table>

Effect estimates presented as incidence rate ratio (IRR) and 95% confidence interval. NC, not calculable; —, no reported AEs and IRRs not calculated.

for moderate/serious events in Cycle 1 only 30% higher in the BoNT-A group than control group. When only related events were considered, participants in the control group had a similar incidence of moderate/serious AEs compared with BoNT-A participants. These results suggest that there may be only a relatively small difference in moderate and serious related events in both study cycles, although a larger trial to confirm this would be beneficial. Our initial sample size calculations may have underestimated the actual number of moderate/serious AEs. This is because previous studies have not reported AEs in the same framework as this study (ie, not reporting on a control group; not grading by likely relationship to intervention). We observed a mean of 0.58 events per child after their first BoNT-A injection. Post hoc power calculations indicated that there was 80% power to detect a statistically significant between-group difference if the rate of moderate/serious AEs in the control group was ≤0.17. Further exploration of the relationship between comorbidities and increased risk of AEs suggested that the presence of a gastrostomy may increase the risk of AEs after BoNT-A. These findings are in line with previous reports of increased risk of respiratory AEs for children with pseudo-bulbar palsy17,22; however our results should be viewed with caution because of the small sample size for this secondary analysis. In addition, a longer-term prospective trial with repeated episodes of BoNT-A in this patient group is required.

CP remains an incurable condition and as such, treatments offered are for symptom control. For children with nonambulatory CP, considered treatment options are usually based on reducing pain, improving health status and quality of life, and reducing carer burden. A range of generalized medical treatments (eg, oral medications, intrathecal baclofen), focal targeted treatments (eg, orthopedic surgery), and therapy interventions are regularly offered for...
symptom control targeting care and comfort goals. Many of these treatments pose significant risk of AEs but remain part of the clinicians’ toolbox. As part of clinicians’ obtaining a valid consent to treatment, families need to consider balancing the risk and benefit. The ethics of withdrawing real therapeutic options to a group with multiple complexities also needs careful consideration. There is an increased risk in the incidence of mild AEs; however, this may be considered acceptable risk given the meaningful changes in care and comfort goals. Our recommendation is that intramuscular injections of BoNT-A for nonambulatory children with CP can lead to meaningful changes in care and comfort goals but needs to consider relative risk of moderate/severe AEs that may be associated with other comorbidities. Children who have gastrostomies may be at a higher risk of serious AEs, but longer-term prospective evaluation of safety with repeated episodes is needed. Children who have gastrostomies may be at a higher risk of serious AEs, but longer-term prospective evaluation of safety with repeated episodes is needed. Children who have gastrostomies may be at a higher risk of serious AEs, but longer-term prospective evaluation of safety with repeated episodes is needed.

CONCLUSIONS

In a double-blind sham/controlled trial and subsequent follow-up of 1 versus 2 episodes of BoNT-A to address care and comfort goals, there was no evidence of an increased risk of moderate/serious AEs in nonambulatory children with CP receiving intramuscular injections of BoNT-A administered with fentanyl. There is an increased risk in the incidence of mild AEs; however, this may be considered acceptable risk given the meaningful changes in care and comfort goals. Children who have gastrostomies may be at a higher risk of serious AEs, but longer-term prospective evaluation of safety with repeated episodes is needed.

Our recommendation is that intramuscular injections of BoNT-A for nonambulatory children with CP can lead to meaningful changes in care and comfort goals but needs to consider the relative risk of moderate/severe AEs that may be associated with other comorbidities.

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ABBREVIATIONS

AE: adverse event
BoNT-A: botulinum toxin A
CI: confidence interval
CP: cerebral palsy
GMFCS: Gross Motor Function Classification System
ID: identification number
IRR: incident rate ratio
RCT: randomized controlled trial

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An error occurred in the article by Edwards et al, titled “Safety of Botulinum Toxin Type A for Children with Cerebral Palsy” published in the November 2015 issue of Pediatrics (2015;Vol 136(5): 895–904; doi:10.1542/peds.2015-0749). On page 901, under the heading Discussion, in column 2, on line 22, this reads: “In a retrospective safety review study, O’Flaherty reported”. This should have read: “In a prospective safety audit, O’Flaherty reported”.

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