Neuronox versus BOTOX for spastic equinus gait in children with cerebral palsy: a randomized, double-blinded, controlled multicenter clinical trial.
Clinical scenario

The mother brought her 4 years-old son to see me at cerebral palsy clinic for follow-up after treatment with oral antispastic drug (Diazepam(2) 1 tab oral bid) and home program stretching exercise and ambulation training. She complaint that her son still have spasticity both legs. And when he walked, he had equines and tip-toe gait.

I found that he had local spasticity at bilateral gastrocnemius muscles and I plan to use botulinum toxin-A injection to reduce spasticity, improve his gait and function.

Now we have new botulinum neurotoxin type A (Neuronox). Neuronox is cheaper than the other butulinum toxin-A that I ever used. But I suspected about it efficacy.

Clinical question

Is NEURONOX has as efficacy and safety as BOTOX for treatment of spasticity with cerebral palsy?

Type of question : Therapy

PICO model

P : Children cerebral palsy with spastic equinus foot
I : Botulinum neurotoxin type A injection
C : Botox and Neuronox
O : Reduce spasticity and improve gait and gross motor functional outcome
Background and rationale

Cerebral palsy (CP) is a disorder of movement and posture that results from a non progressive lesion or injury of the immature brain. Abnormal control of motor movement is the key defining feature of CP with muscle spasticity occurring in 88% of patient. Muscle spasticity can lead to fixed contractures, bony torsional abnormalities in the limbs and joint contracture. Equinus gait deformity is a common problem in CP, results from dynamic overactivity or spasticity of gastronemius-soleus muscle complex alone or in combination with other muscle controlling the ankle or from fixed contracture of the ankle. Equinus gait in CP can results in knee and ankle problems, abnormal motion during gait, impaired balance and proprioception and permanent foot deformities that may require multiple surgical intervention.

Botulinum neurotoxin type A (BoNT-A) has been widely used for the treatment of spastic gait in individuals with CP since 1993, when its use was first described. Its efficacy in reducing spasticity and improving ambulation in CP has been validated in many study. Numerous BoNT-A formulations are available, including BOTOX, Dysport, Xeomin and Neuronox. Neuronox, a newly manufactured BoNT-A has been approve for treatment if diseases such as blepharospasm, cervical dystonia, strabismus and CP. Although various BoNT-A products are available and prescribe for similar clinical purposes, equivalence of their efficacy and toxicity has not been confirmed.

Selection of the article

To search the article related to my question I decided to find a good randomized controlled trials of the botulinum toxin-A in treatment of spastic equinus gait in cerebral palsy. The type of study will be best fit to my question.

• Searching strategies:
1. First searched in Medline at National library of Medicine-Pubmed. The searching keywords were:
   - cerebral palsy AND spasticity the results showed 1253 articles.
   - #7 : Equinus foot the results showed 543 articles.
   - #9 : Botulinum toxin-A AND cerebral palsy the results showed 308 articles
   - #7 AND #9 the results showed 21 articles
   - #10 : Neuronox the results showed 5 articles
#9 AND #10 the result showed 1 article
2. Second search in Scopus

I searched by entering the key words: cerebral palsy AND spastic equinus, Neuronox AND Botox.

The article I chose was a randomized controlled trials. This matches well with my scenario because it has the same PICO model as of my patients.
Summary of the article

**Title**: Neuronox versus Botox for spastic equinus gait in children with cerebral palsy

**Authors**: KEEWOM KIM, HYUNG-IK SHIN, BUM SUN KWON, SANG JUN KIM, IL-YOUNG JUNG, MOON SUK BANG

**Source**: Developmental Medicine and Child Neurology; Mar 2011;53,3; Proquest Health and Medical complete pg.239

**Objective**: To evaluate the efficacy and safety of a newly manufactured butulinum toxin, Neuronox compared with Botox for the treatment of the spastic equinus gait in children with cerebral palsy

**Study design**: A randomized, double-blinded, controlled multicentre clinical trial

**Study setting**: Seoul National University hospital, Bundang Seoul National University Hospital and Ilsan Dongguk University Hospital between July 2007 and January 2009

**Method**:

Participants: Inclusion criteria
1. Children aged between 2 and 10 years diagnosis of cerebral palsy
2. Gross Motor function Classification system (GMFCS) level I, II or III
3. Tip-toeing gait

Exclusion criteria
1. history of anaphylactic reaction to botulinum toxin-A
2. bleeding tendency
3. history of treatment with anticonvulsants, neuroleptics, anticoagulants, aminoglycosides, muscle relaxants, parasympathetic antagonist or dopaminergics
4. previous surgery on the muscle or ligaments of lower extremities
5. fixed contracture of lower limb joints
6. severe athetoid
7. received the botulinum toxin-A injection less than 3 months
Sample size estimation:

The number of participants necessary to yield statistical power of 0.8 was estimated as 55 for each group, based on a previous study that reported a response rate of 41% with BOTOX injection. The study recruited 127 participants and the ITT group comprised 119 participants (60 in the NEURONOX group; 59 in the BOTOX group).

Enrollment and baseline evaluation:

- A total of 127 children were initially enrolled in the study
- 5 children excluded during screening test because of medical history or other medical conditions
- 122 children were randomly assigned to the BOTOX (n=61) or NEURONOX (n=61) group (1:1 ratio)
- After assignment, 1 in the NEURONOX group and 2 of BOTOX group refused the injection
- 119 children (60 in NEURONOX group; 59 in the BOTOX group) constituted the intention-to-treat (ITT) population
- The ITT population comprised 76 males and 43 females
- GMFM level I – 57, level II – 29 and level III – 33
- 21 – right hemiplegia, 19 – left hemiplegia and 79 – diplegia
- During evaluation period, 8-in NEURONOX group and 6-in BOTOX group withdrawn from the study because of adverse events
- After scheduled follow-up period, 2- in NEURONOX group and 2-in BOTOX group were excluded from the per-protocol population
- The per-protocol population comprised 50 in NEURONOX group and 51 in BOTOX group

Randomization and masking:

1. The participants were randomly assigned to either BOTOX or NEURONOX intervention
2. A block randomization method to generate a random code for each hospital with allocation ratio 1:1
3. The assigned code for participants was sealed until the scheduled follow-ups were completed for statistical analysis
4. The participants, the physician who administered the injection and the physician who evaluated the outcomes were all blinded to which drug was assigned.
5. An independent research nurse who prepared the drug vials for injection was aware of the assignment.
6. The vials were wrapped to conceal the contained BoNT-A from physician and participants.

Follow-up and observation:

Participant underwent screening by means of a basic blood laboratory test and an antibody assay for BoNT-A. Once the results were confirmed as normal, the physicians performed baseline evaluation (V1) and then BoNT-A injection.

Follow-up evaluations were carried out at 4(V2), 12(V3), and 24(V4) weeks after the intervention.

Definitions of outcomes

- Gait patterns were recorded by a video camera and analysed for outcome measures.
- Outcomes measures
  1. Physician’ Rating Scale (PRS) score
  2. Passive range of motion (PROM) of ankle dorsal/plantar flexion and knee flexion
  3. Gross Motor Function Measure 88 (GMFM-88) score
- **Primary outcome** – measure the response rate at V3, defined as the proportion of the individuals whose PRS score improved from V1 to V3 by 2 or more point.
- **Secondary outcome** – measure response rate at the V2 and V4 change in PRS score and GMFM score.

Safety measures

Adverse events were classified as mild, moderate, serious depending on the clinical severity, which was determined by the evaluating physician.

Laboratory tests, including basic blood test, antibody assay and urine analysis were performed at V1 and V4. The antibody test used the mouse protection bioassay based on the methods described by Sankhla et al.
Statistical analysis:

- The purpose of the study was to test the non-inferiority of NEURONOX compared to BOTOX.
- The non-inferiority margin was derived from historical placebo-controlled trials reporting response rate for BOTOX 21 to 36% point higher than placebo.
- The margin for the difference in response rate was set at 20% to ensure that NEURONOX was as effective as BOTOX.
- The one-sided 90% confidence interval (CI) of the difference in response rate at V3 between the NEURONOX and BOTOX group was within the -20% non-inferiority margin.
- Post-injection clinical outcomes compared with pre-injection values using the paired \( t \)-test or the Wilcoxon signed-rank test.
- The secondary outcomes compared at each visit between the two treatment group:
  - a two-sample \( t \)-test to assess the PRS score, PROM and GMFM.
  - \( x^2 \) test to assess the response rate and occurrence of adverse events.
- The all comparison between two groups considering serial evaluations was performed by calculating the area under curve.
- \( p \)-values less than 0.05 were considered statistically significant.
- Statistical power of 0.8.

Results:

Response rate in the physician’ Rating Scale

- ITT group analysis, the response rate at V3 was 48.3% in NEURONOX group and 49.2% in BOTOX group, the difference in response rate was -0.8% and lower bound of the 90%CI of the difference was -12.57% (Table II).
- Per-protocol group analysis, the response rate at V3 was 56% in NEURONOX group and 54.9% in BOTOX group, the difference in response rate was 1.10% and lower bound of the 90%CI of the difference was -11.58% (Table II).
- The response rates at V2 and V4 were not significantly difference between two groups \((V2,p=0.25;V4,p=0.46; x^2 \) test\).
- The area under curve for the PRS score were not statistically difference between two groups \((p=0.96; \text{t}-\text{test}; \text{Fig.2})\).
The passive range of motion

- The difference in PROM between the groups was not significant at each visit (V2, \( p=0.32 \); V3, \( p=0.66 \); V4, \( p=0.90 \); two sample \( t \)-test)
- The overall serial measurements (\( p=0.56 \); \( t \)-test of area under curve)

Gross Motor Function Measure

- GMFM scores increased significantly at all follow-up visit
- The NEURONOX group showed mean increases of 2.14 at V2, 3.77 at V3, and 4.76 at V4
- The BOTOX group showed mean increases of 2.65 at V2, 5.25 at V3, and 6.63 at V4 (\( p<0.01 \) for all longitudinal analysis)
- The summary measure for the serial evaluations of the GMFM score using the area under curve did not reveal a significant difference between the NEURONOX and BOTOX groups (\( p=0.16; t \)-test)
- Comparisons at each visit revealed no significant difference in the change in GMFM scores at V2 (\( p=0.41 \); two-sample \( t \)-test)
- At V3 and V4 the BOTOX group showed a larger increased in GMFM scores than the Neuronox group (\( p=0.03 \) and 0.05 respectively; two-sample \( t \)-test) in the ITT Safety measures

Adverse events

- 26 mild adverse events (13 in NEURONOX group and 13 in BOTOX group)
- 8 moderate adverse events (2 in NEURONOX group and 6 in BOTOX group)
- No severe adverse event
- No participants showed a positive antibody assay against BoNT-A
- The frequency of adverse events was not significantly different between NEURONOX and BOTOX groups (\( p=0.97; x^2 \) test)
<table>
<thead>
<tr>
<th>Items</th>
<th>Neuronox (n=60)</th>
<th>BOTOX (n=59)</th>
<th>Total (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (66.67)</td>
<td>36 (61.02)</td>
<td>76 (63.87)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (33.33)</td>
<td>23 (38.98)</td>
<td>43 (36.13)</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>4.42 (1.93)</td>
<td>4.24 (2.22)</td>
<td>4.33 (2.07)</td>
</tr>
<tr>
<td>Body weight (kg), mean (SD)</td>
<td>16.83 (4.17)</td>
<td>16.34 (4.86)</td>
<td>16.58 (4.51)</td>
</tr>
<tr>
<td>Previous BoNT-A injection, n (%)</td>
<td>35 (58.33)</td>
<td>29 (49.15)</td>
<td>64 (53.78)</td>
</tr>
<tr>
<td>GMFCS level, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>29 (48.33)</td>
<td>28 (47.46)</td>
<td>57 (47.90)</td>
</tr>
<tr>
<td>II</td>
<td>16 (26.67)</td>
<td>13 (22.03)</td>
<td>29 (24.37)</td>
</tr>
<tr>
<td>III</td>
<td>15 (25.00)</td>
<td>18 (30.51)</td>
<td>33 (27.73)</td>
</tr>
<tr>
<td>Type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemiplegia</td>
<td>10 (16.67)</td>
<td>11 (18.64)</td>
<td>21 (17.65)</td>
</tr>
<tr>
<td>Left hemiplegia</td>
<td>9 (15.00)</td>
<td>10 (16.95)</td>
<td>19 (15.97)</td>
</tr>
<tr>
<td>Diplegia</td>
<td>41 (68.33)</td>
<td>38 (64.41)</td>
<td>79 (66.39)</td>
</tr>
</tbody>
</table>

BoNT-A, botulinum neurotoxin type A; GMFCS, Gross Motor Function Classification System.
Figure 1: Study flowchart. A total of 127 participants were enrolled; 119 underwent the intervention to make up the intention-to-treat (ITT) population and 101 completed the study without violation of protocol to make up the per-protocol (PP) population. Eight individuals in the Neuronox group were excluded after the intervention, of whom one experienced an adverse event, two retracted their consent, three did not attend the scheduled follow-up, and two were classified as protocol violators. Six individuals in the BOTOX group were excluded after the intervention, of whom one was excluded because of a drug-related adverse event (muscle weakness), four retracted their consent, and one did not attend the scheduled follow-up. Two individuals in each group were excluded after final evaluation because of violation of the study protocol.

<table>
<thead>
<tr>
<th>Analysis set</th>
<th>Participant number</th>
<th>Response rate in Neuronox group, n (%)</th>
<th>Response rate in BOTOX group, n (%)</th>
<th>Difference in response rate (95% CI)</th>
<th>90% lower limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>119</td>
<td>29/50 (48)</td>
<td>29/59 (49)</td>
<td>-0.82% (-18.78 to 17.14%)</td>
<td>-12.57%</td>
</tr>
<tr>
<td>PP</td>
<td>101</td>
<td>29/50 (56)</td>
<td>29/51 (58)</td>
<td>1.10% (-15.29 to 20.48%)</td>
<td>-11.58%</td>
</tr>
</tbody>
</table>

ITT, intention to treat; PP, per protocol; CI, confidence interval.
Conclusion:

The outcomes of NEURONOX, based on physician's rating scale proved to be as effective and safe as those of BOTOX for the treatment of spasticity in individuals with cerebral palsy.
Critical appraisal of the article

General step for selection of the article

Journal:


Title:

Neuronox versus BOTOX for spastic equinus gait in children with cerebral palsy: a randomized, double-blinded, controlled multicentre clinical trial

The title is clear in target population, intervention and type of study design but not well depicted what are the study outcomes.

Authors:

KEEWON KIM, HYUNG-IK SHIN, BUM SUN KWON, SANG JUN KIM, IL-YOUNG JUNG, MOON SUK BANG

KEEWON KIM the first author is working at the department of Rehabilitation Medicine, College of Medical Sciences, Seoul National University, Seoul, South Korea, h-index = 0

HYUNG-IK SHIN the author of correspondence work at the department of rehabilitation medicine, Seoul national university Bundang hospital, Seongnam, Korea. Based on Scopus database searched, results showed 14 cited documents, 61 citations, h-index = 5

Abstract:

The abstract was structured format and contained relevant Information about the study including objectives, study design, outcome measurements, results and conclusion but not specifying that the trial is non-inferiority trial.

Generalizability:

It was matched to my clinical question including intervention target
population and type of study

Critical appraisal

1. Are the results valid?

Were subjects randomly assigned to the treatment group?
Yes, the participants were randomly assigned to either BOTOX or NEURONOX intervention using a block randomization method to generate the random code for each hospital with the allocation ratio of 1:1, the assigned code for participants was sealed until the scheduled follow-up were complete for statistical analysis but the study did not described about the block size

Were all the subjects accounted at the end of the study?
Yes, 122 children were randomly assigned to the BOTOX (n=61) and NEURONOX (n=61), after assignment 1 of the NEURONOX group and 2 of the BOTOX group refused the injection. Thus 119 individuals (60 in NEURONOX group and 59 in BOTOX group) constituted the intention-to-treat population and underwent the intervention. During the evaluation period 8 in NEURONOX group and 6 in BOTOX group withdrawn from the study and after scheduled follow-up period 2 in NEURONOX group and 2 in BOTOX group were exclude from the study. The per-protocol population comprised 50 in NEURONOX group and 51 in the BOTOX group.

Was the study blinded?
Yes, the participants, the physician who administered the injection and the physician who evaluated outcomes were all blinded to which drug was assigned.

Were the study groups similar at the start of the investigation?
Yes, at baseline the two groups did not differ in terms of age, sex, history of botulinum toxin-A injection, distribution of GMFCS, and type of cerebral palsy.

Were the study group treated equally?
Yes, both group were treated equally.

2. What are the results?
In the intention-to-treat group analysis, the difference in response rates was -0.8% and the lower bound of the 90% CI of the difference was -12.57%. In the per-protocol group analysis, the difference in response rates was 1.10% and the lower bound of 90% CI was -11.58%. The lower of the 90% CI was within the non-inferiority margin of -20% in both ITT and per-protocol group.

In my opinion the non-inferiority margin of this trial is too large. The margin of non-inferiority is often chosen as smallest value that would be a clinically important effect. If relevant, the margin should be smaller than the clinically relevant effect chosen to investigate superiority of reference treatment against placebo. In this trial the non-inferiority margin was derived from historical placebo-controlled trials reporting a response rate for BOTOX 21 to 36% points higher than that for placebo. In this trial, the non-inferiority margin was -20%. The margin was as effect as the placebo effect.

<table>
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ITT, Intention to treat; PP, per protocol; CI, confidence interval.
3. How can I apply the results to patient care?

Can I apply these results to my patient?
No, because the efficacy was not clear. The non-inferiority margin is too large and it as effect as the placebo effect.

Were disease-oriented or patient-oriented outcome considered?
Yes, the outcome was assess the physician’ rating scale, gross motor function measure and passive range of motion, there were the clinical outcome.

What are the benefits versus costs of this treatment?
In this trial, the clinical improvement in the NEURONOX group was not inferior to the BOTOX group, but the efficacy was not clear, even though it can reduced cost of treatment.

Conclusion

Topic of this paper correlates to my question. It is well research study design. There were some weak point about the non-inferiority margin is too large and it as effective as the placebo effect cause magnitude of effect was small.
So, the answers of my clinical scenario are I cannot recommend that the NEURONOX has as effective as BOTOX for treatment of spastic equinus gait in children with cerebral palsy.
<table>
<thead>
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<th>PAPER SECTION And topic</th>
<th>Item</th>
<th>Descriptor</th>
<th>Reported on Page #</th>
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</thead>
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<tr>
<td>TITLE &amp; ABSTRACT</td>
<td>1</td>
<td>How participants were allocated to interventions (e.g., &quot;random allocation&quot;, &quot;randomized&quot;, or &quot;randomly assigned&quot;), specifying that the trial is a non-inferiority or equivalence trial.</td>
<td>239</td>
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<tr>
<td>INTRODUCTION Background</td>
<td>2</td>
<td>Scientific background and explanation of rationale, including the rationale for using a non-inferiority or equivalence design.</td>
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<tr>
<td>METHODS Participants</td>
<td>3</td>
<td>Eligibility criteria for participants (detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment) and the settings and locations where the data were collected.</td>
<td>240</td>
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<tr>
<td></td>
<td>4</td>
<td>Precise details of the interventions intended for each group detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy, and how and when they were actually administered.</td>
<td>241</td>
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<tr>
<td></td>
<td>5</td>
<td>Specific objectives and hypotheses, including the hypothesis concerning non-inferiority or equivalence.</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Clearly defined primary and secondary outcome measures detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).</td>
<td>241</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>How sample size was determined detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice. When applicable, explanation of any interim analyses and stopping rules (and whether related to a non-inferiority or equivalence hypothesis).</td>
<td>Not clear</td>
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<td></td>
<td>8</td>
<td>Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)</td>
<td>240</td>
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<tr>
<td></td>
<td>9</td>
<td>Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.</td>
<td>Not clear</td>
</tr>
<tr>
<td>Section</td>
<td>Number</td>
<td>Description</td>
<td>Page</td>
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</tr>
<tr>
<td>Randomization -- Implementation</td>
<td>10</td>
<td>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</td>
<td>Not clear</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>11</td>
<td>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.</td>
<td>241</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>Statistical methods used to compare groups for primary outcome(s), specifying whether a one or two-sided confidence interval approach was used. Methods for additional analyses, such as subgroup analyses and adjusted analyses.</td>
<td>242</td>
</tr>
<tr>
<td>RESULTS</td>
<td>13</td>
<td>Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.</td>
<td>241</td>
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<tr>
<td>Participant flow</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Recruitment</td>
<td>14</td>
<td>Dates defining the periods of recruitment and follow-up.</td>
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<tr>
<td>Baseline data</td>
<td>15</td>
<td>Baseline demographic and clinical characteristics of each group.</td>
<td>240</td>
</tr>
<tr>
<td>Numbers analyzed</td>
<td>16</td>
<td>Number of participants (denominator) in each group included in each analysis and whether the analysis was “intention-to-treat” and/or alternative analyses were conducted. State the results in absolute numbers when feasible (e.g., 10/20, not 50%).</td>
<td>242</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17</td>
<td>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval). For the outcome(s) for which non-inferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.</td>
<td>242</td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.</td>
<td>Not clear</td>
</tr>
<tr>
<td>Adverse events</td>
<td>19</td>
<td>All important adverse events or side effects in each intervention group.</td>
<td>243</td>
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<tr>
<td>DISCUSSION Interpretation</td>
<td>20</td>
<td>Interpretation of the results, taking into account the non-inferiority or equivalence hypothesis and any other study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.</td>
<td>Not clear</td>
</tr>
<tr>
<td>Generalizability</td>
<td>21</td>
<td>Generalizability (external validity) of the trial findings.</td>
<td>243</td>
</tr>
<tr>
<td>Overall evidence</td>
<td>22</td>
<td>General interpretation of the results in the context of current evidence.</td>
<td>243</td>
</tr>
</tbody>
</table>

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Neuronox versus BOTOX for spastic equinus gait in children with cerebral palsy: a randomized, double-blinded, controlled multicentre clinical trial

KEE WON KIM 1 | HYUNG-IK SHIN 2 | BUM SUN KWON 3 | SANG JUN KIM 1 | IL-YOUNG JUNG 1 | MOON SUK BANG 1

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AIM The aim of this study was to evaluate the efficacy and safety of a newly manufactured botulinum toxin, Neuronox, compared with BOTOX for the treatment of the spastic equinus gait in children with cerebral palsy.

METHOD A total of 127 children with cerebral palsy, aged 2 to 10 years, who presented at three university hospitals with spastic equinus gait were assessed for eligibility to participate in this double-blinded, randomized, controlled trial. Of the 119 eligible participants (mean age 4.33y; SD 2.07; 76 males and 43 females; 79 with diplegia and 40 with hemiplegia), 57 were classified as Gross Motor Function Classification System level I, 28 as level II, and 33 as level III. Participants were randomly assigned to receive an injection of Neuronox (n=60) or BOTOX (n=59) to the calf muscles at a dose of 4U/kg for those with hemiplegia and 8U/kg for those with diplegia. Assessments were performed at baseline (V1) and at 4 (V2), 12 (V3), and 24 (V4) weeks after the intervention. The primary outcome measure was response rate at V3, with a positive response being defined as at least a 2-point increase in the Physicians’ Rating Scale (PRS) score. The non-inferiority margin was set as -20% for the difference in the response rate. The secondary outcome measures included PRS score, passive range of motion (PROM) of the ankle and knee, and Gross Motor Function Measure 88 (GMFM-88). Any adverse events were investigated for safety implications.

RESULTS The response rate of the Neuronox group at V3 was not inferior to that of the BOTOX group (90% lower limit = 11.98%). There were significant improvements in PROM, PROM of ankle dorsiflexion, and GMFM scores at V2, V3, and V4 in both groups. The changes in PROM score were not statistically different between the two groups in serial evaluation (p = 0.96). PROM of the ankle dorsiflexion increased without any significant difference between the two groups, either overall (p = 0.56) or at each visit (V2, p = 0.32; V3, p = 0.66; V4, p = 0.90). The increase in GMFM score in serial measurements were not significantly different between the two groups (p = 0.18), whereas it was larger in the BOTOX group than in the Neuronox group at V2 and V4 (p = 0.03 and 0.05 respectively). The frequency of adverse events was not significantly different between the two groups (p = 0.97), and drug-related complications of Neuronox treatment were not addressed.

INTERPRETATION The outcomes of Neuronox, based on PROM, proved to be as effective and safe as those of BOTOX for the treatment of spasticity in individuals with cerebral palsy.

Botulinum neurotoxin type A (BoNT-A) has been widely used for the treatment of spastic gait in individuals with cerebral palsy (CP) since 1993, when its use was first described. Its efficacy in reducing spasticity and improving ambulation in those with CP has been validated in many studies, including recent randomized controlled trials reported by Moore and Lukban et al.

Numerous BoNT-A formulations are available, including BOTOX (Allergan Inc., Irvine, CA, USA), Dysport (Ipsen Ltd, Slough, Berkshire, UK), Neuronox, also known in Korea as Meditoxin (Med-Tox, Ochang-eup, Cheongwon-gun, Changcheongbuk-do, Korea), and Xeomin (Merz Pharmaceuticals, Frankfurt, Germany). Neuronox, a newly manufactured BoNT-A, has been approved for use in 15 countries in Asia and South America, including India, Thailand, Hong Kong, and Colombia, for the treatment of diseases such as blepharospasm, cervical dystonia, strabismus, and CP. Although various BoNT-A products are available and prescribed for similar clinical purposes, equivalence of their efficacy and toxicity has not been confirmed. In particular,
few studies have assessed the clinical outcomes of Neuronox, although one study reported that BOTOX and Neuronox produced equivalent decreases in muscle force generation in a murine model. The efficacy and safety of Neuronox for the treatment of spasticity in individuals with CP has not yet been studied.

Based on the hypothesis that Neuronox is not inferior to BOTOX, we aimed to compare the efficacy and safety of Neuronox and BOTOX in the treatment of spastic equinus gait in children with CP. In addition, adverse events occurring during the course of the study were recorded and compared in the Neuronox and BOTOX groups.

**METHOD**

This study was designed as a randomized, double-blinded, active-drug-controlled, parallel-group, phase III clinical trial and conducted at three university hospitals, Seoul National University Hospital, Bundang Seoul National University Hospital, and Ilsan Dongguk University Hospital, in the Republic of Korea between July 2007 and January 2009. It was approved by the relevant institutional review boards, conducted in compliance with the principles of good clinical practice, and performed in accordance with the Declaration of Helsinki. The study protocol was explained to the parent(s) of eligible children with CP. Children participated in the study only if their parents provided written informed consent. The study was also explained to the children themselves.

**Participants**

Children who had a diagnosis of CP, were aged between 2 and 10 years, and who were classified as Gross Motor Function Classification System (GMFCS) level I, II, or III were eligible for participation in the study. They had to show tip-toeing gait as a result of spastic calf muscles and be able to receive physiotherapy following a standardized protocol for lower limb spasticity. The participants were recruited from individuals who visited the outpatient departments of the university hospitals because of lower limb spasticity resulting from CP. Participants were excluded if they had a history of anaphylactic reaction to BoNT-A, a bleeding tendency, or a history of treatment with anticonvulsants, neuroleptics, anticoagulants, aminoglycosides, muscle relaxants, parasympathetic antagonists, or dopaminergics. Individuals who had previously undergone surgery on the muscles or ligaments of the lower extremities, who had fixed contracture of the lower limb joints, or who exhibited severe athetoid movements were also excluded from the study. Specifically, passive ankle dorsiflexion below neutral with the knee extended was considered as fixed contracture of the ankle. If individuals had received a BoNT-A injection less than 3 months before the start of the study, they were enrolled after a 3-month interval.

A total of 127 children were initially enrolled in the study but five were subsequently excluded during screening tests because of medication history or other medical conditions. Thus, 122 children were randomly assigned to the BOTOX (n=61) or Neuronox (n=61) group (1:1 ratio). After assignment, one individual in the Neuronox group and two in the BOTOX group refused the injection. Thus, 119 individuals (60 in the Neuronox group; 59 in the BOTOX group) constituted the intention-to-treat (ITT) population and underwent the intervention. Demographic and clinical data are presented in Table I. The ITT population comprised 76 males and 43 females, of whom 57 were classified as GMFCS level I, 29 as GMFCS level II, and 33 as GMFCS level III. Twenty-one had right hemiplegia, 19 had left hemiplegia, and 79 had diplegia. At baseline the two groups did not differ in terms of age, sex, history of BoNT-A injections, distribution of GMFCS, and type of hemiplegia. The per-protocol population comprised 50 individuals from the Neuronox group and 51 individuals from the BOTOX group. Figure 1 shows the study flowchart. During the evaluation period, eight individuals from the Neuronox group and six from the BOTOX group were withdrawn from the study before completion because of adverse events. After the scheduled follow-up period, two individuals from the Neuronox group and two individuals from the BOTOX group were excluded from the per-protocol population owing to the violation of study protocols.

**Randomization**

The eligible participants were randomly assigned to either BOTOX or Neuronox intervention using a block randomization method to generate a random code for each hospital with the allocation ratio of 1:1. The assigned code for participants was sealed until the scheduled follow-ups were completed for statistical analysis. Thus, the participants, the physician who administered the injection, and the physician who evaluated the outcomes were all blinded to which drug was assigned. An

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**Table I: Characteristics of study participants**

<table>
<thead>
<tr>
<th>Items</th>
<th>Neuronox (n=60)</th>
<th>BOTOX (n=59)</th>
<th>Total (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (66.67)</td>
<td>36 (61.02)</td>
<td>76 (63.87)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (33.33)</td>
<td>23 (38.98)</td>
<td>43 (36.13)</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>4.42 (1.93)</td>
<td>4.24 (2.22)</td>
<td>4.33 (2.07)</td>
</tr>
<tr>
<td>Body weight (kg), mean (SD)</td>
<td>16.83 (4.17)</td>
<td>16.34 (4.86)</td>
<td>16.56 (4.51)</td>
</tr>
<tr>
<td>Previous BoNT-A injection, n (%)</td>
<td>35 (58.33)</td>
<td>29 (49.15)</td>
<td>64 (53.78)</td>
</tr>
<tr>
<td>GMFCS level, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>29 (48.33)</td>
<td>28 (47.46)</td>
<td>57 (47.90)</td>
</tr>
<tr>
<td>II</td>
<td>16 (26.67)</td>
<td>13 (22.03)</td>
<td>29 (24.37)</td>
</tr>
<tr>
<td>III</td>
<td>15 (25.00)</td>
<td>18 (30.51)</td>
<td>33 (27.73)</td>
</tr>
<tr>
<td>Type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemiplegia</td>
<td>10 (16.67)</td>
<td>11 (18.64)</td>
<td>21 (17.65)</td>
</tr>
<tr>
<td>Left hemiplegia</td>
<td>9 (15.00)</td>
<td>10 (16.95)</td>
<td>19 (15.97)</td>
</tr>
<tr>
<td>Diplegia</td>
<td>41 (68.33)</td>
<td>38 (64.41)</td>
<td>79 (66.39)</td>
</tr>
</tbody>
</table>

BoNT-A, botulinum neurotoxin type A; GMFCS, Gross Motor Function Classification System.
Follow-up evaluations were carried out at 4 (V2), 12 (V3), and 24 (V4) weeks after the intervention. The ITT population comprised 119 participants who underwent the baseline evaluation and intervention and the per protocol population comprised 101 participants who went through the final evaluation (V4) without violation of the study protocol.11

**Therapeutic efficacy evaluation**

Clinical assessments were performed by experienced physicians. Although the evaluators were not the same at each centre, they all had at least 5 years’ clinical experience of children with CP and they had received clinical training at the same centre. The physicians who performed the evaluation were blinded to the allocation of the BoNT-A formulations. Gait patterns were recorded by a video camera and analysed for outcome measures. The outcome measures were Physicians’ Rating Scale (PRS) score,12 passive range of motion (PROM) of ankle dorsal/plantar flexion and knee flexion, and Gross Motor Function Measure 88 (GMFM-88) score.13 PROM of the ankle was assessed with the knee extended. The primary outcome measure was the response rate at V3, defined as the proportion of the individuals whose PRS score improved from V1 to V3 by 2 or more points. In individuals who received injections to the calf muscles of both legs, an increase of two or more points on both sides was required to record a positive response. The response rates at the V2 and V4, change in PRS score and GMFM score, were evaluated as secondary outcome measures.

**Safety measures**

All adverse events and drug reactions were recorded for safety purposes. Adverse events were classified as ‘mild’, ‘moderate’, or ‘serious’ depending on the clinical severity, which was determined by the evaluating physicians. The association between the adverse event and the injection was determined by physicians taking into consideration temporal relation, clinical history, circumstances, and medical knowledge. Adverse events were recorded along with a description of the diagnosis and the involved organ. At each visit, vital signs were checked and physical examinations were performed to investigate for any unexpected outcomes. Laboratory tests, including basic blood test, antibody assay, and urine analysis, were performed at the V1 and V4. The antibody test used the mouse protection bioassay based on the methods described by Sankhla et al.14

**Statistical analysis**

The purpose of the study was to test the non-inferiority of Neuronox compared with BOTOX. The non-inferiority margin was derived from historical placebo-controlled trials reporting a response rate for BOTOX 21 to 36% points higher than that for placebo.15,16 Following the guidelines of the Food and Drug Administration,17 the margin for the difference in response rate was set at 20% to ensure that Neuronox was as effective as BOTOX. Statistical analysis evaluated whether the one-sided 90% confidence interval (CI) of the difference in response rate at V3 between the Neuronox and BOTOX groups was within the −20% non-inferiority

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*Figures and tables are not provided in this text.*
To assess longitudinal improvement, postinjection clinical outcomes were compared with pre-injection values using the paired t-test or the Wilcoxon signed-rank test. The secondary outcomes were compared at each visit between the two treatment groups using a two-sample t-test to assess the PRS score, PROM, and GMFM and a χ² test to assess the response rate and the occurrence of adverse events. The overall comparison between the two groups considering serial evaluations was also performed by calculating the area under curve.¹⁸ p values less than 0.05 were considered statistically significant. The number of participants necessary to yield statistical power of 0.8 was estimated as 55 for each group, based on a previous study that reported a response rate of 41% with BOTOX injection.¹² The current study recruited 127 participants and the ITT group comprised 119 participants (60 in the Neuronox group; 59 in the BOTOX group).

RESULTS
Response rate in the Physicians' Rating Scale
In the ITT group analysis, the response rate at the V3 was 56.0% in the Neuronox group and 54.9% in the BOTOX group. The 90% CI of the difference (lower limit –11.58%) did not exceed the non-inferiority margin of –20%. The response rates at V2 and V4 were not significantly different between the two groups (V2, p=0.25; V4, p=0.46; χ² test). The areas under the curve for the PRS score were not statistically different between the two groups (p=0.96; t-test; Fig. 2).

The passive range of motion
PROM of ankle dorsiflexion at V2, V3, and V4 was significantly increased compared with that at V1 in both the Neuronox and BOTOX groups. The difference in PROM between the groups was not significant at each visit (V2, p=0.32; V3, p=0.66; V4, p=0.90; two sample t-test) or in overall serial measurements (p=0.56; t-test of area under curve). The range of knee flexion and ankle plantar flexion did not change noticeably in either group in the longitudinal comparison between the baseline and follow-up visits.

Gross Motor Function Measure
After the BoNT-A injection, GMFM scores increased significantly at all follow-up visits. The Neuronox group showed mean increases of 2.14 at V2, 3.77 at V3, and 4.76 at V4, and the BOTOX group showed mean increases of 2.65 at V2, 5.25 at V3, and 6.63 at V4 (p<0.01 for all longitudinal analysis). The summary measure for the serial evaluations of the GMFM score using the area under curve did not reveal

<table>
<thead>
<tr>
<th>Analysis set</th>
<th>Participant number</th>
<th>Response rate in Neuronox group, n(%)</th>
<th>Response rate in BOTOX group, n(%)</th>
<th>Difference in response rate (95% CI)</th>
<th>90% lower limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>119</td>
<td>29/60 (48)</td>
<td>29/59 (49)</td>
<td>–0.82% (–18.78 to 17.14%)</td>
<td>–12.57%</td>
</tr>
<tr>
<td>PP</td>
<td>101</td>
<td>28/50 (56)</td>
<td>28/51 (55)</td>
<td>1.10% (–18.29 to 20.48%)</td>
<td>–11.58%</td>
</tr>
</tbody>
</table>

ITT, intention to treat; PP, per protocol; CI, confidence interval.

Figure 2: Changes in Physicians' Rating Scale (PRS) score, passive range of motion (PROM) of ankle dorsiflexion, and Gross Motor Function Measure (GMFM). After the injection of Neuronox or BOTOX, (a) PRS score and (b) PROM of ankle dorsiflexion were increased and then maintained until 24 weeks after the injection. The comparison of area under curve for each outcome measure revealed no significant difference between the two treatment groups. The error bar indicates the standard deviation.
a significant difference between the Neuronox and BOTOX groups \( (p=0.16; \; t\text{-test}). \) Comparisons at each visit revealed no significant difference in the change in GMFM scores at V2 \( (p=0.41; \; \text{two-sample } t\text{-test}). \) However, at V3 and V4, the BOTOX group showed a larger increase in GMFM scores than the Neuronox group \( (p=0.03 \text{ and } 0.05 \text{ respectively}; \; \text{two-sample } t\text{-test}) \) in the ITT population but not in the per-protocol population \( (p=0.07 \text{ and } 0.08 \text{ respectively}; \; \text{two sample } t\text{-test}). \)

### Safety measures

No participants in this study showed a positive antibody assay against BoNT-A either at baseline or at the postintervention test. A total of 34 adverse events were reported in 18 out of 119 participants (15.1%): nine children in the Neuronox group experienced a total of 15 events and nine children in the BOTOX group experienced a total of 19 events. When the events were classified according to severity, 26 (13 in each group) events were considered ‘mild’ and eight (two in the Neuronox group and six in BOTOX group) were ‘moderate’. There were no ‘severe' adverse events. The most frequently reported complications were nasopharyngitis in six children in total (three in each group) and pyrexia in five children (two in the Neuronox group and three in BOTOX group). Other reported complications, including pneumonia, pain, joint contracture, and conjunctivitis, were considered to be unrelated to the treatment.

The frequency of adverse events was not significantly different between the Neuronox and BOTOX groups \( (p=0.97; \; \chi^2 \text{ test}). \) Four participants experienced noteworthy adverse events during the study period that required admission to hospital for treatment. Two participants in Neuronox group developed dacrostenosis (obstruction of lacrimal duct) and lower limb fracture and two in the BOTOX group suffered haemoptysis and joint contracture. These four participants were withdrawn from the study and recovered after appropriate management. Neither careful review of their history nor clinical examinations revealed probable causality with BoNT-A injection. One adverse event experienced by a participant in the BOTOX group, transient subjective muscular weakness, was determined to be related to BoNT-A injection. Blood tests revealed a marked increase in lymphocytes \( (p=0.029) \) in the Neuronox group and an increase in neutrophils \( (p=0.001), \) monocytes \( (p=0.001), \) and lymphocytes \( (p=0.014) \) in the BOTOX group 12 weeks after the injection (V4). However, those changes were of no clinical significance.

### DISCUSSION

BoNT-A is known to reduce muscle spasticity by blocking the release of acetylcholine in the neuromuscular junction \(^{19,20}\) and has been prescribed for children with CP to help manage spasticity of the lower limbs.\(^{6,21}\) This randomized, double-blinded, controlled study has clearly demonstrated that BoNT-A injections at the gastrocnemius muscle improve spastic equinus gait in children with CP and that the safety and efficacy of Neuronox is not inferior to that of BOTOX. This indicates that Neuronox can be a reliable option for BoNT-A injection.

The results of the current study are similar to those of previous studies of BoNT-A injections. Koman et al.\(^{12}\) reported that serial treatment with BoNT-A resulted in improved gait in children with CP that was maintained over a 2-year period of follow-up. The response rate in their study was 55% at 1-year follow-up and 44% at 2-year follow-up. The overall response rate in our study, after either Neuronox or BOTOX injection, was 54.6%. Studies evaluating the effect of Dysport in individuals with CP have reported an increase in GMFM score after injection that was not much different from that recorded in our study.\(^{4,22}\) Thus, it is reasonable to claim that our treatment protocol was clinically appropriate to determine an effect of BoNT-A injection. In addition, as the efficacy of Dysport has been documented in previous studies to be equivalent to that of BOTOX,\(^{23}\) our results suggest that Neuronox has similar efficacy to Dysport as well as to BOTOX. Furthermore, when reported individual adverse events were analysed and compared with those reported in previous studies,\(^{19,24-26}\) we found that Neuronox can be considered to be as safe as BOTOX and Dysport.

Because the participants exhibited different levels of GMFCS at baseline (from I to III), we conducted further analyses to test whether the GMFCS level influenced the efficacy of the BoNT-A injection. GMFCS levels at baseline were similar in the two groups (Table I). The response rate, in terms of PRS score, according to GMFCS level was not statistically different between the Neuronox and BOTOX groups at all follow-up evaluations, except that among participants classified as GMFCS level II, those in BOTOX group showed a higher response rate than those in the Neuronox group at V1 (\( p=0.047; \; \chi^2 \text{ test}) \). When the groups were combined, there was a tendency for response rate at V2 to be higher at higher GMFCS levels \( (p=0.006; \; \text{Cochran–Armitage trend test}) \); more specifically, response rate was highest among participants classified as GMFCS level II, followed by level III, and then level I. Among participants of all GMFCS levels, the change in PROM of ankle dorsiflexion was not significantly different between the treatment groups (V2, \( p=0.099; \) V3, \( p=0.324; \; \text{ANOVA} \) except at V1 \( p=0.046; \; \text{ANOVA} \)). Ankle dorsiflexion PROM increased more in those classified as GMFCS level III than in those classified as GMFCS I at V1 \( (p=0.016; \; t\text{-test}) \). The improvement in GMFM was greater in those classified as GMFCS level II than other levels at all visits (V1, \( p=0.006; \) V2, \( p=0.019; \) V3, \( p=0.015; \; \text{ANOVA} \)). The treatment groups yielded a similar increase in GMFM score at all visits for those classified as GMFCS levels I and II, but the BOTOX group excelled over the Neuronox at V3 in those classified as GMFCS level III \( (p=0.027; \; t\text{-test}) \).

Our study has a few limitations that should be mentioned. First, the study was not controlled with a placebo, which is necessary in order to show the net effect of a study drug. Because treatment with BoNT-A injections for individuals with CP has already been established, injecting participants with a placebo was not considered to be ethically appropriate. Second, the study protocol did not apply variable doses of BoNT-A. According to the severity of the spasticity, different doses would produce optimal outcomes. The dose of 4U/kg Neuronox vs BOTOX for Spasticity in Cerebral Palsy Moon Suk Bang et al. 243

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used in our protocol might have been insufficient in some cases. In future studies, more variable dosages of Neuronox can be applied based on the current results.

Importantly, this study is noteworthy as the first well-designed, strictly conducted phase III clinical trial to validate the efficacy of a newly manufactured BoNT-A with clinical application for the treatment of spastic CP. The results of this study are expected to provide physicians with more choices for the treatment of spasticity in CP.

ACKNOWLEDGEMENTS

We express our gratitude to all the parents and children who participated in this study. We also thank Medy-Tox Inc. for their financial contribution to the study.

REFERENCES