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INPLASY

Effects of Botulinum Neurotoxin on Muscle Mass and Volume in Individuals with Spastic Cerebral Palsy: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 May 2024 and was last updated on 29 May 2024.

INTRODUCTION

Review question / Objective P: patients exhibiting lower limb spasticity due to cerebral palsy; I: local injections of BoNT in the gastrocnemius muscle; O: a change in the volume or mass of the gastrocnemius muscle and a change in the volume or mass of triceps surae muscles or the whole distal lower limb muscles before and after intervention.

Condition being studied Effects of botulinum neurotoxin on lower leg muscle mass and volume in individuals with spastic cerebral palsy.

METHODS

Search strategy We searched the literature for all relevant articles in the PubMed, Embase, Web of Science, and Cochrane Library databases from their inception to May 15, 2024. A combination of “cerebral palsy” and “botulinum toxin” was used as keywords to search for eligible studies. The references in the located articles were also manually screened to broaden the scope of our search.

Participant or population Patients exhibiting lower limb spasticity due to cerebral palsy.

Intervention Local injections of BoNT in the gastrocnemius muscle, and some might include other muscle.

Comparator Compare a change in the volume or mass of the gastrocnemius muscle and a change in the volume or mass of triceps surae muscles or the whole distal lower limb muscles before and after intervention.

Study designs to be included RCT or non-RCT (cohort study).

Eligibility criteria Studies involving patients exhibiting lower limb spasticity due to CP were included. Patients in the treatment arm must have

received local injections of BoNT in the gastrocnemius muscle. No restrictions were set for the control arms. The included studies reported muscle volume or muscle mass of the gastrocnemius, triceps surae, or distal lower limb at baseline and after BoNT. Proxies for muscle volume and muscle mass, such as muscle thickness [18] and lean soft tissue mass [19], were also acceptable. No restrictions were imposed on the follow-up time after intervention or the tools for muscle measurement. Due to the small number of studies on the use of BoNT in individuals with CP, randomized controlled trials and nonrandomized controlled studies published in English were included. We excluded case reports and conference proceedings because of the high risk of publication bias.

Information sources We searched the literature for all relevant articles in the PubMed, Embase, Web of Science, and Cochrane Library databases from their inception to May 15, 2024. A combination of "cerebral palsy" and "botulinum toxin" was used as keywords to search for eligible studies. The references in the located articles were also manually screened to broaden the scope of our search.

Main outcome(s) The primary outcome was a change in the volume or mass of the gastrocnemius muscle. The secondary outcome was a change in the volume or mass of triceps surae muscles or the whole distal lower limb muscles. Effect sizes were calculated by comparing the muscle volume or mass before versus after BoNT injection. Follow-ups were categorized into 4 time periods. The first follow-up period was from 0 to 6 weeks following BoNT injection, the second follow-up period was between 6 and 13 weeks following injection, the third follow-up period was between 14 weeks and 25 weeks following injection, and the fourth follow-up period was 26 weeks or later following injection.

Data management Data before and after BoNT injection were used to calculate muscle volume or mass changes. Summary effect sizes were calculated using random effects meta-analyses. Results are presented with standardized mean differences (SMDs) and 95% confidence intervals (CIs). I^2 values were used to assess between-study heterogeneity with a cutoff point of 50%. Meta-regression was used to assess the moderator effects of GMFCS level and age on the effect size. Specifically, the proportion of participants with GMFCS level III-V was calculated to assess the influence of motor function on effect sizes. In the meta-regression analysis, a p value < 0.05 indicated statistical significance. In the sensitivity analysis, we excluded studies using ultrasound as the muscle measurement tool because clear ultrasonic assessments depend more on operator skill than magnetic resonance imaging (MRI) and dual-energy x-ray absorptiometry (DXA). Publication bias was evaluated using funnel plots and Egger's regression test, and statistical significance was set at a two-tailed p value of <0.1. Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ, USA) was used for analysis.

Quality assessment / Risk of bias analysis Methodologic quality was assessed by 2 authors (ACL and YCS) using the risk of bias in nonrandomized studies of interventions (ROBINS-I) tool. Any disagreements were resolved first through discussion between the 2 authors and subsequently through the adjudication of the senior author (YCL) if consensus was not reached.
We assessed the risk of bias in the included studies using the ROBINS-I tool (Figure 2). Six studies compared outcomes before and after the intervention within the same group [8, 10, 12, 13, 16, 17]. Thus, we categorized questions pertaining to comparisons between groups as "not applicable" (N/A). Peeters et al. [14] noted differences in body height and mass at a between-group p value < 0.05 but did not specify strategies to address confounding factors. With regard to completion, Park et al. [12], Lorenzo et al. [16], Lee et al. [17], and Peeters et al. [14] did not explicitly state whether all follow-ups were completed; we categorized these studies as "unclear." Moreover, Alexander et al. [13] only indicated that some follow-ups were incomplete without describing the reasons for the loss to follow-up or indicating strategies employed to address incomplete follow-up.

Strategy of data synthesis Data before and after BoNT injection were used to calculate muscle volume or mass changes. Summary effect sizes were calculated using random effects meta-analyses. Results are presented with standardized mean differences (SMDs) and 95% confidence intervals (CIs). I^2 values were used to assess between-study heterogeneity with a cutoff point of 50%. Meta-regression was used to assess the moderator effects of GMFCS level and age on the effect size. Specifically, the proportion of participants with GMFCS level III-V was calculated to assess the influence of motor function on effect sizes. In the meta-regression analysis, a p value < 0.05 indicated statistical significance. In the sensitivity analysis, we excluded studies using ultrasound as the muscle measurement tool because clear ultrasonic assessments depend

more on operator skill than magnetic resonance imaging (MRI) and dual-energy x-ray absorptiometry (DXA). Publication bias was evaluated using funnel plots and Egger's regression test, and statistical significance was set at a two-tailed p value of <0.1. Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ, USA) was used for analysis.

Subgroup analysis A meta-regression was conducted for muscle volume or mass of the gastrocnemius at the first and second follow-up periods only because few studies included information on other outcomes at later follow-up periods. At the first follow-up, older patients exhibited a larger decrease in gastrocnemius volume or mass after BoNT (β = −0.1215, P = 0.026), whereas no association was observed between GMFCS level and change in muscle morphology (P = 0.8003). At the second follow-up period, patients in studies with lower proportions of individuals with GMFCS III to V exhibited a larger decrease in gastrocnemius volume or mass (β = 1.1845, P = 0.0191), and no association was observed between age and gastrocnemius morphology (P = 0.1274).

Sensitivity analysis Sensitivity analysis was conducted for muscle volume or mass of the gastrocnemius at the first follow-up period only because few studies included information on other outcomes at later follow-up periods. After excluding studies that used ultrasonography for muscle measurement, the sensitivity analysis included 2 studies, and the results were similar to those of the main analysis (SMD −0.320, 95% CI −0.668 to 0.027, I2 = 26.4%).

Language restriction There is no language limits.

Country(ies) involved R.O.C. (Taiwan).

Keywords cerebral palsy; botulinum neurotoxin; muscle mass; muscle volume.

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