Author's response to reviews

Title: Effectiveness of strength training in combination with Botulinum Toxin-A on hand activity in children with cerebral palsy: A pre-post intervention study

Authors:

Ann-Kristin G. Elvrum (ann-kristin.elvrum@stolav.no)
Siri M. Brændvik (siri.merete.brandvik@svt.ntnu.no)
Rannei Sæther (rannei.sather@ntnu.no)
Torarin Lamvik (torarin.lamvik@stolav.no)
Beatrix Vereijken (beatrix.vereijken@svt.ntnu.no)
Karin Roeleveld (karin.roeleveld@svt.ntnu.no)

Version: 2 Date: 14 March 2012

Author's response to reviews: see over
Dear Editor,

Thank you for the opportunity to resubmit a revised version of our manuscript (MS: 6216851364780052) “Effectiveness of strength training in combination with Botulinum Toxin-A on hand activity in children with cerebral palsy: A pre-post intervention study” by Ann-Kristin G. Elvrum, Siri M. Brændvik, Rannei Sæther, Torarin Lamvik, Beatrix Vereijken and Karin Roeleveld.

We appreciate both reviewers’ comments regarding our manuscript and Jules Becher’s recommendations. Below you will find our point-by-point response to the reviewers’ comments.

**Reviewer: Guy Molenaer.**

The article is well written and elaborated. It provides the reader with clear data nicely integrated in their comments taking in account the most recent articles and up to date research on this subject.

**Level of interest:** An article of importance in its field

**Response:** Thank you for these positive remarks.

**Reviewer: Jules Becher.**

In patient selection (participants and recruitment), MACS level 1 or 2 is selected, assuming functional bimanual use. This is an incorrect statement: the MACS scores the overall performance in hand function, but not the way it is performed.

**Response:** We agree with the reviewer, and realize that this was erroneously stated in the submitted version. In fact, one of the criteria for inclusion was that the participants had an active grasp function in the involved extremity corresponding to category 5 (fair active assist) on the Modified House
Functional Classification System. This was described in our first submission to BMC pediatrics, but unfortunately it was not included in the second submission. In the revised version we have now specified this correctly (page 6/para 1).

Randomization occurred in matched pairs by tossing a coin: this method is sensitive for selection bias.

**Response:** We agree that tossing a coin is sensitive for selection bias and we will omit this in future studies. However, there were no significant differences between the groups in the baseline assessments, except for pronation resistance torque and gender, indicating that significant selection bias is unlikely. In the revised version we have discussed this in the limitations of the study (page 16/para 2). Regarding the gender differences, we have added a comment in the discussion section, see our response to this comment further below.

In the selection of patients, there is no need described, no goals for the patient for the therapy on activity level, only an increased muscle tone and difference in active and passive range of motion.

**Response:** We agree that this could have caused a problem. The aim of this study was to explore whether treatment at the level of body functions would also have any positive treatment effects at the activity level. We chose to use impairments at the body function level as the indicators for inclusion. Therefore we did not know whether our participants had any needs or goals at the activity level. It is possible that some of the participants did not experience any problems performing daily activities despite increased muscle tone and limited range of motion. However, AHA and Melbourne test performance were reduced leaving room for improvement. In the revised version we have discussed this in the limitations of the study (page 16/para 2). Moreover, we have to admit that it is more likely that the improved limb functions will be implemented in activities when these activities are explicitly described as individual activity goals at the start of the therapy. Therefore some text is added at the end of the discussion (page 15/para 1).

**Outcome measure**

Main outcome measure was "hand activity", and was measured with the AHA and Melbourne test. According to ICF, AHA is a bimanual capacity test, not a performance test, and Melbourne test is an artificial unilateral hand capacity test, as the best performing hand will always be used as dominant hand. The chosen outcome measures do not give any information about the change in performance in the use of the hands in daily life. The term hand activity suggests the measurement on activity level, but should be bimanual capacity for AHA, and the Melbourne is more an impairment measurement of the affected side. So, the primary outcome measure is not adequate.
Response: We agree that Melbourne can be regarded both as an impairment measure (body functions), but also as a test of unilateral capacity in the activity domain. The Melbourne test has items that include concepts within both the body function and the activity domains. A recent study (Hoare et al., 2011) has linked the Melbourne test to ICF-CY, and found that this assessment evaluates both change at the body function domain (19/37), the activity domain (1/37) and a combination of the two domains (16/37). We therefore argue that the Melbourne test also is a measure within the activity domain.

We also agree that AHA is not capturing fully how the child is actually performing activities in daily life, but the literature strongly supports that AHA captures significant aspects of bimanual performance. In the revised version we have added a comment addressing this issue in the discussion (page 15/ para 1). The AHA intends to measure the competence with which a child uses his/her affected hand when engaged in bimanual activities, i.e. not hand function in terms of capacities but rather performance—how the child actually uses the affected hand in meaningful and common occupation (Krumlinde-Sundholm and Eliasson 2003). Hoare et al (2011) have linked AHA to ICF-CY and state that AHA is “the only commonly used upper limb specific activity-level measure of performance for children with hemiplegic cerebral palsy”. Further he states that “changes on the AHA are therefore more likely to reflect what a child may do in their usual environment or assess the transfer of intervention effects into daily life”.

In sum, we have kept these two instruments as outcome measures of hand activity, but we have addressed the reviewer’s concerns in the discussion as stated above.

Statistical analysis:

The data were not normally distributed, so only non-parametric tests could be used. The number of patients, 5 in each group, in a very heterogeneous group (group B 4 male, 1 female; group BT 1 male and 1 bilateral involved child, 4female) is an acceptable explanation for this. There is no power calculation about the required number of patients, but based on the AHA, it is very likely that the numbers are too small.

Response: We did not perform an “a priory” power calculation. However, post-hoc analyses suggest that given the sample size, our study had 80% power to detect a difference in AHA of three units from Baseline to Post-intervention with a p-value < 0.05. In contrast, the smallest detectable difference for a real change is reported to be 5 AHA-units (Eliasson et al 2011). Thus, our study had enough power to detect clinical significant changes.
It is unclear if difference in muscle strength has been tested at baseline.

**Response:** This was tested at baseline and no difference was found between the groups. This is now clarified in the paper (page 11/para 1).

In these small numbers, it is impossible to perform a proper trial analysis with analysis of variance and confounders.

**Response:** We agree, and have therefore not tried to perform such analyses. We also agree that the small sample size is a significant limitation, and that lack of statistical significant differences therefore must be interpreted with caution. However, since many of the borderline non-significant differences and the statistically significant differences were in the same direction we have presented some of the former findings as trends. We have discussed this limitation on page 16 para 2 in the revised version.

Results: Results are described: there is a tendency to suggest positive effects, despite the lack of significant differences. There is no attention paid for differences in sex.

**Response:** Regarding the “tendency” to suggest positive effects, we refer to our response to the previous comment. Regarding the differences in sex between the groups we have added a comment in the revised version in the discussion of the limitations of the study (page 16/para 2). As far as we know there is no clear evidence for differences in strength gains between boys and girls at this age group. The updated position statement paper on youth resistance training from the National Strength and Condition Association (Faigenbaum et al, 2009) states in the review of available literature that “there is no clear evidence of any major difference in strength between preadolescent boys and girls”. Thus it is unlikely that the differences in improvements of strength measurements between the groups were caused by differences in gender.

The discussion is very long-winded in relation to the results. The conclusion does not mention that only the small number of patients already could explain the lack of significant differences between the 2 treatments

**Response:** We have changed and shortened the discussion, and included some remarks about limitations with the study. We agree that the small number of participants could explain the lack of significant differences between the two treatments.

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal
Response: Both BoNT-A treatment and strength training are interventions at the impairment level that need further investigation. Our study numbers are small and should only be regarded as a pilot study which is now emphasized in the revised version. However our study has several interesting findings that may be addressed in future research:

1. Active supination range seems to improve more when strength training is performed in the BoNT-A effect period.

2. Only improving supination range and strength may not change considerably the way the involved hand is used in bimanual activities.

3. Strength training may counteract strength losses caused by BoNT-A treatment

We hope that you will find that we have amended the paper in accordance with the reviewer’s comments, and that you will find it suitable for publication in BMC Pediatrics.

Kind regards, on behalf of all authors,

Ann-Kristin Gunnes Elvrum
Clinic of Clinical Services, St. Olavs University Hospital
Olav Kyrres gt. 17
7006 Trondheim,
Norway
Ann-Kristin.Elvrum@stolav.no