Author/s:
Hastings-Ison, T;Graham, K

Title:
Botulinum neurotoxin A, blinding, and bias

Date:
2020-02-01

Citation:
Hastings-Ison, T. & Graham, K. (2020). Botulinum neurotoxin A, blinding, and bias. Developmental Medicine and Child Neurology, 62 (2), pp.259-. https://doi.org/10.1111/dmcn.14297.

Persistent Link:
https://hdl.handle.net/11343/286023

MS TANDY HASTINGS-ISON (Orcid ID : 0000-0002-9001-1410)

DR KERR GRAHAM (Orcid ID : 0000-0001-6607-7631)

Article type : Letter to the Editor

[Letter to the Editor]

Botulinum neurotoxin A, blinding, and bias

Tandy Hastings-Ison[1]

Kerr Graham[1,2]

Correspondence to kerr.graham@rch.org.au

doi: 10.1111/dmcn.

1 Hugh Williamson Gait Laboratory, Royal Children's Hospital, Parkville, Victoria; **2** University of Melbourne, Department of Paediatrics, Royal Children's Hospital, Parkville, Victoria, Australia.

Blinding plays a vital role in randomized clinical trials (RCTs): to maximize internal validity and to minimize bias in reporting outcomes.[1] Studies without blinding and those with unsuccessful blinding are at risk of reporting biased outcomes.[2] The majority of RCTs reporting the outcome of botulinum neurotoxin type (BoNT-A) injections in children with cerebral palsy, published in *Developmental Medicine & Child Neurology* and in other journals, claim the status of being 'double-blind'. To the best of our knowledge, only three RCTs have reported on the effectiveness of blinding and all three studies report defective blinding of patients, parents, and/or assessors.[3–5]

In a placebo-controlled, RCT of injections of BoNT-A in the upper limb of children with hemiplegia, we designed the study as double-blind.[3] However, we asked both the parents of the children and the study assessor which group their child had been allocated to at follow-up and the majority guessed correctly.[3] In a second RCT, investigating the analgesic properties of BoNT-A injections, the hip adductor and hamstring muscles of 16 children were injected with either BoNT-A or saline, 7 to 10 days before surgical lengthening of the hip adductors.[4] Parents identified group allocation correctly in 11 of 16 children and the study assessor in 14 of 16 children.[4] Unblinding was reported in a separate abstract and not in the main study paper.

As time moved on, ethical standards changed. Sham injections were preferred by Copeland et al. in their RCT of BoNT-A for care and comfort goals in non-ambulatory children with CP.[5] Immediately after injection, blinding was effective for both parents and study personnel. However, at the crucial 4-week follow-up, 77% of parents correctly identified group allocation. Given that most of the outcome measures were subjective, this opens the door to a placebo effect and bias.[1,2]

In these three studies, in the majority of occasions, parents and assessors were able to identify if a trial patient had been injected with BoNT-A, placebo, or a sham injection.[3–5] Many studies have reported that BoNT-A is effective in reducing muscle tone and the effects are easily identified by a therapist using standard tools such as the Modified Ashworth Scale or the Modified Tardieu Scale.[3–5] What is a little surprising is that parents were almost as accurate in identifying group allocation without using formal tools.

Unblinding is of much more concern when the primary outcome measures are subjective, for example pain scales or quality of life measures. It has less impact when the primary outcome measures are objective, for example gait analysis.

We therefore suggest the following guidelines for RCTs of BoNT-A therapy in children with CP: (1) the rating of the three RCTs described above on quality scales such as CONSORT and PEDro should reflect their self-reported, lack of effective blinding;[3–5] (2) those designing RCTs should expect unblinding unless novel steps are taken to avoid it;[1,2] (3) assessment of the success of blinding should be an essential condition for future RCTs;[1,2] (4) reviewers should anticipate unblinding and ask authors for evidence for the effectiveness of blinding procedures;[1,2] (5) authors of systematic reviews and meta-analyses should not accept the description of an RCT as ‘double-blind’ without supporting evidence; and (6) item 11b of

the CONSORT statement should be revised to require the assessment and reporting of blinding success in all RCTs which claim to be blinded, as proposed by Kolahi et al.[1,2]

REFERENCES

1. Kolahi J, Bang H, Park J. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. *Community Dent Oral Epidemiol* 2009; **37**: 477–84.

2. Boutron I, Estellat C, Guittet L, et al. Methods of blinding in reports of randomized controlled trials assessing pharmacologic treatments: a systematic review. *PLoS Med* 2006; **3**: e425.

3. Corry IS, Cosgrove AP, Walsh EG, McClean D, Graham HK. Botulinum toxin A in the hemiplegic upper limb: a double-blind trial. *Dev Med Child Neurol* 1997; **39**: 185–93.

4. Barwood S, Baillieu C, Boyd R, et al. Analgesic effects of botulinum toxin A: a randomized, placebo-controlled clinical trial. *Dev Med Child Neurol* 2000; **42**: 116–21.

5. Copeland L, Edwards P, Thorley M, et al. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. *J Pediatr* 2014; **165**: 140–6.e4.