Reviewer’s report

Title: Efficacy of Botulinum Toxin A in Modifying Spasticity to Improve Walking and Quality of Life in Post-Stroke Lower Limb Spasticity - a Randomized Double-blind Placebo Controlled Study.

Version: 1 Date: 25 Dec 2018

Reviewer: Joerg Wissel

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Efficacy of BoNT A Modifying Spasticity to Improve Walking and Quality of Life in PSLLS - a Randomized Double-blind Placebo Controlled Study

NURL-D-18-00451R1

Since the first randomized controlled trials (RCTs) with Botulinumtoxin Typ A (BoNT A) in the indication post-stroke lower limb spasticity (PSLLS) in the chronic phase following stroke consistent data with significant reduction of spastic muscle tone in the ankle from BoNT A have been reported.

In all studies published primary efficacy criteria in those single injection RCTs was to reduce velocity dependent increase in muscle tone in the ankle joint and efficacy was measured with the Ashworth Scale (AS), Modified Ashworth Scale (MAS) or Tardiue Scale (TS).

As well the high safety profile of BoNT A injections in PSLLS indications were confirmed by those studies. Therefore meta-analysis of the field published sufficient efficacy in reducing spastic ankle tone and high safety of BoNT A in the management of spastic gait pattern in adult patients with PSLLS.

On the other hand none of these RCTs were able to show effectiveness in improving longitudinal gait parameters, therefore no study could show improvement in gait function or active function of the lower limb or significant changes in quality of life related to BoNT A treatment in the lower limb compared with placebo injections.

Based on these data published another well designed RCT in this domain of PSLLS management with BoNT A using reliable and valid measures is welcome and this study design by Gupta et al. is especially welcome as it will use a measurement of longitudinal gait parameters to show changes in the different study groups as primary efficacy criteria. This study will include a gait velocity measurement with a device named Gait Rite and will also include in evaluation established secondary efficacy criteria including measures of impairment (muscle tone), activities / motor performance (2 Min. walk test, Berg Balance, TUG, ABILICO), goal attainment (GAS), ADL (SMAF) and QOL (SF12), as well as associated health economic analysis.

The study design (RCT with adequate blinding of placebo controlled injections) and patient numbers (planed sample size 80 patients) seems to be adequate to detect significant changes following a single
injection protocol and include following baseline evaluation and placebo controlled, EMG guided injection of clinically identified lower muscles a 3 weeks, 3 month and 5 month follow-up evaluation of the full evaluation data set. Muscles will be clinically identified and selected when a moderate to severe spastic muscle tone MAS 3+ (MAS 3 and 4) is present.

Both groups will receive a standardized physiotherapy (2 x 45 minutes physio per week, Borg’s scale 4-6) and home exercise training program of adequate intensity, frequency and duration. As well the intensity of the home exercise program will be evaluated by phone calls and ActivPal.

All in all the data that will be gathered in this prospective trial will allow to analysis a valid and reliable data set on the effects of a single BoNT A injection session with a limited dose of onabotulinumtoxinA (maximum allowed 400 units) of clinically selected individual set of muscles of the lower limb in a cohort of ambulating subacute and chronic stroke survivors that are selected by adequate inclusion and exclusion criteria.

A qualitative evaluation in a subgroup of the study population (25% of patients) will allow to detect difficulties that come up during the study.

Restrictions that may limit interpretation of the study results may arise from inclusion and exclusion criteria, the missing evaluation criteria passive range of motion and the limited dose of BoNT A available for injection in this protocol.

No selection criteria limit inclusion of patients for the study population to a certain time since stroke or a cohort of first ever stroke. Therefore the study population will include patients with multiple and first ever stroke and subacute and chronic stroke patients as well. Patients will be randomized to verum or placebo treatment and it is by chance whether more chronic stroke survivors or more patients with multiple stroke will be randomized in one or the another group. Since multiple strokes are known to be more related with gait disturbances and time since last stroke is of particular interest as in chronic stroke cases (duration of first ever or last stroke event and start of study > 6 month) contractures of the ankle, knee or hip joints may be more frequent those criteria should be captured in both cohorts. No information about contractures prior to study begin will be available as the evaluation criteria of passive range of motion (pROM) in the ankle, knee and hip joint of the spastic limb is not included in the study design.

Another factor that should be recognized may result from exclusion criteria for patients with aphasia. This may result in a study population with more right hemisphere stroke lesions. No information will be available about specific neuropsychological deficits, e.g. neglect to the left, as testing for neglect is not included in the study design.

Another area that may cause limitations in the interpretation of the study results may arise from not documenting data about sensory evaluation of the patients included into the study (e.g. sensory loss from stroke or polyneuropathy).

As the individual spastic gait pattern may include many lower limb muscles, e.g. in patients with stiff knee gait pattern with additional adduction of the hip and spastic equinovarus and clawed toes and a striatal big toe the dose of maximum 400 units onabotulinumtoxinA may be not sufficient to treat all spastic muscles involved to allow an increased walking speed.

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If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
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Yes

Are the conclusions drawn adequately supported by the data shown?
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