The efficacy of Botulinum Toxin A on improving ease of care in the upper and lower limbs: a systematic review and meta-analysis using the GRADE approach

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ABSTRACT

Objectives: A systematic review and meta analysis using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach; evaluating Botulinum Toxin type A efficacy on improving ease of care in the upper/lower limb.

Data Sources: Pubmed, Cinahl, Amed, Embase and Cochrane databases. English Language. Search to July 2014.

Review Methods: All randomized, placebo controlled trials on adults with difficulty in caring for the upper/lower limb resulting from spasticity of any origin and treated with a single dose of Botulinum Toxin A. Evidence quality was assessed by GRADE.

Results: Thirty-two studies were reviewed. Meta analysis was carried out on eleven upper limb and three lower limb studies. Evidence quality for the upper limb was moderate. A significant result for Botulinum Toxin A was found at four to twelve weeks for the upper limb (SMD 0.80 CI 0.55, 1.06, $p<0.0001$) The effects were maintained for up to six months (SMD 0.48 CI 0.34, 0.62, $p<0.0001$).

Evidence quality was very low for the lower limb. Meta analysis was only possible for global assessment of benefit. No significant effect was found. (Patient: RR 1.37 CI (0.94, 2.00) $p=0.11$, Clinician: RR= 1.06 (0.84, 1.34) $p=0.60$.)

Conclusion: Botulinum Toxin A improves ease of care in the upper limb for up to six months. No conclusion can be drawn for the lower limb.

INTRODUCTION

This is the second paper of three, which examine the efficacy of Botulinum Toxin A using the Grades of Assessment, Development and Evaluation (GRADE) approach.[1] The first review focused on the topics of pain and spasticity and found very low quality evidence with no significant effects on pain for the upper and lower limbs, while evidence quality was moderate with significant effects in favour of Botulinum Toxin A for reducing spasticity[2].

This review looks at the effect of Botulinum Toxin A on improving ease of care. Tasks performed for the patient by a carer or by the patient's unaffected limb are often referred to as passive function or self care activities[3]. Problems with these tasks can arise from the complications of spasticity and soft tissue changes leading to; skin breakdown, mal odour, abnormal limb position and difficulty washing and dressing the limb[4]. This all has an adverse effect on caregiver burden[4].

Botulinum Toxin blocks the release of acetylcholine from nerve endings and can selectively and reversibly induce muscle weakness and help reduce spasticity[5]. This temporary relief of muscle overactivity can allow easier extrinsic stretching of soft tissue structures and interrupt the muscle overactivity, which exacerbates tendon shortening[6]. This can in turn allow access to improved hygiene and dressing of the limb.

Several reviews and three Meta analyses have already reported that Botulinum Toxin A is effective in improving ease of care in stroke patients[7-12]. The Meta analyses have generally reviewed the global assessment of benefit scales and looked at the upper limb primarily.[7-9] Passive range of movement has been studied in a few reviews but with less significant outcomes.[13-14] A recent review found a moderate treatment effect

using the disability assessment scale but this was combined with other measures that looked at more active or global constructs.[15] No reviews have looked at goal attainment or lower limb studies separately.

This is the first systematic review of Botulinum Toxin A using ease of care outcomes and GRADE. The GRADE approach is becoming more widely recognised, is recommended for systematic reviews and guideline development, and is now used by Cochrane reviewers among other clinical groups[16].

The following clinical questions will be addressed; Should Botulinum Toxin A be used to:

- improve ease of care in the upper limb?
- improve ease of care in the lower limb?

A subsequent paper will address active movement and quality of life.

METHODLOGY

This study defined Botulinum Toxin as any standard preparation of the Type A toxin for clinical use to reduce spasticity.

Studies were included in the review if they were randomised controlled trials, included the use of Botulinum Toxin A versus a placebo/saline injection/control group, on either upper or lower limb in adult inpatients or outpatients, with outcome measures relating to ease of care. Muscle spasticity of any origin was considered; this allows for a comprehensive review and is more representative of the clinical setting.

Studies were excluded if they lacked a control group, were observational studies, on paediatrics or used other preparations of Botulinum Toxin besides Type A. Repeated injection studies were also excluded unless data from the initial injection could be used independently. All non English studies were excluded from this review.

The outcomes considered were passive range of movement, global assessment of benefit scales (also called clinical global impression, global assessment scale), disability assessment scale, carer burden scales and goals/goal attainment scale. These outcomes were selected from the recommendations in the Royal College of Physicians spasticity guidelines[17] and from initial literature searches. Outcomes were rated from highest to lowest in terms of patient importance as per the GRADE protocol. Goals and patient rating scales were rated highest, followed by carer burden scales and passive range of movement was rated lowest: as improvement may or may not directly help the patient.

A literature search was carried out for all relevant studies from 1989 (date of approval of Botulinum Toxin for clinical use)[8] up to 31st July 2014. The primary database searched was Pubmed using the MeSH terms of "muscle spasticity" and "Botulinum toxins". The limits and exclusions set were: adults, humans, English language and randomised controlled trials. (See Appendix I) The search was repeated adding all individual outcome measure names but no new, relevant studies were found. Searches with the same terms and limitations were carried out for Embase, Amed, Cinahl, and Cochrane.

Study quality was established using the GRADE approach as detailed in the previous paper[2]. The following definition was used: "quality of evidence" relates to the extent which one can be confident that an estimate of effect is correct.[1] Initial summary of findings were carried out for qualitative syntheses and then where possible a meta analysis was carried out on subgroups with appropriate data. Data from the relevant studies was extracted by the author using a preprepared form. The data was reviewed and cross checked for anomalies. Decisions on quality were made using guidance from GRADE publications and the website.[1,18-28]

Studies were chosen for Meta analysis if they provided sufficient data as a group in either dichotomous form (when data allowed results to be divided into improved versus no change/worse) or as means and standard deviations. Data was used from between one and six months post intervention; results were then analysed for four to twelve weeks (to analyse the effect over the active time for Botulinum Toxin) and for twelve to twenty four weeks (to gauge any significant lasting effects of treatment). Results given for week twelve could be used in either analysis but only once for each study, i.e. not duplicated.

Dichotomous data was analysed using the Mantel-Haenszel method to provide risk ratios (RR). Continuous data was analysed using the inverse-variance method to give a Weighted Mean Difference (WMD) for individual outcome measures where possible. The standardised mean difference (SMD) was used to pool the results of all outcome measures together as it allows for a variety of measurement methods. Random effects models were used in the presence of significant unexplained heterogeneity.

For dose ranging studies, treatment groups were combined to give a single pair wise comparison, to avoid potential bias in choosing results for analysis and as recommended by the Cochrane Handbook for systematic reviewers[29]. When multiple joint results were presented the most commonly measured joint was used and any variations noted. Significance was set at $p < 0.05$.

Data was analysed using the statistical pack Revman 5.2 from the Cochrane Collaboration.

RESULTS

Qualitative analysis

In the upper limb, fourteen studies looked at passive range of movement[30-43], four at the disability assessment scale[43-46], nine at the global assessment of benefit[32,37,38,44,46-50], six at carer burden scales[30,41,47,51-53] and six at goal setting[32,37,39,41,47,51]. The majority of trials used stroke patients with a few including acquired brain injury or using mixed neurological diagnoses. Methodology and results presentation varied greatly across trials.

The Disability Assessment Scale was the most consistently applied tool. Goal setting in particular was often poorly explained, making it difficult to ascertain whether the nature of the goals was impairment, activity or participation based. Only two studies used the validated Goal Attainment Scale and one used the Canadian Occupational Performance Measure.

Significant improvement for treatment groups was found for all studies using the global assessment of benefit and the disability assessment scale, eight using passive range of movement and three who used Carer burden scales. Both trials using the Goal Attainment Scale found significant improvements with Botulinum Toxin. Other goal setting studies were less positive; two studies noted improvements but no difference was found between groups (these studies included targeted additional therapy in their trials) and two studies failed to present their results.

In the lower limb, five trials examined passive range of movement[37,54-57], seven measured global assessment of benefit[37,54,55,57-60], two looked at carer burden with the hygiene score[54,61] and only one trial set goals[37]. Treatment was either aimed at the hip adductors or the triceps surae. The patient groups were more varied in the lower limb; stroke, acquired brain injury, multiple sclerosis and cerebral palsy. Again, the methodology and presentation of the results varied widely across trials making comparison difficult.

Results were less notable for the treatment groups in the lower limb; two trials found improvements in passive range of movement but failed to reach significance, four trials found significant improvements in global assessment of benefit. The results for goal setting were not presented. Both trials that used the hygiene score found a

significant improvement for Botulinum Toxin groups but, unfortunately, their results were not suitable for Meta analysis.

Quantitative Analysis

A Meta analysis of the upper limb results for weeks four to twelve, demonstrated a significant effect for all outcomes in favour of Botulinum Toxin with moderate quality of evidence, with the exception of the risk ratio analysis of clinician rated scores; these were of a lower quality due to small event numbers[31-33,35,38,41, 44-47,49]. (See Tables 1 and 2)

Overall pooled results gave a standardised mean difference of 0.80 (CI 0.55, 1.06), Z=6.17, p< 0.0001. This equates to a large effect size using Cohen's descriptions. [62] (See Figure 1)

The risk ratio was also calculated for the global assessment of benefit measures in the upper limb to calculate the number needed to treat (NNT). Patient rated = RR 2.21, (CI 1.67, 2.93), P<0.0001, NNT=5. Clinician rated = RR 2.51, (CI 1.21, 5.20), P=0.01, NNT=6.

A Meta analysis of upper limb outcomes for weeks 12 to 24, demonstrated a continued significant effect in favour of Botulinum Toxin for individual outcomes except the goal attainment scale where analysis was not possible. (See Table 2) Pooled analysis of outcomes gave a continued significant effect but with a moderate/low effect size; SMD 0.48 (CI 0.34, 0.62), Z= 6.62, P<0.0001.

Meta analysis of the lower limb studies was only possible for the global assessment of benefit and only in dichotomous form[54,55,58]. Both the patient and clinician rated scores failed to demonstrate a significant effect and were rated as low and very low

quality evidence respectively. (See Figures 2a and 2b) (Full details of grading can be found in Appendices II and III)

DISCUSSION

In this review significant results in favour of Botulinum Toxin A were found for the upper limb for all outcomes. The lower limb is less investigated in the literature and the results were not significant or were not suitable for a Meta analysis.

The quality of evidence was moderate overall for the upper limb. Most studies were graded down for inconsistencies or lack of clarity on randomisation, blinding, methodology and presentation of results.

Previous Meta analyses[8,9] on global assessment of benefit concur with the findings of this review and although the secondary analysis of dichotomous outcomes was a lower quality of evidence due to low event numbers, the numbers needed to treat are promising.

Passive range of movement has not been found to be significantly altered in other reviews[13,14], with the exception of shoulder external rotation at four to six weeks.[14] This review included a greater number of studies in the analysis, didn't use median values and chose change from baseline scores rather than final values; which may explain the different result here. Although passive range of movement does not measure ease of care directly, the carers ability to passively open fingers or move a shoulder or hip does impact on the effort required for washing and dressing and as an outcome measure is used frequently in the clinical setting. For these reasons it has been included in this review.

Foley et al[15] also found a significant effect using the Disability Assessment Scale but with only a moderate effect size of 0.53. However their study included both the Barthel and Action Research Arm test as outcome measures, which look at global daily functions and active upper limb movements respectively. The greater effect size here may be attributed to using outcomes more specific to ease of care.

The Disability Assessment Scale is a valuable outcome to use clinically and for future trials; it has been validated in stroke, covers areas of self care that are important to the patient and includes the patient choosing a goal for their target area. It was also developed primarily to detect a change from a focal treatment such as Botulinum Toxin[63].

The Goal Attainment Scale needs further investigation as it also showed a significant result but with small sample sizes; it remains a useful clinical tool, as it is an objective and measurable way of setting goals with patient involvement. The setting of a patient tailored goal is extremely important and ensures that the treatment is focussed on the individual and their priorities[64]. Ascertaining the nature of the goals set was difficult as few studies provided details. The majority of goals in the two studies reviewed here were around self care and clinically goals are often set around hygiene and self care; therefore the results have been included in this review. However an argument could easily be made for inclusion in a review of active outcomes in some cases.

A more consistent approach to the use of carer burden scales would allow this important outcome measure to be used in future Meta analyses.

Any official guideline recommendation for the use of Botulinum Toxin A to reduce problems with ease of care will have to balance the positive outcomes against costs and any possible harm from its use. An interesting outcome in this review was the

potential longevity of the toxin's effects. A significant effect was demonstrated for up to six months for most outcomes. Although further trials are needed to confirm the length of efficacy as the small sample sizes reduce the quality of evidence.

While these results do suggest that Botulinum Toxin A could be a potentially cost effective option for improving ease of care in the upper limb; this may be further enhanced by concurrent targeted therapy[12]. In this review, only two trials used targeted therapy in conjunction with Botulinum Toxin; both found significant results. It is likely that the addition of targeted physiotherapy and occupational therapy with the injection would produce enhanced results, as it allows for stretching and splinting of the relaxed soft tissue structures, while electrical stimulation has been postulated to increase the uptake of the toxin[6]. A review of observational studies may also support this, as rehabilitative therapies are more often used in conjunction with Botulinum Toxin A outside the artificial constraints of a controlled trial.

The lower limb evidence suffers from fewer trials to review. Where studies have been carried out the methodology is often lacking. It is worth noting that in one study, which was highly scored for quality, patient rated scales showed significant improvement for Botulinum Toxin A[58]. Further studies are needed with clear parameters for measuring care outcomes. The absence of goal setting methods in the lower limb was particularly evident. Carer burden scales would also provide useful information. The studies that did use a hygiene scale found positive results but the results were not suitable for Meta analysis. As the overall quality of evidence is very low, no conclusions can be drawn for the use of Botulinum Toxin A on improving ease of care in the lower limb. Clinically, treatment should be in conjunction with targeted goal setting and the use of carer burden scales to ensure the reduction of spasticity is meaningful for the patient[17].

A drawback of many studies was that ease of care limitations were not a primary focus of the trial or the inclusion criteria. Often studies had equivocal results, which could have been attributed to the selection of higher functioning patients with minimal care restrictions. Most of the studies focused on measuring spasticity as their primary measure; this affected their inclusion criteria and subject population, and explains why often results were not reported fully. It can be noted that in studies where the focus was on care measures such as the disability assessment scale then the inclusion criteria was more appropriate and better results were gained.

A major limitation recognised by this review is the use of only one author to carry out the search and critique the articles. PRISMA recommends that the use of at least two investigators reduces the risk of rejecting relevant reports[65]. Every attempt was made to minimise bias by the use of pre-drawn up forms, criteria and by double checking results. A second author was used for statistical analysis and robustness. It is a possibility that relevant studies have been missed in the search or that unwitting bias has been allowed into some decisions. Other criticisms may be directed at some of the subjective decisions on grading the quality of evidence. The decisions are based on uniform criteria and any diversions are fully explained. As documented by GRADE; as long as decisions are justified with clear reasoning then different recommendations can be valid and must be judged by the clinician on this basis[1]. The decision to group dose ranging studies may also be an area for debate. A Meta analysis in this area is often problematic. Trials look at differing indications, injection techniques, doses and muscles as well as a wide variety of outcome measurement; this is often alongside the use of ordinal measures with parametric statistical tests.[66] Therefore any results and conclusions must take into account these limitations.

Randomised controlled trials need to carry out studies with carefully selected outcomes, inclusion criteria and methodology to enable a comprehensive Meta analysis with high quality evidence in the future. Lower limb studies are especially needed to provide clear data for analysis. Focusing on carer burden scales and goal setting would provide more meaningful results for patients and clinicians. Observational studies need to be reviewed and may provide additional information especially on the effect of additional therapies.

This review supports the use of Botulinum Toxin A for improving ease of care in the upper limb; demonstrated by the global assessment of benefit, disability assessment scale, goal attainment scale and passive range of movement outcome measures. The benefit may last for up to six months in some cases. No decision can be made for the lower limb.

Clinical Messages

- Botulinum Toxin A can be recommended for improving ease of care in the upper limb; effects are evident for up to six months.

- No conclusions can be drawn for the lower limb.

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Table 1. Grades of evidence for the efficacy of Botulinum Toxin A on improving ease of self care in the upper and lower limb.

	PROM UL	DAS UL	GAS UL	GAB Pt UL (SMD)	GAB Cl UL (SMD)	GAB Pt UL (RR)	GAB Cl UL (RR)	Carer burden	PROM LL	Goals LL	GAB Pt LL	GAB Cl LL	Hygiene scale
Type of study	RCT (n=6)	RCT (n=3)	RCT (n=2)	RCT (n=4)	RCT (n=3)	RCT (n=4)	RCT (n=3)	RCT (n=5)	RCT (n=3)	RCT (n=1)	RCT (n=3)	RCT (n=2)	RCT (n=2)
Study Quality	-1	-1	0	-1	-1	-1	-1	-1	-1	N/A	-1	-2	-1
Study Consistency	0	0	0	0	0	0	0	0	0	N/A	0	0	0
Study Directness	0	0	0	0	0	0	0	0	0	N/A	0	0	0
Study precision	0	0	-1	0	0	0	-1	-1	-2	N/A	-1	-2	-2
Upgrades	None	None	None	None	None	None	None	None	None		None	None	None
Overall Grade	Mod	Mod	Mod	Mod	Mod	Mod	Low	Low	V Low		Low Low	V	V Low

PROM, passive range of movement; UL, upper limb; DAS, disability assessment scale; GAS, goal attainment scale; GAB, global assessment of benefit; Pt, patient rated; Cl, clinician rated; SMD, standardised mean difference; RR, risk ratio; LL, lower limb; Mod, moderate; V Low, very low; N/A, not possible to grade due to lack of evidence.