Effectiveness of botulinum toxin type A on gait and quality of life in adult post-stroke patients with lower limb spasticity: a systematic review protocol

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Review question/objective: The objective of this review is to examine the current best available evidence on the effectiveness of botulinum toxin type A on gait (velocity and distance) and quality of life (QoL) in adult post-stroke patients with lower limb spasticity.
More specifically, this review aims to determine the effectiveness of botulinum toxin type A on adult post-stroke patients with lower limb spasticity in relation to:

- Gait velocity
- Walking distance
- QoL.

Keywords Botulinum; mobility; quality of life; spasticity; stroke

Background

Stroke is a leading cause of mortality and morbidity globally. It is the third most common cause of disability globally among people over 65 years of age.[1] Post-stroke spasticity is one of the important impairments following stroke along with cognitive and other sensory motor problems. Prevalence post-stroke spasticity ranges from 4% to 42.6%.[2]

Spasticity is one of the upper motor neuron symptoms experienced by the stroke survivors and defined as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex (muscle tone) as one component of the upper motor neuron syndrome.[1]

Post-stroke spasticity typically affects one-half of the body, usually the upper and the lower limb, giving rise to spastic hemiparesis. Spasticity can significantly impair functions, such as mobility and activities of daily living of stroke survivors. In the lower limb, post-stroke spasticity manifests as adducted hip, stiff knee and most commonly equinovarus foot.[3] Equinovarus deformity in the ankle and foot is caused by spastic or overactive gastrocnemius, soleus and/or tibialis posterior muscles. Other foot muscles, such as flexor hallucis longus and flexor digitorum longus can also be involved causing clawing of toes. The other spastic lower limb muscles, such as the quadriceps, can cause stiff knee gait,[4] hamstrings knee flexion and the hip adductors (adductor magnus, brevis and longus) adduction of the hip. Spastic lower limb gives rise to the characteristic hemiplegic or circumducting gait.

Lower limb muscles are important for transferring from bed to chair, standing from a sitting position and maintaining standing balance before taking steps to walk. The deformities caused by the spastic lower limb muscles in isolation or with other impairments can potentially impede all aspects of mobility as outlined. Post-stroke spasticity can also result in spasm, pain and contracture (permanent deformity), further compounding mobility. Inability to move and lack of independence give rise to activity limitation and participation restriction, leading to poor quality of life (QoL). In some cases, spasticity associated with weakness and lack of voluntary control can lead to adverse health outcomes such

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as falls and fractures.[5] The burden of post-stroke spasticity is high on the stroke survivor's active function, QoL and also on the carer. Besides the human cost, there is a significant economic cost associated with post-stroke spasticity.[6]

Spasticity is managed by multidisciplinary rehabilitation team and by oral antispasticity medications such as baclofen, dantrolene, diazepam and clonidine and by blocking nerves with phenol or alcohol. The evidence on the efficacy of oral medications is marginal and their use is associated with adverse effects.[7] Botulinum toxin type A is an important adjunctive treatment along with stretching, strengthening exercise and bracing intervention for spasticity.

Botulinum toxin (BT) is a neurotoxin and works by blocking the acetylcholine at the neuromuscular junction weakens the muscle. This is a reversible action which lasts for two to four months[8], and the injection has to be repeated. There are three varieties of botulinum toxin type A – onabotulinum toxin or Botox (by Allergan), abobotulinum toxin or Dysport (Ipsen) and incobotulinum toxin or Xeomin (Merz), the first two of which are used widely. A number of studies have shown that the botulinum toxin is safe and effective in reducing focal spasticity.[8,9] It has been argued that the botulinum toxin should be the first-line treatment for post-stroke spasticity.[10]

Botulinum toxin is expensive and the licensed indication in many countries is often restricted to the post-stroke upper limb spasticity.[11] There is a number of studies demonstrating a reduction of upper limb spasticity measured by the Modified Ashworth Scale and associated disability with botulinum toxin.[12] The effectiveness of the toxin in improving function is less certain – more so in the lower limbs.[8] Studies have revealed strong evidence that the BT in the lower limb reduces spasticity. There have not been many randomized controlled trials (RCTs) in the lower limb showing improvement in lower limb functioning such as gait (velocity and/or distance) and improving the QoL. This may be the reason the toxin is still not approved by the pharmaceutical benefit scheme for use in the lower limb in many countries including Australia. A systematic review and meta-analysis revealed that use of BT was associated with a small but statistically significant increase in gait velocity.[3] Since then, some RCTs have been carried out with BT in lower limb. From a stroke survivor's perspective, the ability to walk remains one of the most important goals. Botulinum toxin is also useful for passive functions such as hygiene, preventing contracture and lessening the carer's burden and in combination with physiotherapy is found to reduce the economic cost in patients with post-stroke spasticity.[6] There is a recent systematic review and meta-analysis using on the efficacy of botulinum toxin type A for improving activity restriction and QoL of patients using the GRADE approach.[13] This systematic review included RCTs comprising a heterogeneous group of patients with spasticity in upper or lower limb from different causes and was not specific to post stroke lower limb spasticity. Currently, no systematic review is available synthesizing evidence from RCTs focusing on the efficacy of botulinum toxin in improving gait and walking distance and QoL among post-stroke patients with lower limb spasticity.

Hence, the present systematic review aims to synthesize and evaluate the current best available evidence, drawn from RCTs, on the effectiveness of botulinum toxin type A therapy on gait velocity, walking distance and QoL, specifically in adult post-stroke patients with lower limb spasticity. The studies to be included in this review will not be restrictive of the injection technique or dosage of botulinum toxin A used to enable a comprehensive assessment of the effectiveness of the treatment. Findings from the present review will serve to inform the usefulness of botulinum toxin type A in improving the functional outcomes of patients with post-stroke lower limb spasticity over the course of rehabilitation.

Inclusion criteria

Types of participants

This review will consider studies that include adult patients aged 18 years or above, who are recovering from either first or a subsequent count of stroke, with the presentation of unilateral spasticity in any part of the lower limb. There will be no restrictions on the muscles of the lower limb at which spasticity is manifested. Participants of any ethnicity, socioeconomic background, gender or ambulation status will be included.

Studies in which participants are pregnant, or have fixed contracture, or immobile or spasticity due to upper motor conditions other than stroke will be excluded. Lowerlimb post stroke spasticity of any duration or severity will be included in the review.

Types of intervention(s)

This review will consider studies that evaluate the effectiveness of botulinum toxin type A (Botox or Dysport or Xeomin) of any dosage or duration on gait, walking distance and QoL in post-stroke lower limb spasticity. Injection at any spastic lower limb muscle will be included. Studies using different techniques (ultrasound guided or EMG guided) of botulinum toxin type A injection for post stroke lower limb spasticity will be included. Participants who have received botulinum toxin type A treatment will be compared against those who have received control-placebo and/or usual care such as physiotherapy.

Outcomes

This review will consider the following measures as outcomes: gait velocity, walking distance and QoL in adult post-stroke patients with lower limb spasticity. Studies in which gait velocity or walking distance was measured using three-, six- or 10-min walk tests. The final determined value of gait velocity will be expressed in meters per second (m/s), and the final determined value of walking distance will be expressed in meters (m).

Studies in which QoL of adult post-stroke patients with lower limb spasticity is measured by SF-36 or others will be considered.

Types of studies

This review will consider only RCTs for inclusion.

Search strategy

The search strategy aims to find published peer-reviewed studies. A three-step search strategy will be utilized in this review. An initial limited search of PubMed and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English only will be considered for inclusion in this review. For a thorough search of existing literature on this topic, all published studies until present will be considered.

The databases to be searched include PubMed, Embase, Web of Science, CINAHL, ProQuest Theses and Dissertations, Google Scholar, WHO International Clinical Trial Registry Platform (WHO-ICTRP), ClinicalTrials.gov, Cochrane Clinical Trial Register (CCTR), Australian New Zealand Clinical Trials Registry (ANZCTR) and EU Clinical Trials Register (EUCTR).

Initial keywords to be used will be botulinum toxin, spasticity, muscle overactivity, hypertonia and stroke as MeSH, keywords and subject headings.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers (WHC and ADG) for methodological quality prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. In the case of missing data, authors of included primary studies will be contacted.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-square and also explored using subgroup analyses based on different study designs included in this review. The different study designs will be explored as subgroup analyses where possible. In cases where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

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Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number