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Botulinum toxin as early intervention for spasticity after stroke or non-progressive brain lesion: A meta-analysis

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ABSTRACT

Spasticity is a functionally limiting disorder that commonly occurs following stroke or severe brain injury, and may lead to disability and pain. In tandem with neurorehabilitation, botulinum toxin type A (BoNT-A) is the recommended first-line treatment for spasticity and, to date, the majority of trials have reported BoNT-A use in patients >6 months after ictus. The present meta-analysis aimed to evaluate the effects of early BoNT-A injection for post-stroke spasticity on improvements in hypertonicity, disability, function and associated pain. A literature search yielded six studies reporting the effects of BoNT-A treatment within 3 months post-stroke; three in the upper limb and three in the lower limb. All six studies permitted concomitant rehabilitation. Reduction in hypertonicity was compared in all six studies and revealed a significant treatment effect ($P = 0.0002$) on the most affected joints between weeks 4 and 12 following injection. However, no significant effects of treatment were observed for improvement in disability at week 4 or improvement in function at weeks 4 and 20–24. A trend towards reduction in spasticity-related pain at week 4 following BoNT-A treatment ($P = 0.13$) was also observed. These results demonstrate the beneficial effects of BoNT-A treatment on improving hypertonicity within 3 months post-stroke and emphasise the importance of concomitant neurorehabilitation therapy.

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1. Introduction

Spasticity may evolve early in the post-stroke period [1], with an incidence rate of ~19% within 3 months of the ictus [2] and >33% within 12 months [3,4]. In a post-stroke spasticity (PSS) cohort, 87 out of 100 patients, who had no functional arm movement following their first ictus, developed spasticity within 6 weeks, as measured using muscle activation recordings [5]. It was reported that in the initial 1–2 weeks and at 3 months following stroke, spasticity was most common in the anti-gravity muscles; additionally, the severity of upper limb spasticity increased over time [6]. A study of lower limbs reported a similar finding that 88% of study participants developed spasticity within 2 weeks of severe brain injury [7].

Spasticity was reported to be the major independent contributor to contracture in the first 4 months following stroke, followed by weakness thereafter [8]. In a clinic-based longitudinal study in an Asian population, upper limb PSS occurred in 33% of patients at 3 months post-stroke, and of the patients with moderate spasticity (Modified Ashworth Scale [MAS] = 2) at 3 months, almost half developed severe spasticity (MAS = 3) [9].

Botulinum toxin type A (BoNT-A) is indicated for use in the treatment of spasticity [10–12]. A previous meta-analysis performed on randomised, controlled clinical trials demonstrated that BoNT-A is safe and efficacious for the treatment of upper and lower limb spasticity [13]. Similarly, BoNT-A treatment has been shown to improve associated reactions in upper limb PSS [14], reduce predetermined disability parameters (including pain) [15–18], reduce carer burden [17–19], and improve person-centred goals [20] and self-reported efficacy [21]. Systematic reviews have also established the robust efficacy of BoNT-A over other pharmacologic therapies, including BoNT-B, for the treatment of upper limb PSS [22,23], and the therapeutic benefit of BoNT-A has been reported to be maintained after repeated treatment cycles [24,25].

Abbreviations: AE, adverse event; ARAT, Action Research Arm Test; BoNT-A, botulinum toxin type A; DS, Disability scale; GAS, Goal Attainment Scaling; MAS, Modified Ashworth Scale; PSS, post-stroke spasticity; ROM, range of motion; SMD, standard mean difference; VAS, visual analogue scale.

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However, the majority of studies to date report the application of BoNT-A injection in the chronic stage of hemiparesis [26,27] (i.e. >6 months and an average of 2.5 years post-stroke) wherein spasticity has been established [1,28]. Although this late intervention may be effective in the treatment of spasticity, severe spasticity can result in intrinsic muscle and viscoelastic changes, with resultant stiffness and contractures in the affected limb that impede movement [6]; therefore, it is possible that earlier intervention may decrease early-onset muscle stiffness and achieve a better long-term outcome.

As stated in the Royal College of Physicians national guidelines for BoNT-A use, the aim of spasticity management and treatment with BoNT-A is to relieve symptoms, improve function and prevent deterioration [29]. In current practice, treatment with BoNT-A is not initiated until secondary complications develop [30]; however, musculoskeletal deterioration may occur prior to spasticity treatment, and this late initiation could prevent full recovery [31].

As spastic hypertonicity can develop during the first 12 weeks following a central nervous system lesion [1,32], corresponding early initiation of therapy may be beneficial on a symptomatic level. In addition, this could reduce further spasticity development, thereby supporting rehabilitative approaches and preventing contractures and deformities that may evolve over the course of the disease [33].

Intensive, repetitive and task-specific motor re-learning-based neurorehabilitation therapies are an integral part of PSS management to regain motor control [34–36], complemented by BoNT-A therapy aimed at reducing muscle overactivity [1]. While the data appear robust regarding multi-modal therapies, they are only indicative of use for chronic PSS (i.e. >3 months post-stroke) [1,36]; data on the early application of these interventions, however, are insufficient. Previous studies have associated early post-stroke rehabilitation, including functional electrical stimulation, with improved functional outcomes [37–40]. The aim of the present study was to systematically review the effects of early BoNT-A injection for PSS and non-progressive brain lesions in terms of improvements in hypertonicity, disability, function, and associated pain.

2. Methods

2.1. Literature search strategy

A literature search of EMBASE, SCIENCEDIRECT and PUBMED was performed to identify published randomised controlled trials and abstracts on the effects of BoNT-A which was administered within the first 3 months following stroke or after stroke illness, and focusing on its impact on hypertonicity, disability, function, and pain. The search included articles from January 2001 until December 2015, with the search terms summarised in Fig. 1. Cross-referencing of cited articles was performed and, where necessary, research authors were contacted.

2.2. Types of studies and data extraction

Studies were included in the meta-analysis if they met the following inclusion criteria:

- Double-blind or single-blind, randomised controlled trial
- Study population ≥17 years of age, primarily diagnosed with stroke, as defined by the World Health Organization, including non-progressive brain lesions such as post-traumatic brain injury and hypoxic encephalopathy
- Onset of stroke ≤3 months before BoNT-A intervention, with description of the involved upper and lower limb muscles
- Outcome measures included reduction of muscle tone in spasticity, disability, function, and related pain.
- Description of the type, dosing schedule, number, and body region(s) of BoNT-A administration, and the other treatment strategies used for rehabilitation.
- Description of the methodology for randomisation and data analyses

The following exclusion criteria were also applied:

- Studies that were not randomised or had no control or placebo groups
- Editorial articles and abstracts that were not clinical in nature
- Case reports, expert reviews, and retrospective studies
- Studies that analysed chronic stroke (onset >3 months)
- Studies in which patients suffered spasticity as a consequence of another illness, such as demyelinating diseases, viral diseases, or heredodegenerative disorders
- Studies of BoNT-A injections that did not involve the upper and lower limbs

2.3. Statistical methods

Qualitative analyses of pooled study data were performed. Review Manager Version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; http://tech.cochrane.org/revman) was used for meta-analysis. The standardised mean difference (SMD) was used to compute effect sizes, given that the different studies reported statistics and variances in different units. This required approximations and assumptions to arrive at a common measure of difference. A random effects model was used since the true effect was not a primary objective.

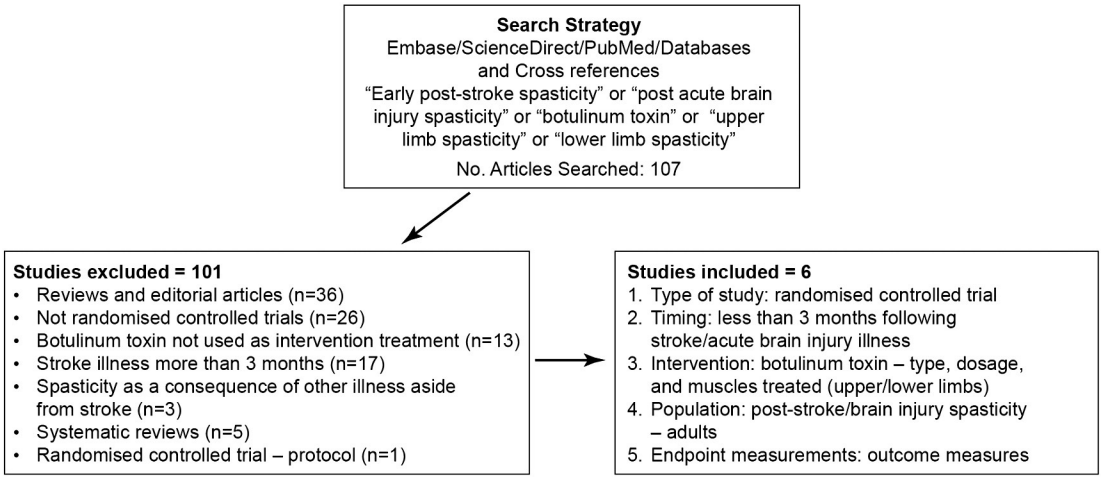

Fig. 1. Methodology of the literature search.

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