

Addition of botulinum toxin type A to casting may improve wrist extension in people with chronic stroke and spasticity: A pilot double-blind randomized trial

Hayley Scott, Natasha A. Lannin, Coralie English, Louise Ada, Tamina Levy, Rhiannon Hart, Maria Crotty

ABSTRACT

Aims: Does the addition of botulinum toxin type A increase the effect of casting for improving wrist extension after stroke in people with upper limb spasticity? **Methods:** Randomized trial with concealed allocation, assessor blinding and intention-to-treat analysis which was part of a larger trial included 18 adults with upper limb spasticity two years after stroke (89%) or stroke-like conditions (11%). The experimental group (n=7) received botulinum toxin type A injections to upper limb muscles for spasticity management

followed by two weeks of wrist casting into maximum extension. The control group (n=11) received two weeks of casting only. Range of motion (goniometry) measured at baseline and after two weeks of casting. **Results:** Passive wrist extension for the experimental group improved over two weeks from 22 degrees (SD 16) to 54 degrees (SD 16), while the control group improved from 21 degrees (SD 29) to 43 degrees (SD 26). The experimental group increased passive wrist extension 13 degrees (95% CI 4 to 31) more than the control group which was not statistically significant. **Conclusion:** Joint range of motion improved over a two-week period for both groups. Botulinum toxin type A injection followed-by casting produced a mean, clinically greater range of motion than casting alone, therefore, a fully-powered trial is warranted.

Keywords: Contracture, Muscle spasticity, Rehabilitation, Serial casts, Stretch

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INTRODUCTION

Botulinum toxin type A has been shown to reduce spasticity after stroke [1, 2]. However, it is often the decrease in joint range of motion which limits the ability to use the limb, rather than the presence of spasticity itself [3]. The most common rehabilitation intervention used to increase joint range is stretch. A systematic review of stretch showed that there was little effect (MD 2 degrees, 95% CI 2 to 6) of short term stretch after stroke across seven randomized trials [4]. However, there was a larger effect (MD 15 degrees, 95% CI 4 to 26) of long-term stretch in the lower limb after traumatic brain injury if it was applied continuously via casting in one randomized trial [4], with another randomized trial of casting after traumatic brain injury showing similar results in the upper limb (MD 22 degrees, 95% CI 13 to 31) [5].

Clinically, in the presence of spasticity, it is assumed that using botulinum toxin type A plus casting will increase range of motion more than casting used in isolation. Presumably this is because both impairments are being targeted—the contracture via casting and the spasticity via botulinum toxin type A. There is little evidence to support this hypothesis. Randomized trials showed no effect of adding botulinum toxin type A to casting after traumatic brain injury [6] (MD 2 degrees, 95% CI 9 to 13) or in children with cerebral palsy [7] (MD 5 degrees, 95% CI 4 to 13). Adding botulinum toxin type A to casting to reduce contracture has not been examined in a randomized trial after stroke. However, a single-group study [8] of botulinum toxin type A followed by three weeks of casting resulted in reduction in contracture of 7 degrees (95% CI 5 to 9) in people with chronic stroke and moderate to severe spasticity (Grade 3–4 on the modified Ashworth scale).

The aim of this study, therefore, was to investigate if the addition of botulinum toxin type A to casting is more effective than casting alone in increasing range of motion after stroke in people with moderate to severe spasticity.

MATERIALS AND METHODS

Design

This study was part of a larger randomized trial which investigated the effect of botulinum toxin type A alone, therapy alone and therapy plus botulinum toxin type A in patients with spasticity as a result of a neurological condition [9]. A component of the therapy was two weeks of casting in order to increase range of motion. This study therefore investigated the effect of the addition of botulinum toxin type A to casting on contracture (Figure 1). Participants were recruited from people presenting to the spasticity clinic of a metropolitan hospital in Adelaide, Australia with spasticity as defined as a Tardieu scale [10] score ≥ 2 out of 4. They were randomly allocated to the

experimental group (two weeks of casting plus botulinum toxin type A) or the control group (two weeks of casting only). The allocation sequence was generated using a computerized random number generator by someone not involved in the study and concealed using consecutively numbered, sealed, opaque envelopes which were opened by the injecting physician following baseline assessment. Therapists who applied the casts were blind to whether participants had been injected. Outcomes were measured at baseline before randomization and injection (week 0) and then again at least one hour after cast removal (week 2) by a researcher blind to group allocation. Data entry and analyses for this study were also conducted blind to group allocation. La Trobe University and Flinders University Human Research Ethics Committees approved this study. All participants provided written, informed consent prior to data collection.

Participants

Patients were included if they were aged over 18 years, were diagnosed with a stroke (or stroke-like condition), and had sufficient cognitive ability (defined as a score of more than 23 on Mini Mental State Examination [11]) and English language to be able to participate. They were excluded if they had: an allergy to proposed injection agents, or had had a botulinum toxin type A injection in the previous five months. Participants were included in this specific study if they had a cast applied in maximum wrist extension.

Intervention

The experimental group received botulinum toxin type A injections and then received two weeks of casting the wrist into maximum extension. The injection of BOTOX™ into their spastic muscle(s) was administered by a rehabilitation physician according to Australian practice recommendations [12, 13]. The treating physician used goal setting with participants and their carers to identify areas of concern specific to their spastic upper limb movement, and muscle choice for injection was based on these goals and the distribution of upper limb spasticity. BOTOX™ was supplied to participants through the Australian Pharmaceutical Benefits Scheme (PBS) and the maximum dose of at any one time point was 400 units. The forearm and hand was placed in a series of synthetic casts for two weeks so that the spastic wrist flexors were in a stretched position; some participants wore casts that also included the elbow (positioned in extension) and/or their fingers and thumb (positioned in extension). The position of the limb in the cast was determined by the therapist and by the participant's perception of a 'strong stretch' [5]. Second and third casts were applied (approximately 5–6 days after application of the previous cast) to gradually increase the stretch on muscles. Participants were monitored for sensation, pain,

circulation and skin breakdown; casts were modified or ceased in the presence of complications.

Outcome measure

Passive wrist extension was measured using goniometry and reported in degrees. Participants sat at a table with the arm on a table. A measurer stabilized the forearm in pronation and passively extended the wrist in maximum extension to the limit of comfort. Another measurer placed a goniometer along the forearm and the hand, and measured wrist extension (where zero is the wrist in neutral). The procedure [14] was carried out by trained measurers who were registered physiotherapists and occupational therapists.

Data analysis

Measures of central tendency (mean or median) and measures of dispersion (SD, IQR) were used to present characteristics of the participants. The size of the effect was determined as the mean between-group difference (95% CI). Primary analysis was by intention-to-treat, where each participant’s data were analyzed in the group to which they were randomly assigned irrespective of intervention received or refused [15]. Missing data was replaced by the group means.

RESULTS

Flow of participants through the study

Eighteen participants from the original trial were eligible because they had casts applied to increase wrist extension and were included in this study. Seven participants had been randomized to the experimental group and 11 had been randomized to the control group. There were two participants lost to follow-up (Figure 1).

The mean age of the participants was 60 years (SD 13) and 14 (78%) were male. Most had suffered a stroke (n = 17, 89%), two years previously. The control group was

slightly younger, contained two participants with a non-stroke brain injury, had slightly worse upper limb activity and a lower quality of life (Table 1).

Adherence to trial method

All participants received at least two casts over a two-week study period. The median number of casts per participants applied was three with one participant (5%) receiving four. The mean length of time that a cast was worn continuously was 5 days (SD 1); and the mean duration of casting was 16 days (SD 2). The most common types of cast were either a short-arm cast or a short-arm cast with a finger platform and dorsal cut-out. The other casts were long-arm casts (with and without a finger platform). Just under half of the participants (n = 8, 44%) had their type of cast changed over the study period, with the most common change being from a short arm cast to a short arm cast plus a finger platform. Minor adverse events (n = 20 events) including swelling, redness, skin breakdown/blister and sensory discomfort were noted, but none were serious enough to lead to early cast removal.

Experimental participants received botulinum toxin type A injections into muscles affected by spasticity. Most participant had injections into flexor carpi radialis and ulnaris as well as flexor digitorum superficialis and profundus, with a total dose ranging from 100–400 units (Table 2).

Effect of intervention

Group data are presented in Table 3. Passive wrist extension improved over the two weeks from 22 degrees (SD 16) to 54 degrees (SD 16) in the experimental group, and from 21 degrees (SD 29) to 43 degrees (SD 26) in the control group. The experimental group increased passive wrist extension 13 degrees more than the control group which was not statistically significant (95% CI -4 to 31).

DISCUSSION

After two weeks of casting, passive wrist extension improved in both groups (with or without botulinum toxin type A). This pilot study found that the addition of botulinum toxin type A to the casting increased passive wrist extension although the amount of improvement was not statistically significant. However, the mean difference between the groups was 13 degrees which is approaching clinical significance. These findings suggest that a larger fully powered trial is warranted.

The large gain in range of motion as a result of casting with the addition of botulinum toxin type A (32 degrees, SD 19) in this pilot study was larger than previously found in a group of people with stroke (7 degrees, SD 3) [8], people with traumatic brain injury (14 degrees, SD 8) [6]

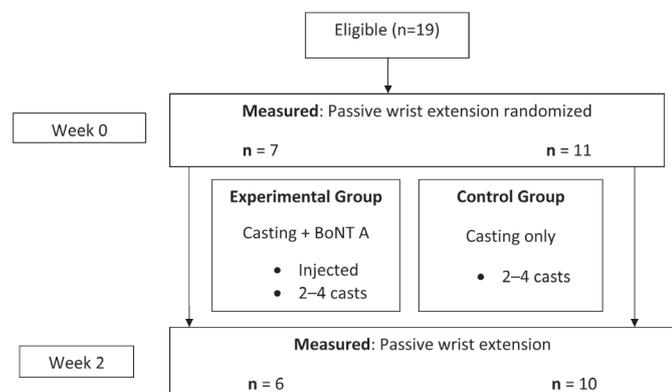


Figure 1: Design of and flow of participants through the study.

Table 1: Characteristics of participants at baseline

Characteristics	Group	
	Exp n=7	Con n=11
Age in years, mean (SD)	62 (10)	58 (14)
Sex male (%)	7 (100)	7 (64)
Side of hemiplegia, n left (%)	4 (57)	6 (55)
Type of neurological condition, n (%)		
Stroke (infarct)	6 (86)	6 (55)
Stroke (haemorrhage)	1 (14)	3 (27)
Non-stroke brain injury	0 (0)	2 (18)
Time since stroke (month), median (IQR)	24 (5–38)	23 (11–95)
Spasticity (Tardieu Scale, 0-4), mean (SD)	2.9 (0.4)	2.5 (0.5)
Upper limb activity (Box and Block Test, blocks/60s), median (IQR)	0 (0–24)	0 (0–6)
Quality of life (EQ-5D, 0-100), mean (SD)	71 (20)	55 (16)

Exp: Experimental Group Received Casting + BoNT-A, Con: Control Group Received Casting, EQ-5D EuroQual 5-dimension (3 level).

Table 2: Characteristics of BoNT-A injections (n = 7)

Participant	Drug	Side injected	Muscles injected	Total dose (units)	Average dose (units/mm)
UL01	BOTOX™	Right	FCR, FCU, FDS, FDP	100	25
UL05	BOTOX™	Left	FCR, FCU, FDS, FDP, biceps, brachialis,	400	35
UL08	BOTOX™	Left	FCR, FCU	100	50
UL17	BOTOX™	Left	FCR, FDS, biceps, pronator teres, pronator quadratus,	200	40
UL26	BOTOX™	Left	FCR, FCU, FDS, FDP, biceps, brachialis	300	30
UL28	BOTOX™	Right	FCR, FCU, FDS, FDP	300	75
UL34	BOTOX™	Right	FCR, FCU, FDS, FDP, FPL, biceps, brachialis	300	50

FCU: Flexor Carpi Ulnaris, FCR: Flexor Carpi Radialis, FDS: Flexor Digitorum Superficialis, FDP: Flexor Digitorum Profundus, FPL: Flexor Pollicis Longus, FPB: Flexor Pollicis Brevis

Table 3: Mean (SD) for each group, mean (SD) difference within groups, and mean 95% CI) difference between groups for passive wrist extension.

Outcome	Groups				Difference within groups		Difference between groups
	Week 0		Week 2		Week 2 minus 0		Week 2 minus 0
	Casting + BoNT-A n= 7	Casting n=11	Casting + BoNT-A n= 7	Casting n=11	Casting + BoNT-A	Casting	Casting + BoNT-A minus Casting
Passive wrist ext Goniometry (deg)	22 (16)	21 (29)	54 (16)	43 (26)	32 (19)	19 (17)	13 (4 to 31)

BoNT-A: Botulinum Toxin Type A

or people with cerebral palsy (6 degrees, SD 8) [7]. The degree of spasticity was similar across studies and ranged from 2.5–3.5 on the Modified Ashworth Scale. However, all previous studies had casted the ankle whereas, this study casted the wrist, which may account for the difference in reduction in contracture. The participants were people living with chronic stroke who had moderate to severe spasticity and were severely disabled as reflected in the median score of zero on the Box and Block Test. The large gain in range of motion as a result of casting with or without the addition of botulinum toxin type A (24 degrees, SD 18) may not have been maintained in the long-term due to the inability to move the upper limb. For example, a group of severely disabled people with traumatic brain injury lost 60% of the gains in range of motion made as a result of casting within one month [5].

The main limitation of this pilot randomized trial is that the measure of passive wrist extension was not torque-controlled [16]. However, both groups received continuous stretch in the form of casting, so both groups would interpret ‘discomfort’ in the same way, so the between-group effect is not likely to be influenced by this lack of standardization of torque. Given that a larger trial is warranted, it should also include a measure of activity [17] as well as measures taken beyond the intervention to determine the long-term effects of casting with the addition of botulinum toxin type A.

The small sample size of the current study is typical of a pilot study. We were interested in determining if casting plus botulinum toxin type A was potentially more beneficial than casting alone, and if so, to determine a likely effect size for a fully powered study. The control group increased their passive wrist extension from 21 to 43 degrees. A between-group difference of 15 degrees (i.e., the experimental group increasing passive wrist extension from 21–58 degrees) represents about a third of the available range in wrist extension. Power analysis using the change in passive wrist extension of the current study suggests that a sample size of 46 participants (23 in each group) is required to detect a clinical between-group difference of 15 degrees at an alpha of 0.05 and beta of 0.80. Allowing for a 10% dropout, a fully-powered study would consist of 52 people with chronic stroke, spasticity ≥ Grade 2 on the modified Ashworth scale, and about 20 degrees of passive wrist extension.

Implications for rehabilitation

- Spasticity and contracture are disabling impairments in chronic stroke.
- Common interventions include botulinum toxin type A for spasticity management and casting for contracture management.
- This pilot double-blind randomized trial suggests that joint range of motion increases more after a combination of botulinum toxin type A and casting than casting alone.

Author Contributions

Hayley Scott – Substantial contribution to design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be studied

Natasha A. Lannin – Substantial contribution to design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be studied

Coralie English – Substantial contribution to design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be studied

Lousie Ada – Substantial contribution to design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be studied

Tamina Levy – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be studied

Rhiannon Hart – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be studied

Maria Crotty – Substantial contribution to design, Revising it critically for important intellectual content, Final approval of the version to be studied

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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REFERENCES

1. Simpson DM, Alexander DN, O'Brien CF, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: A randomized, double-blind, placebo-controlled trial. *Neurology* 1996 May;46(5):1306–10.
2. van Kuijk AA, Geurts AC, Bevaart BJ, van Limbeek J. Treatment of upper extremity spasticity in stroke

- patients by focal neuronal or neuromuscular blockade: A systematic review of the literature. *J Rehabil Med* 2002 Mar;34(2):51–61.
3. O'Dwyer NJ, Ada L, Neilson PD. Spasticity and muscle contracture following stroke. *Brain* 1996 Oct;119(5):1737–49.
 4. Katalinic OM, Harvey LA, Herbert RD, Moseley AM, Lannin NA, Schurr K. Stretch for the treatment and prevention of contractures. *Cochrane Database Syst Rev* 2010 Sep 8;(9):CD007455.
 5. Moseley AM, Hassett LM, Leung J, Clare JS, Herbert RD, Harvey LA. Serial casting versus positioning for the treatment of elbow contractures in adults with traumatic brain injury: A randomized controlled trial. *Clin Rehabil* 2008 May;22(5):406–17.
 6. Verplancke D, Snape S, Salisbury CF, Jones PW, Ward AB. A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury. *Clin Rehabil* 2005 Mar;19(2):117–25.
 7. Kay RM, Rethlefsen SA, Fern-Buneo A, Wren TA, Skaggs DL. Botulinum toxin as an adjunct to serial casting treatment in children with cerebral palsy. *J Bone Joint Surg Am* 2004 Nov;86-A(11):2377–84.
 8. Yasar E, Tok F, Safaz I, Balaban B, Yilmaz B, Alaca R. The efficacy of serial casting after botulinum toxin type A injection in improving equinovarus deformity in patients with chronic stroke. *Brain Inj* 2010;24(5):736–9.
 9. Lannin NA, English C, Levy T, Ratcliffe J, Ada L, Crotty M. Design and feasibility of a randomized clinical trial to evaluate the effect of intensive rehabilitation following botulinum toxin injections in neurological patients with spasticity. *Neurorehabilitation and Neural Repair* 2012;26:5.
 10. Patrick E, Ada L. The Tardieu scale differentiates contracture from spasticity whereas the Ashworth scale is confounded by it. *Clin Rehabil* 2006 Feb;20(2):173–82.
 11. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 Nov;12(3):189–98.
 12. Pharmaceutical benefits advisory committee. Botulinum Toxin A: Final public summary document. 2008. [Available at: <http://www.pbs.gov.au/medicine/item/10993N-10997T-10998W-10999X-11000Y-11004E-11016T-11023E>]
 13. Sheehan G, Lannin NA, Turner-Stokes L, Rawicki B, Snow BJ; Cerebral palsy institute. Botulinum toxin assessment, intervention and after-care for upper limb hypertonicity in adults: International consensus statement. *Eur J Neurol* 2010 Aug;17 Supp 2:74–93.
 14. Norkin CC, White DJ. *Measurement of Joint Motion: A Guide to Goniometry*. Philadelphia: FA Davis; 1988.
 15. Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials* 2000 Jun;21(3):167–89.
 16. Folpp H, Deall S, Harvey LA, Gwinn T. Can apparent increases in muscle extensibility with regular stretch be explained by changes in tolerance to stretch? *Aust J Physiother* 2006;52(1):45–50.
 17. Lewinter M, Mikkelsen S. Patients' experience of rehabilitation after stroke. *Disabil Rehabil* 1995 Jan;17(1):3–9.

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