Botulinum Toxin Injection for Hypertonicity of the Upper Extremity Within 12 Weeks After Stroke: A Randomized Controlled Trial

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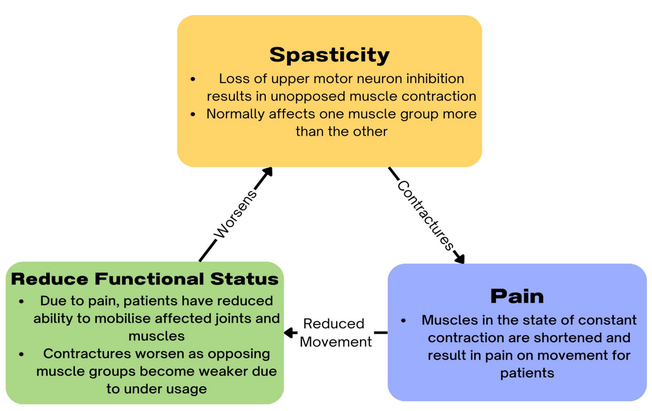
Introduction

Spasticity is defined as a motor disorder. About 19% of stroke patients develop spasticity within 3 months post-stroke, with a recent study suggesting that up to 80% of patients without functional arm movement may develop spasticity within 6 weeks of their first stroke.

Botulinum neurotoxin type A (BoNT-A) is commonly administered in post-stroke patients to reduce spasticity.



Previous studies regarding the effectiveness of BoNT-A administration were done in patients with chronic spasticity, more than 6 months post-stroke (average of 2.5 years). Since chronic spasticity leads to changes in the structural properties of affected muscles, leading to stiffness and contractures, early intervention may decrease early-onset stiffness and achieve a better long-term outcome. Only a small Phase II trial so far been conducted to study the efficacy of early administration of BoNT-A and was deemed to not be sufficiently powered. Thus, this study sought to be the first fully powered study to evaluate the efficacy and safety of early injection (within 2-12 weeks) of BoNT-A in reducing post-stroke spasticity.

The purpose of the study was to evaluate the efficacy of early injection of BoNT-A in treatment of early upper limb post-stroke spasticity.

Methods

163 patients across 5 multi-nation neurological centres were recruited for the study within 2-12 weeks of their first ever stroke. Sample size (n=163) was calculated using non-parametric Wilcoxon test to ensure adequate powering of the study.

Ethical approval was obtained from all participating institutions.

Inclusion Criteria	Exclusion Criteria
• 2-12 weeks after first ever stroke, confirmed by CT MRI • Modified Ashworth Scale (MAS) score of 1+ or higher in elbow and wrist joint • Weakness of at least MRC grade 2 in relevant joints	• Pregnancy / Lactation • Pre-stroke Rankin score greater than 1 • Known hypersensitivity to test materials • Preexisting neuromuscular or neurogenic disorder • Previous treatment with botulinum toxin

This was a randomised, double-blinded, placebo-controlled trial. Participants were randomly sorted in a 1:1 ratio into intervention group and placebo group. The former received 1 injection of 500U Dysport Botulinum toxin complex, whereas the latter received 1 injection of 500U placebo drug. Investigators were permitted to adjust the dose per targeted upper-limb muscle group depending on the level of hypertonicity, as long as the total dosage per patient was 500U.

Participants were allowed to continue with any pre-existing antispasmodic medications and physiotherapies, but were not permitted to add on any drugs during the trial period.

The primary outcome measured was participants' Modified Ashworth Scale (MAS) score in the most affected joint 4 weeks post-injection. Secondary outcomes measures, such as the Barthel index, modified Rankin Scale scores, Functional Motor Assessment Scale scores, passive and active range of motion, as well as spascity-related pain scores were measured at 2, 4, 8, 12 and 24 weeks.

ANCOVA testing was used to analyze the difference in primary and secondary efficacy outcomes between the placebo and BoNT-A groups.

References

1. Rosales RL, Kong KH, Goh KJ, Kumthornthip W, Mok VC, Delgado-De Los Santos MM, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke. Neurorehabilitation and Neural Repair. 2012 Feb 27;26(7):812–21. doi:10.1177/1545968311430824

Results

All 163 patients who were enrolled in the study received either BoNT-A (n=80) or placebo (n=83) and were included in primary and secondary outcome analysis. For sensitivity analysis, 10 patients were excluded due to major protocol deviations.

At 4 weeks post-injection, BoNT-A was significantly more effective in improving MAS scores than placebo for all patients. Those with a higher baseline MAS score showed a larger treatment effect size estimate (greater mean decrease in MAS score) at 4 weeks. Participants' country and time to injection after stroke onset showed no interaction with treatment outcomes.

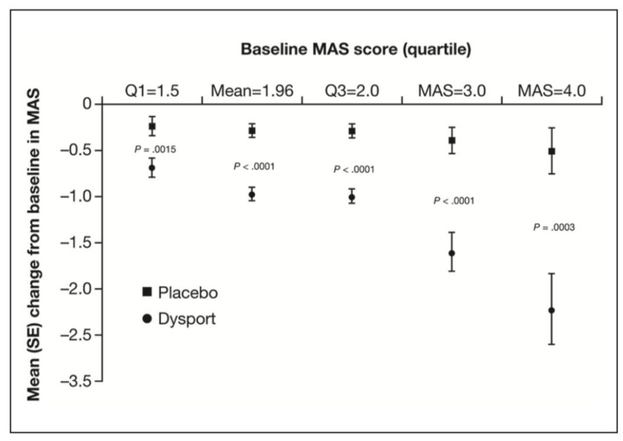


Fig 2: Results of primary outcome analysis. Mean (SE) change from baseline MAS score at week 4. Endpoint of MAS score 1+ is coded as 0.5.

Secondary effect analyses showed that MAS scores for most affected joints significantly improved with BoNT-A all time points during the 24 weeks. Spasticity-related pain was also decreased at 4 and 24 weeks, and patients had increased passive range of motion of the elbow and wrist, and improved finger active movement. Total Barthel index, modified Rankin score and Functional Motor Assessment Scale scores showed no significant change.

	Assessment Week					
	2	4	8	12	24	*P* Value
MAS score[b]						
Most affected joint	−0.66 (−0.84, −0.49)	−0.67 (−0.88, −0.47)	−0.60 (−0.82, −0.39)	−0.66 (−0.88, −0.43)	−0.54 (−0.79, −0.30)	<.0001, All weeks
Total Barthel index score	−0.17 (−0.79, 0.45)	0.29 (−0.44, 1.01)	−0.21 (−1.02, 0.60)	0.04 (−0.78, 0.85)	0.00 (−0.86, 0.87)	
Modified Rankin score	0.04 (−0.15, 0.22)	0.06 (−0.14, 0.27)	0.15 (−0.06, 0.36)	0.04 (−0.19, 0.28)	0.09 (−0.14, 0.32)	
Total Motor Assessment Scale	−0.02 (−0.67, 0.64)	−0.21 (−1.05, 0.62)	−0.66 (−1.64, 0.32)	−0.45 (−1.44, 0.54)	−0.70 (−1.82, 0.41)	
Global Pain Scale	−3.50 (−9.43, 2.43)	−7.87 (−13.28, −2.46)	−5.84 (−12.61, 0.94)	−5.93 (−12.63, 0.77)	−7.15 (−13.76, −0.54)	.0043, Week 4 .0340, Week 24
Goniometry: elbow						
Active movement	2.80 (−3.98, 9.58)	5.16 (−1.94, 12.25)	3.78 (−4.29, 11.85)	5.06 (−3.05, 13.18)	5.23 (−2.87, 13.34)	
Passive movement	4.07 (1.55, 6.59)	4.67 (1.13, 8.22)	2.86 (−1.24, 6.97)	2.14 (−2.15, 6.42)	4.52 (1.13, 7.90)	.0015, Week 2 .0097, Week 4 .0089, Week 24
Goniometry: wrist						
Active movement	0.34 (−5.50, 6.19)	0.71 (−5.45, 6.88)	3.21 (−3.48, 9.90)	3.80 (−3.77, 11.36)	2.73 (−6.31, 11.77)	
Passive movement	2.78 (−4.19, 9.75)	7.31 (0.68, 13.94)	6.08 (−0.18, 12.34)	6.43 (−0.74, 13.59)	9.40 (2.43, 16.38)	.0307, Week 4 .0082, Week 24
Goniometry: finger						
Active movement	0.18 (−0.05, 0.41)	0.31 (0.05, 0.57)	0.33 (0.06, 0.60)	0.35 (0.05, 0.65)	0.17 (−0.13, 0.47)	.0191, Week 4 .0181, Week 8 .0227, Week 12

Fig 3: Analysis of secondary outcome measures, taken at 2,4,6, 12 and 24 weeks post-injection. Statistically significant findings are highlighted in yellow.

Discussion / Conclusion

Safety and uses of BoNT-A

This is the first trial showing that BoNT-A with physiotherapy is effective and safe in the treatment of early post-stroke spasticity of the upper extremity. BoNT-A resulted in a decrease in MAS scores across all patients, but was more effective in patients with higher baseline MAS scores. BoNT-A is effective in reducing spasticity related pain.

Limitations

Results show that the participants' Barthel index, which assesses 10 different activities of daily living, and their modified Rankin scale score, which assesses the degree of disability post-stroke, showed no significant improvements. This is as both scales measure patients' gross functions.

In clinical practice, upper limb spasticity is only treated when it is symptomatic. However, the issue of whether upper limb spasticity was symptomatic or not was not evaluated in this study.

Further research

Having established the safety and efficacy of BoNT-A in early poststroke upper limb spasticity, the next step would be to study the effects of BoNT-A in early symptomatic poststroke upper limb spasticity. In this respect, the use of patient reported outcome measures (PROM), such as Goal Attainment Scale would provide meaningful outcomes.

Positive effects of BoNT-A were seen throughout the study period of 6 months, lasting longer than the expected duration of 3-4 months. Further trials would be helpful to determine whether this is replicable.