

BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A

L Shaw,¹ H Rodgers,^{1,2*} C Price,²
F van Wijck,³ P Shackley,⁴ N Steen,⁴
M Barnes,⁵ G Ford,¹ L Graham,⁵ on behalf of
the BoTULS investigators

¹Institute for Ageing and Health (Stroke Research Group), Newcastle University, Newcastle upon Tyne, UK

²Northumbria Healthcare NHS Foundation Trust (North Tyneside General Hospital and Wansbeck General Hospital), North Shields and Ashington, UK

³School of Health Sciences, Queen Margaret University, Edinburgh, UK

⁴Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

⁵International Centre for Neurorehabilitation, Newcastle upon Tyne, UK

*Corresponding author



Executive summary

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Executive summary

Background

Between 50% and 70% of stroke patients have ongoing upper limb functional limitations. Upper limb spasticity may contribute to reduced function, pain and deformity. Botulinum toxin type A is used increasingly to treat focal spasticity in neurological rehabilitation, but its impact on upper limb function after stroke is unclear.

Aim

The Botulinum Toxin for the Upper Limb after Stroke (BoTULS) trial evaluated the clinical effectiveness and cost-effectiveness of botulinum toxin type A plus an upper limb therapy programme in the treatment of post-stroke upper limb spasticity.

Design

A multicentre open-label parallel-group randomised controlled trial and economic evaluation.

Setting

Twelve stroke services in the north of England. Referrals were received from stroke units, outpatient clinics, day hospitals, community rehabilitation teams, stroke clubs and day centres.

Participants

Three hundred and thirty-three patients with upper limb spasticity at the shoulder, elbow, wrist or hand and reduced upper limb function due to stroke more than 1 month previously were enrolled in the trial between July 2005 and March 2008.

Intervention and control treatments

The intervention group received botulinum toxin type A injection(s) (Dysport®) plus a 4-week programme of upper limb therapy. The control

group received the upper limb therapy programme alone. Participants were clinically reassessed at 3, 6 and 9 months to determine the need for repeat botulinum toxin type A injection(s) and/or therapy.

Main outcome measures

The primary outcome was upper limb function 1 month after study entry measured by the Action Research Arm Test (ARAT). A successful outcome was defined as:

1. a change of three or more points on the ARAT scale for a participant whose baseline ARAT score was between 0 and 3
2. a change of six or more points on the ARAT scale for a participant whose baseline ARAT score was between 4 and 51
3. a final ARAT score of 57 for a participant whose baseline ARAT score was 52–56.

Outcome assessments were undertaken at 1, 3 and 12 months by an assessor who was blinded to the study group allocation. Upper limb impairment and activity limitation were assessed by: Modified Ashworth Scale; Motricity Index; grip strength; ARAT; Nine-Hole Peg Test; upper limb basic functional activity questions and the Barthel Activities of Daily Living (ADL) Index. Stroke-related quality of life/participation restriction was measured using the Stroke Impact Scale, European Quality of Life-5 Dimensions (EQ-5D) measure of health-related quality of life and the Oxford Handicap Scale. Upper limb pain was assessed using numerical rating scales. Participant-selected upper limb goal achievement (1 month only) was measured using the Canadian Occupational Performance Measure. Adverse events were compared. Health-care and social services resource use was compared during the first 3 months postrandomisation. EQ-5D data were used to calculate the quality-adjusted life-years (QALYs) associated with intervention and control treatments, and the incremental cost per QALY gained of botulinum toxin type A plus therapy compared with therapy alone was estimated. The sensitivity of the base-case results to alternative assumptions was investigated, and cost-effectiveness acceptability curves, which summarise the evidence

of botulinum toxin type A plus therapy being cost-effective for a range of societal willingness to pay for a QALY values, presented.

Results

Randomisation groups were well matched at baseline. There was no significant difference between the groups for the primary outcome of improved arm function at 1 month. This was achieved by 30/154 (19.5%) in the control group and 42/167 (25.1%) in the intervention group ($p = 0.232$). The relative risk of having a 'successful treatment' in the intervention group compared with the control group was 1.3 [95% confidence interval (CI) 0.9 to 2.0]. No significant differences in improved arm function were seen at 3 or 12 months.

In terms of secondary outcomes, muscle tone/spasticity at the elbow was decreased in the intervention group compared with the control group at 1 month. The median change in the Modified Ashworth Scale was -1 in the intervention group compared with zero in the control group ($p < 0.001$). No difference in spasticity was seen at 3 or 12 months.

Participants treated with botulinum toxin type A showed improvement in upper limb muscle strength at 3 months. The mean change in strength from baseline (upper limb component of the Motricity Index) was 3.5 (95% CI 0.1 to 6.8) points greater in the intervention group compared with the control group. No differences were seen at 1 or 12 months.

Participants in the intervention group were more likely to be able to undertake specific basic functional activities, e.g. dress a sleeve, clean the palm and open the hand for cutting fingernails. At 1 month, 109/144 (75.7%) of the intervention group and 79/125 (63.2%) of the control group had improved by at least one point on a five-point Likert scale for at least one of these tasks ($p = 0.033$). At 3 months the corresponding proportions were 102/142 (71.8%) of the intervention group and 71/122 (58.2%) of the control group ($p = 0.027$). Improvement was sustained at 12 months for opening the hand for cleaning the palm and opening the hand for cutting the nails, but not for other activities.

Pain rating improved by two points on a 10-point severity rating scale in the intervention group compared with zero points in the control group ($p = 0.004$) at 12 months, but no significant differences were seen at 1 or 3 months.

There were a number of occasions when there were statistically significant differences in favour of the intervention group; however, these differences were small and of uncertain clinical relevance. These differences were: 3 months – upper limb function (change in ARAT score from baseline), pain (EQ-5D) and participation restriction (Oxford Handicap Scale); 12 months – anxiety/depression (EQ-5D) and participation restriction (Oxford Handicap Scale).

No differences in grip strength, dexterity, or the Barthel ADL Index were found at any time point. There were no differences between the groups for achievement of patient-selected goals. There was a higher incidence of general malaise/flu-like/cold symptoms in participants treated with botulinum toxin type A with a relative risk of 7.6 (95% CI 1.8 to 32.3). Only one serious adverse event (dysphagia) was potentially related to botulinum toxin type A.

Time since stroke and severity of initial upper limb function were preplanned subgroup analyses. There was no significant difference in either subgroup for achievement of ARAT 'success' following treatment with botulinum toxin type A.

The base-case incremental cost-effectiveness ratio was £93,500 per QALY gained and estimation of the cost-effectiveness acceptability curve for botulinum toxin type A plus the upper limb therapy programme indicated that there was only a 0.36 probability of its being cost-effective at a threshold ceiling ratio of £20,000 per QALY.

Conclusions

The addition of botulinum toxin type A to an upper limb therapy programme to treat spasticity due to stroke did not enhance improvement in upper limb function when assessed by the prespecified primary outcome measure at 1 month. However, improvements were seen in muscle tone at 1 month, upper limb strength at 3 months, upper limb functional activities related

to undertaking specific basic functional tasks at 1, 3 and 12 months, and upper limb pain at 12 months. Botulinum toxin was well tolerated and side effects were minor.

The addition of botulinum toxin type A to an upper limb therapy programme for the treatment of upper limb spasticity due to stroke was not estimated to be cost-effective at levels of willingness to pay for a QALY set by NHS decision-makers.

Implications for health care

Management of spasticity should focus upon realistic goals for treatment. These results will help to inform clinicians which outcomes may be improved by the addition of botulinum toxin type A to an upper limb therapy programme to treat upper limb spasticity due to stroke. Most patients will not achieve an enhanced improvement in active upper limb function by the addition of botulinum toxin to an upper limb therapy programme. However, botulinum toxin type A may have a role to play in improving the ability of some patients to undertake some basic upper limb functional tasks and may reduce pain at 12 months. Despite some clinical benefits, the addition of botulinum toxin type A to an upper limb therapy programme does not appear to be a cost-effective treatment for the patients included in this study.

Implications for research

Further research is needed to increase our understanding of the natural history and impact of spasticity following stroke, and to explain the relationship between spasticity and functional limitation. Studies are needed to improve the measurement of spasticity and to develop valid measures for all upper limb joints for use in clinical practice and multicentre studies. The optimum dosage and pattern of injections of botulinum toxin type A to treat upper limb spasticity due to stroke and the efficacy of repeat injections need to be defined.

Trial registration

This trial is registered as ISRCTN78533119; EudraCT 2004-002427-40; CTA 17136/0230/001.

Publication

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 02/41/06. The contractual start date was in February 2005. The draft report began editorial review in May 2009 and was accepted for publication in January 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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