

ORIGINAL REPORT

ASSOCIATED REACTIONS AFTER STROKE: A RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF BOTULINUM TOXIN TYPE A

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Objective: To measure the impact of botulinum toxin A on associated reactions in patients following stroke.

Design: Randomized placebo-controlled trial.

Patients: Forty patients with spasticity in their paretic arm (median time since stroke: 2.7 years) were randomized to botulinum toxin A (Dysport®; 1000 mouse units (MU) divided between elbow, wrist and finger flexors) or placebo.

Methods: Associated reactions were measured using hand dynamometry. The effort used was measured using maximum voluntary grip in the unaffected arm. Measurements were recorded at 2 pre-treatment and 3 post-intervention times. Activities that patients felt caused associated reactions and activities that were affected by associated reactions were recorded.

Results: Peak associated reactions force was reduced at week 6 with botulinum toxin A compared with placebo (mean group difference 19.0 N; 95% confidence interval (CI): 7.2, 30.9; $p < 0.01$) and week 2 ($p = 0.005$), with the effect wearing off by week 12 ($p = 0.09$). Thirty-one patients noted associated reactions on a regular basis and 24 said that these movements interfered with daily activities. Ten of 12 patients receiving botulinum toxin A and 2 of 12 receiving placebo reported reduction in interference with daily activities ($p = 0.02$).

Conclusion: Botulinum toxin A reduces associated reactions and may be a useful adjunct to other rehabilitation interventions. The impact of associated reactions on daily activities may also be reduced.

Key words: stroke, associated reaction, botulinum toxin.

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INTRODUCTION

During recovery from stroke, abnormal movement in the paretic arm may be observed either following effortful movement of other parts of the body (1) or activities such as sneezing, coughing and yawning (2). These limb movements, termed associated reactions (AR), may become a long-term feature

(3) particularly if there is poor recovery (4). In the upper limb, the predominant synergistic pattern of movement consists of shoulder adduction, retraction and external rotation, elbow flexion and supination, and wrist and finger flexion, although extensor synergies can rarely occur. There are many activities of daily living that promote AR, such as propelling a wheelchair, standing and walking, all of which can cause flexor synergistic movements in the upper limb. In addition the unwanted movements may also interfere with activities of daily living as well as being caused by them. During stroke rehabilitation there is often a conflict between the need to mobilize patients (5) and to prevent them from participating in activities that promote AR (6, 7). The presence of AR during stroke recovery is suggested to hinder development of normal movement (8) and therefore considerable rehabilitation resources may be directed at treating these abnormal movements.

Currently, there is good evidence that botulinum toxin type A (BT-A) reduces upper limb spasticity (9–11). BT-A reduces spasticity by blocking acetylcholine release at the neuromuscular junction (12). However, there has been little evidence of the impact of BT-A on reducing AR and their consequences for patients. Most of the evidence has been identified within the supplementary discussion of trials of BT-A where the primary outcome was to reduce spasticity. It is recognized that the presence of spasticity as conventionally defined is not always associated with AR (13). The use of BT-A to cause focal relaxation of muscles may allow it to have a role in preventing or reducing AR and consequently reduce their impact on activities of daily living. The aim of this study is to quantify the effect of BT-A treatment on the magnitude of AR in the paretic arm after stroke and to assess its impact on activities of daily living.

METHODS

This study is part of a previous study in which we reported the impact of BT-A on disability and carer burden caused by arm spasticity in 40 patients after stroke (11). Ethical approval was obtained from the Research Ethics Committee of the Leeds Teaching Hospitals NHS Trust. This study was carried out in accordance with the Helsinki Declaration.

Patients

Consecutive patients following stroke who were referred for management of upper limb spasticity were invited to participate in this study. Written, informed consent was obtained from all patients. None

of the patients had previously received BT-A or a phenol nerve block for spasticity and all were at least 6 months post-stroke. Patients had to have a stabilized anti-spasticity regimen and were not allowed to alter medication or physical treatments during the study period. Demographic information was obtained from each patient and physical ability was assessed using the Barthel Index (14). Patients were assessed and treated in the Community Rehabilitation Unit in Leeds as outpatients.

The sample size calculation was based on functional change found in a previous study (15). Allowing for a placebo response of 30% and a 90% chance of detecting a difference between placebo and BT-A at the 5% significance level, the sample size required in each group is 19.

Study design

We performed a single centre, randomized, double-blind, parallel trial. Patients received either 1000 mouse units (MU) of BT-A (Dysport®) or equivalent placebo (supplied by Ipsen Ltd, Slough, UK) diluted in 10 ml of 0.9% saline. In an attempt to emulate clinical practice, some flexibility was allowed between patients in the dose of trial drug administered to individual muscles. Dose selection for individual muscles was based on clinical judgement of spasticity and involuntary movement as reported by the patient and ascertained by a single investigator (BBB).

Ordering, labelling, blinding, recording and dispensing of numbered trial drug vials was independently undertaken by the hospital pharmacy department according to an individual patient randomization code produced by the university medical statistics department. Randomization codes were contained in opaque envelopes for each participant. A single investigator (BBB), blinded to treatment allocation, administered the trial drug. BT-A and placebo were identical in appearance and not accompanied by symptoms at injection that would allow them to be distinguished by patient or researcher. Two baseline assessments were made one week apart (weeks -1 and 0) prior to injection of trial drug at week 0 into spastic muscles using anatomical landmarks (16). Patient reported outcomes were documented 2, 6 and 12 weeks post-treatment, with patients not permitted to see responses of previous assessments. The magnitude of the AR was documented as described below at these time-points.

At each visit, patients were asked about their anti-spasticity treatments to ensure that no changes to medical and physical anti-spasticity treatments had occurred. The trial was unmasked once all patient assessments had been completed.

Quantifying associated reactions

Measurement of the AR in the paretic forearm flexor muscles was used as an index for whole upper limb AR. AR were induced by maximum voluntary grip of the unaffected arm; patients were requested not to move their paretic arm voluntarily. The involuntary muscle activity produced by effortful activity in the paretic arm was measured in terms of the force generated by abnormal finger flexion (abnormal grip) using a hand-held strain gauge torsion dynamometer (MIE Medical Research Ltd, Leeds, UK) using a standardized protocol described previously (17). The investigator (BBB) undertaking the measurements was unaware of treatment allocation.

Measurement of peak AR, and AR at 5 sec post cessation of reinforcement, were used to assess the efficacy of BT-A. The analyses included all patients who could complete the measurement protocol whether or not they had measurable AR at baseline. This ensured that the possible emergence of AR after BT-A treatment could also be identified.

Software allowed continuous data acquisition and off-line digital filtering. Surface electromyography (SEMG) was used to confirm the presence of forearm flexor and extensor muscle co-activation during the associated reaction. The raw SEMG signal was amplified, filtered (bandwidth 15–500 Hz at 6 dB) and digitized at 1000 Hz. Stored SEMG data was digitally rectified and low-pass filtered (-3 dB at 20 Hz) to provide an SEMG envelope for off-line analysis.

Measuring the impact of associated reactions on activities of daily living

Patient-reported outcome was based on goal attainment scaling. This identified the patients’ perception of how the unwanted involuntary movement (AR) affected their daily activities. This technique is widely used in rehabilitation to evaluate response to treatment (18). At baseline, all patients were asked which activities of daily living provoked involuntary arm movements and whether the involuntary arm movements interfered with the activity being performed. Patients then rated the maximum muscle tightness (resulting in elbow and finger flexion) during these activities of daily living in their affected arm on a 10-point categorical scale with the limits set by “no tightness” to “worst tightness ever”. A higher score indicated increasing severity of AR.

On subsequent post-treatment visits each patient was asked whether the effect of the involuntary arm movement during activities of daily living had improved, stayed the same or worsened. Patients then rated the severity of arm muscle tightness during activities of daily living on the 10-point categorical scale.

Statistical analysis

Treatment effect was determined by comparing the change scores between week 0 and week 6 in the BT-A and placebo groups. Week 6 was chosen as the primary end-point as any muscle relaxing effect of BT-A is well established by this time. If a treatment effect was evident then further analysis of data was undertaken at week 2 to gauge speed of onset, and at week 12 to gauge duration of effect. Medians and interquartile range (IQR) were used as descriptors. The Wilcoxon matched-pairs test was used to analyse ordinal and skewed data. Student’s *t*-test was used to analyse the forces produced by the associated reactions. χ^2 test was used to analyse the impact of BT-A on activities of daily living. Analyses were performed on an intention to treat basis.

RESULTS

Patients

A total of 40 patients consented to participate in the study (Fig. 1). Baseline demographic data and BT-A dosage are shown in Table I. There were no statistically significant differences between patients’ clinical characteristics in the BT-A and placebo groups.

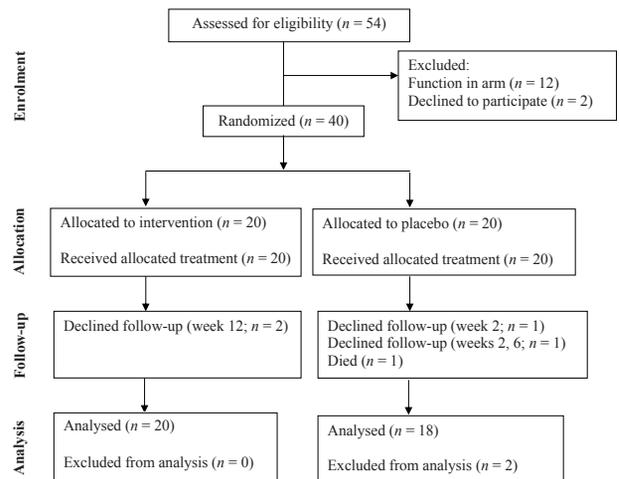


Fig. 1. Patients recruited to trial.

Table I. Clinical characteristics and trial drug dosage

Variables	Botulinum toxin (<i>n</i> = 20)		Placebo (<i>n</i> = 20)	
Females, <i>n</i> (%)	7 (35)		10 (50)	
Median age at stroke (years; range)	60.2 (22.6–77.6)		53.8 (11.2–72.8)	
Median time since stroke (years; range)	3.1 (0.8–33.2)		2.7 (0.5–15.0)	
Cerebral infarct, <i>n</i> (%)	15 (75)		15 (75)	
Right-handed, <i>n</i> (%)	18 (90)		20 (100)	
Right hemiparesis, <i>n</i> (%)	8 (40)		6 (30)	
Median Barthel index (range)	13.5 (4–20)		13.5 (5–20)	
	Botulinum toxin dose (MU)		Saline volume equivalent to dose in MU	
Muscles injected	Median (range)	Patients, <i>n</i>	Median (range)	Patients, <i>n</i>
Biceps brachii	300 (100–400)	19	300 (150–500)	19
Brachioradialis	100 (100–200)	14	100 (100–200)	12
Flexor digitorum superficialis	300 (200–500)	20	300 (200–450)	20
Flexor digitorum profundus	200 (100–300)	20	200 (100–400)	20
Flexor carpi ulnaris	100 (100–200)	13	100 (100–200)	13

MU: mouse units.

Impact of BT-A on AR force

Of the 40 original patients allocated to treatment after stroke, 34 were able to complete the AR measurement protocols described above. In 3 patients, the fingers were so tightly flexed because of spasticity that the instrumentation to measure AR could not be used. Two patients could not comply with the effort protocol using their “unaffected” hand during the measurement process. One patient (placebo group) died of myocardial infarction following randomization and therefore no post-treatment measurements were possible for this patient.

Fig. 2a shows an example of a recording of a patient who had involuntary movement of the paretic arm before treatment with BT-A. Fig. 2b shows an example of a recording of the same patient who reported reduction in involuntary movement of the paretic arm after BT-A. Visual inspection of Fig. 2b suggests that the peak force generated by the AR and muscle co-activation of forearm flexor and extensor muscles was reduced following BT-A injected into the forearm finger flexors and elbow flexors. Quantitative analysis of the AR measurements described below confirmed this observation.

There was reasonable overall baseline stability in the week prior to treatment of peak and decay AR, with no significant differences between results obtained in these weeks (Table II). Table III shows the pre-treatment peak AR, effort and decay AR measurements at week 1 for the placebo group and BT-A group; again, differences are not significant.

Table IV describes the changes in AR between weeks 1 and 6 in the 2 groups. There is a significant reduction in peak AR in the BT-A treated group (mean difference between BT-A group and placebo: 19.0 N; 95% confidence interval (CI) 7.2, 30.9; $p \leq 0.01$). Similar beneficial changes are also observed for speed of decay (i.e. AR force still present at 5 sec post cessation of effortful activity). The mean difference between BT-A group and placebo was 3.4 N (95% CI 1.3, 5.6; $p \leq 0.01$). There was no significant difference in effort used to generate the AR between weeks 1 and 6 and between the 2 groups (mean difference between BT-A group and placebo: 11.5 N; 95% CI –8.1, 31.2).

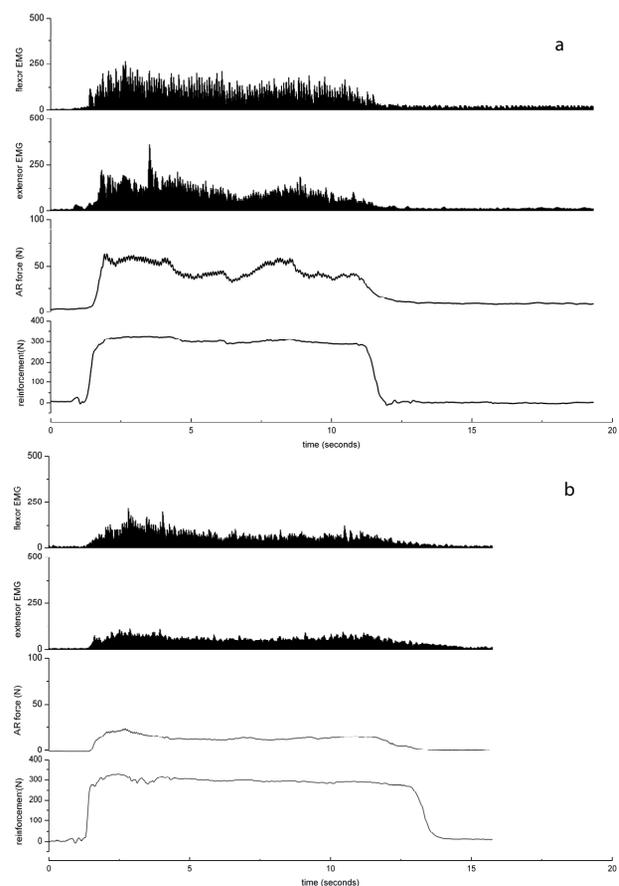


Fig. 2. An example of the effect of botulinum toxin A (BT-A) on the force generated during associated reactions (AR). (a) Unwanted grip force generated by forearm flexors/extensors with effortful activity in a patient before BT-A treatment. (b) Unwanted grip force generated by forearm flexors/extensors with effortful activity after BT-A treatment. Reinforcement (N): maximum grip force of unaffected hand (N); AR force (N): associated reaction force manifest as unwanted flexion of the fingers of the paretic arm; extensor EMG: paretic forearm extensor muscle (μ V); flexor EMG: paretic forearm flexor muscle (μ V).

Table II. Comparison of overall pre-treatment baseline associated reactions (AR) measurement stability

	Week 0 mean (SD)	Week 1 mean (SD)	Mean difference (95% CI)
Peak AR (N)	23.4 (16.9)	26.9 (18.0)	-3.4 (-7.6, 0.7)
Effort (N)	200.6 (57.1)	207.1 (56.2)	-6.5 (-18.2, 5.2)
Decay AR (N)	3.8 (3.1)	4.1 (2.8)	-0.2 (-1.2, 0.8)

Peak AR: maximum involuntary grip force that was generated in the paretic arm during the period of effortful activity. Effort: mean voluntary grip in the non-paretic arm that the patient generated when asked to grip the dynamometer as tightly as possible for 10 sec. Decay AR: amount of involuntary grip force still present in the paretic arm 5 sec after the subject ceased voluntary grip in the non-paretic hand. AR: associated reactions manifest as unwanted finger flexion; N: Newtons; CI: confidence interval; SD: standard deviation.

Reduction in AR was seen at week 2 in both groups with significantly greater reduction in the BT-A group (week 2 mean AR force: 12.3 N, SD 10.5; mean change in AR force from baseline -21.5 N, SD 18.7) compared with placebo (mean 16.8 N, SD 12.5; mean change -5.6 N, SD 9.2; mean group difference: 15.9 N; 95% CI 5.2, 26.5; $p = 0.005$). These effects of BT-A on AR had worn off by week 12 (BT-A: mean 16.7 N, SD 12.5; mean change -13.8 N, SD 22.2; placebo: mean 18.8 N, SD 12.0; mean change -3.1 N, SD 9.7; mean group difference: 10.7 N; 95% CI -1.9, 23.4; $p = 0.093$).

Effects of associated reactions on activities of daily living

AR were classified into 5 categories: upper limb activities (bathing, bed mobility, carrying objects, dressing, driving, kitchen activities, leisure activities, washing, wheelchair use, writing); lower limb activities (balancing, stair climbing, standing, swimming, transferring, walking); autonomic (coughing, micturition, sneezing, yawning); emotional (anger, anxiety); and other factors (cold, effort of movement, extraneous noise, speed of movement). Some patients mentioned a number of activities in each category that produced an abnormal movement. Also, during the course of the study, some patients recorded an AR that they had not previously noted.

Thirty-three patients (BT-A: 15; placebo: 18) reported that they noticed AR on a daily basis, with 24 of these patients reporting that this movement interfered with their activities of daily living. Patients reported a median of 2 activities (range 1-4) that caused AR. There was no significant difference in the number of AR between BT-A and placebo groups at baseline (Table V). Ten of 12 patients receiving BT-A and 2 of 12 patients receiving

Table III. Baseline comparisons of associated reactions (AR) between treatment groups at week 1

	Botulinum toxin group mean (SD)	Placebo group mean (SD)
Peak AR (N)	32.0 (21.4)	21.8 (12.5)
Effort (N)	217.2 (60.2)	197 (51.7)
Decay AR (N)	4.2 (3.5)	4.1 (2.0)

For explanation see Table II

placebo reported a reduction in interference by AR with daily activities ($p = 0.02$). However, there was no reduction in the number of activities that resulted in an AR following administration of BT-A (week 1: median 2, range 1-4; week 6: median 2, range 1-4) compared with placebo (week 1: median 2, range 1-4; week 6: median 2, range 1-4; DF 4, $\chi^2 = 0.693$).

Fig. 3 shows a box-plot comparison between the BT-A and placebo groups of the patients' perceptions of the tightness of the muscles in their affected arm. These results indicate the impact that the muscle tightness had on these patients' lives. Although there is improvement in the score in the BT-A group (week 1: median 6, range 0-10; week 6: median 0, range 0-5) compared with placebo (week 1: median 7, range 0-10; week 6: median 6.5, range 0-10), the changes between the groups did not reach statistical significance (BT-A group: median change 1.0, range -2-10; placebo group: median change 0.0, range -4-10, $p = 0.08$).

DISCUSSION

Our pilot study suggests that AR manifesting as involuntary flexion of the paretic arm in people with stroke can be provoked by a number of activities of daily living and that these unwanted movements interfere with these activities. It is also possible to measure the impact of BT-A on these movements. The patients recruited to this study are representative of the range of patients with post-stroke upper limb spasticity. The patients in the study by Brashear et al. (10) had equivalent levels of spasticity and their demographics were similar to our patient group. In common with that study, we have demonstrated that BT-A is an effective treatment for adverse muscle impairments in patients following a stroke.

This study identified direct adverse effects of a number of AR on patients' daily activities. The range of AR seen in patients after stroke in this study has not been previously documented. Even though the proportion of patients who identified an adverse

Table IV. Comparisons of changes in associated reactions (AR) between weeks 1 and 6

	Botulinum toxin group; mean (SD)			Placebo group; mean (SD)		
	Week 1	Week 6	Change	Week 1	Week 6	Change
Peak AR (N)	32 (21.4)	11.9 (10.1)	-20.0 (20.9)*	21.5 (12.3)	20.9 (15.0)	-0.98 (11.9) *
Effort (N)	217 (60)	203 (57)	-14.2 (32.2) *	193 (52)	195 (45)	2.5 (23.3) *
Decay AR (N)	4.2 (3.5)	1.5 (1.6)	-2.7 (3.2) *	3.9 (2.1)	4.8 (3.7)	0.7 (3.1) *

* $p \leq 0.01$

For explanation see Table II.

Table V. Number of patients reporting an associated reactions (AR) at baseline and after intervention

AR category	Week 1		Week 6	
	Botulinum toxin	Placebo	Botulinum toxin	Placebo
Upper limb	10	22	16	28
Lower limb	15	16	11	11
Autonomic	6	10	6	4
Emotional	6	2	5	3
Other factors	2	3	2	2

AR: associated reactions manifest as unwanted finger flexion. Numbers of patients reporting a particular AR may exceed total number of patients in each group as each patient could report more than one activity in each category. (For explanation of activities in each AR category see Results section).

effect of AR was only 60% of those recruited for the study, there was evidence suggesting that BT-A not only reduced the involuntary movement in terms of the unwanted forces generated within the paretic arm of these patients, but also reduced the adverse effect of AR for those who reported interference with daily activities. Whilst patients reported as many AR following treatment as at baseline, patients' perception of the impact of AR was reduced following BT-A. Our study is in keeping with findings reported by other authors, particularly in relation to improvements in walking balance reported following BT-A treatment for upper limb spasticity (19).

Clinicians are often not aware of the impact of AR on their patients, particularly as AR may develop some time after the onset of the stroke and are not always related to the presence of spasticity as conventionally defined (17). Similarly, patients may not appreciate the connection between certain activities and the development of AR. AR can be dismissed by patients as spontaneous spasms, and patients may not have had a full explanation of AR from their treating clinician. Therefore, once attention was drawn to their AR, participants in this study may have noticed further activities relating to upper limb use that resulted in AR contributing to the increase in reported AR at week 6.

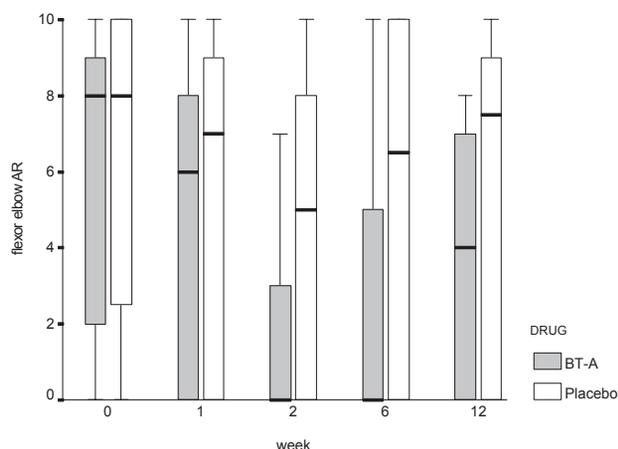


Fig. 3. Effect of botulinum toxin type A (BT-A) on patients' perception of arm tightness induced by effort. The dark line represents the median values and the box represents the interquartile range. AR: associated reaction.

This pilot study has a number of limitations. Firstly, the use of categorical rating scales used to measure patients' perception of their arm tightness during activity is limited by the psychometric characteristics of these measures. However, categorical scales of this type have been used in other studies with moderate to good reliability (9, 20).

Secondly, we have not assessed inter-rater reliability for the measurement techniques described in this study. Future studies should investigate the psychometric properties of these measures.

Thirdly, in using the hand dynamometry method, we assumed that the effort used to produce the AR, and the involuntary force produced by muscle contraction in the forearm musculature, acted as a marker for the overall forces produced during AR in the paretic arm. In determining the impact of BT-A on the forces generated by the AR we have tried to take into account the important confounding variables.

Given the evident distress caused by AR to patients with chronic stroke, we feel that this phenomenon warrants further evaluation in the context of BT-A use in muscle spasticity due to stroke.

In conclusion, this preliminary study suggests that AR can interfere with activities of daily living and that BT-A has a role in reducing these involuntary arm movements caused by effortful activity in people with stroke. Further studies are required to determine the optimal dose and administration of BT-A in reducing AR following stroke.

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