

ORIGINAL ARTICLE

Abnormal vocal cord movement treated with botulinum toxin in patients with asthma resistant to optimised management

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ABSTRACT

Background and Objective: Abnormal vocal cord movement may coexist with asthma and cause additional upper/middle airway obstruction. The condition may be a form of muscular dystonia that could contribute to asthma resistant to optimised treatments. Botulinum toxin causes temporary paralysis of muscle and may be an effective local treatment that improves asthma control.

Methods: In an observational study, we evaluated the benefits of unilateral vocal cord injection with botulinum toxin in 11 patients (total 24 injections). Subjects had asthma resistant to optimised treatment and abnormal vocal cord movement. Responses after botulinum toxin treatment were assessed using asthma control test (ACT) scores, vocal cord narrowing quantified by computerised tomography (CT) of the larynx and spirometry. Side-effects were recorded.

Results: ACT scores improved overall (9.1 ± 2.4 before and 13.5 ± 4.5 after treatment; difference 4.4 ± 4.2 ; $P < 0.001$). There was also an improvement in airway size on CT larynx (time below lower limit of normal at baseline $39.4 \pm 37.63\%$ and improved to $17.6 \pm 25.6\%$ after injection; $P = 0.032$). Spirometry was not altered. One patient experienced an asthma exacerbation but overall side-effects were moderate, chiefly dysphonia and dysphagia.

Conclusions: Although a placebo effect cannot be ruled out, local injection of botulinum toxin may be an effective treatment for intractable asthma associated with abnormal vocal cord movement. Further mechanistic studies and a double-blind randomised controlled trial of botulinum toxin treatment are merited.

Key words: asthma, botulinum toxin, vocal cord dysfunction.

SUMMARY AT A GLANCE

Abnormal vocal cord movement may contribute to refractory asthma and temporary partial paralysis with botulinum toxin may be an effective local treatment that improves asthma control. Although a placebo effect cannot be ruled out in this study, injection of botulinum toxin appears to be useful and randomised studies are merited.

Abbreviations: ACT, asthma control test; ANOVA, analysis of variance; BMI, body mass index; CT, computerised tomography; EMG, electromyography; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; VCD, vocal cord dysfunction.

INTRODUCTION

Middle airway obstruction (customarily called upper airway obstruction)¹ at the level of the vocal cords may convert mild asthma to severe disease if causing obstruction in addition to asthma itself.² We have recently developed new imaging techniques to aid diagnosis of middle airway obstruction using dynamic 320-slice computerised tomography (CT) technology.^{3–5} Using CT larynx and a novel algorithm, it is possible to detect abnormal vocal cord narrowing in up to 50% of asthmatics. The abnormality was not seen in healthy individuals.⁵ These observations raised the possibility that middle airway obstruction contributes to excessive breathlessness in numerous difficult-to-treat asthmatics—a possibility seldom considered, investigated and treated.²

Our findings are reminiscent of vocal cord dysfunction (VCD) but it is not clear if these disorders are identical. To avoid confusion we have used a descriptive terminology (abnormal vocal cord movement) until this question is resolved. VCD is a condition first described as distinct from asthma,⁶ although subsequent studies have suggested that the conditions may frequently coexist.^{1,5,7} Both abnormal vocal cord

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movement and VCD may represent a form of task-specific muscle spasm (dystonia) similar to that found in writer's cramp, blepharospasm and other comparable conditions,⁸ although diagnostic investigations (for example, using electromyography—EMG) have never been conducted. Treatment of VCD employing speech therapy, psychotherapy and locally using botulinum toxin (to induce temporary paralysis of the vocal cords) has been reported.^{9–11} Notably, use of botulinum toxin for resistant asthma symptoms may yield dramatic improvements in asthma symptoms,^{9,11,12} suggesting the benefit of treating putative vocal cord dystonia.

To date the possible benefits of botulinum toxin treatment have been reported in only a few individual, variably characterised cases. However, these reports suggested that treatment with botulinum toxin might ameliorate asthma symptoms not responsive to generally effective treatments. We therefore postulated that treatment with botulinum toxin by local injection will benefit patients who have asthma, abnormal vocal cord movement and intractable asthma symptoms.

METHODS

Study design

To date only individual case reports of patients treated with botulinum toxin have been published. Based on this limited evidence a randomised controlled trial was not considered merited and an observational study was planned and performed.

Patients were recruited from a severe asthma clinic after treatment for asthma had been optimised.¹³ Patients who remained severely symptomatic (asthma control test (ACT) score <16) in spite of optimised management (including verified adherence) were evaluated using 320-slice dynamic CT larynx ($n = 82$). If abnormal vocal cord movement was detected, patients were referred for speech therapy ($n = 38$) and if therapy was unsuccessful (ACT not improved ≥ 3 and ACT score <16, $n = 22$) they were offered enrolment in the study. Speech therapy was given as proposed for VCD since specific speech therapy for dystonia has not been described. Eleven patients were eventually enrolled as outlined in Figure 1.

The timetable for botulinum toxin administration is also shown in a diagram (Supporting Information Fig. S1). All patients received an initial injection and were eligible to receive repeat injections with botulinum toxin if the injection/treatment was deemed to have failed based on ACT scores.

Patients

Demographic details and disease characteristics of 11 patients (8 female) are shown in Table 1. All patients had doctor-diagnosed asthma and fulfilled criteria for refractory asthma as defined by an ATS Workshop on refractory asthma.¹⁴ Asthma was confirmed by a bronchodilator response >12% in five patients. Forced expiratory volume in 1 s (FEV₁) <80% predicted with FEV₁/forced vital capacity (FVC) <0.7 was used to

verify asthma in four patients because reversibility is often absent in severe asthma.¹⁵ One patient had a positive bronchoprovocation test and in another a doctor diagnosis of asthma and a typical clinical history was used because he was unable to perform spirometry. All patients had ongoing asthma symptoms requiring frequent oral corticosteroids (more than two courses of oral corticosteroids annually) and a history of at least one emergency department or hospital admission. Speech therapy¹⁶ had failed in all patients invited to participate (Fig. 1).

Patients provided written, informed consent and studies were approved by Monash Health Human Research Ethics Committee and Monash Health Therapeutics Committee (reference numbers SHTC-08–12 and 13004Q). The study was registered and included in the Australia New Zealand Clinical Trials Registry (<http://www.ANZCTR.org.au>) (ACTRN: 12613000455763). Outcomes (and other information) have been reported as formulated in the STROBE Statement for observational studies.¹⁷

Diagnosis of abnormal vocal cord movement

Abnormal vocal cord movement was diagnosed in all cases based on evidence within the preceding 12 months of abnormal vocal cord movement detected by 320-slice CT larynx.⁵ CT methods of detection are analogous to orthodox clinical laryngoscopy but can be quantified (see Supporting Information). Briefly, serial measurements of airway lateral diameter (at the level of vocal cords) were obtained over inspiration and expiration. A validated algorithm was used to calculate percentage (%) time the airway was narrowed below the lower limit of normal (LLN). LLN was ascertained in healthy individuals and radiation doses were approximately 0.8–2 mSv per CT larynx.⁵ Laryngoscopy was conducted before treatments to exclude other laryngeal disease but was not used to reassess patients because we have shown close concordance between orthodox laryngoscopy and CT virtual laryngoscopy.^{3,5}

Botulinum toxin injection

Eleven patients received single or repeated botulinum toxin (type A, Botox; Allergan, Sydney, NSW, Australia) injections for a total of 24 injections (Supporting Information Fig. S1 and Table S1). Two methods of injection were used based on previous reports^{9,11} and a novel, clinically pertinent method using endoscopic guidance was added (see Methods: Supporting Information Table S1):

- (i) Transcutaneous unilateral injection under EMG, $n = 9$;
- (ii) Visually guided unilateral injection under general anaesthetic (GA), $n = 6$; and
- (iii) Transcutaneous unilateral injection under endoscopic guidance (endoscopy), $n = 9$.

Transcutaneous injection under endoscopic guidance is demonstrated in Figure S2, Supporting Information. It shows endoscopic visualisation of the injection needle followed by angulation of the needle and injection of the right thyro-arytenoid muscle. Dose of botulinum toxin (Botox) used was 2.5 U^{18,19}

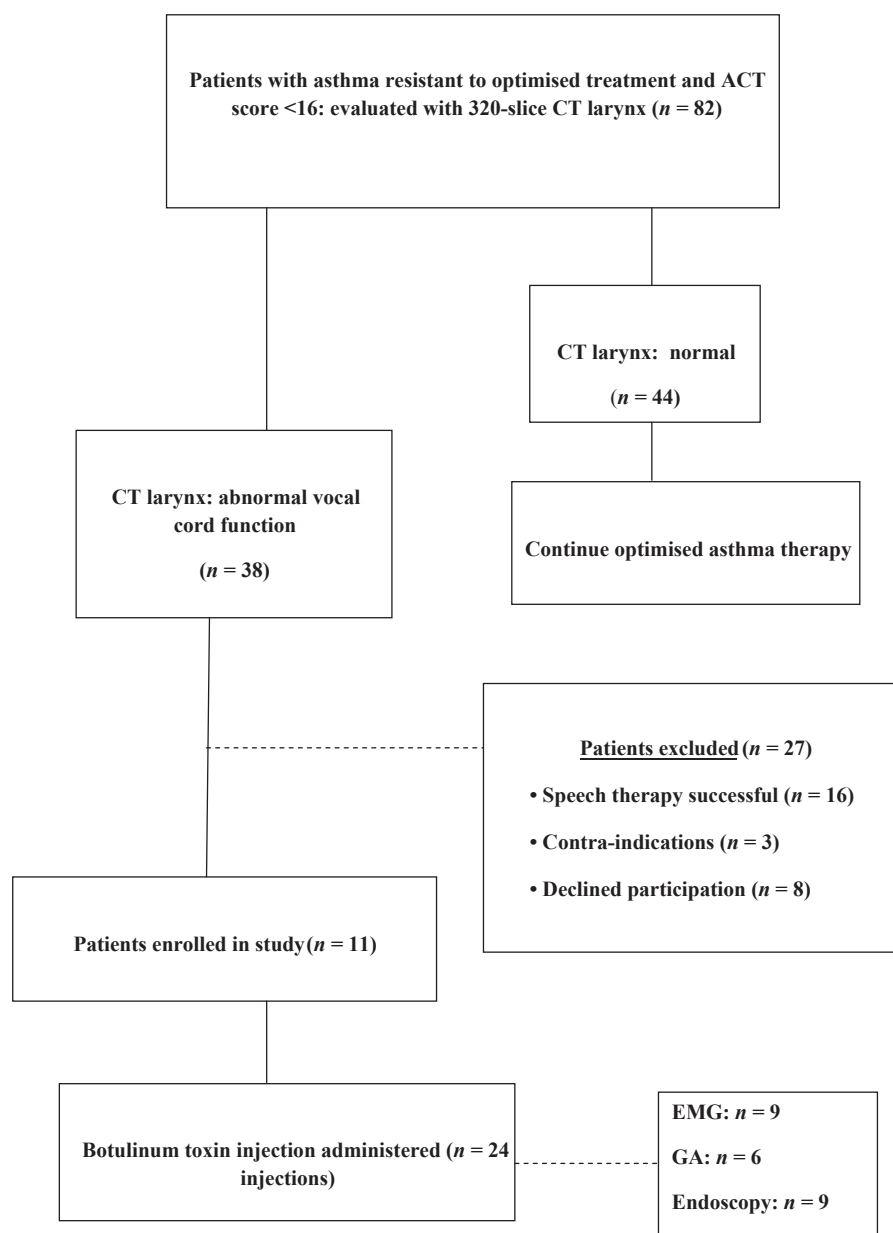


Figure 1 Consort diagram to clarify participation in the study. ACT, asthma control test; CT, computerised tomography; EMG, electromyography; GA, general anaesthetic; Endoscopy, injection under endoscopic guidance.

(25 U/mL dilution of botulinum toxin in saline; 100 μ L injected). Repeat injections were done in symptomatic cases since dystonia may require recurrent treatment.⁸

Lung function testing

Lung function testing was performed as detailed in the Supporting Information. All flow-volume loops were visually inspected to look for indications of upper/middle airway obstruction.

Outcomes and statistical analysis

Two co-primary outcomes were assessed: change in asthma control test (ACT) score (see Supporting

Information) and change in % time below LLN measured on CT larynx. ACT is responsive to treatment interventions with a minimum clinically important difference of ≥ 3 points.²⁰ Assuming a standard deviation of ~ 4 we calculated a sample size to detect a difference of > 1 standard deviation ($\alpha = 0.05$; power = 0.9). Twenty-four injections provided sufficient statistical power.

Secondary outcomes assessed 1 and 3 months after every injection were changes in pulmonary function (FEV_1 and FEV_1/FVC), oral glucocorticosteroid use and inhaled glucocorticosteroid medication use (dose). Side-effects and complications (yes/no, duration, severity—mild or severe) were assessed at clinic

Table 1 Baseline demographics and asthma disease characteristics of 11 patients treated with botulinum toxin by injection

Patient	Age	BMI (kg/m ²)	Asthma diagnosis	Asthma treatment [†]	FEV ₁ (% predicted)	FEV ₁ /FVC (%)	Best BD (%)	ACT score: baseline
P1	72	31.8	H	FP, SALM	ND	ND	-	13
P2	55	35.3	H, FEV ₁ < 80%	CIC, FORM	77	68	10	10
P3	66	31.2	H, FEV ₁ < 80%	FP, SALM	72	66	7	8
P4	58	33.6	H, BD	BUD, FORM	58	48	16	12
P5	38	44	H, BD	FP, SALM	52	66	32	5
P6	52	31.4	H, FEV ₁ < 80%	CIC, FORM	32	36	9	10
P7	55	25.9	H, BP+	BUD, FORM	106	78	5	12
P8	69	34	H, BD	FP, SALM	69	66	12	9
P9	70	23.4	H, BD	BUD, FORM	104	67	12	9
P10	65	28.5	H, BD	CIC, FORM	81	76	19	13
P11	70	41.8	H, FEV ₁ < 80%	FP, SALM	65	68	9	9
60.9 ± 10.4		32.8 ± 6.1			74.6 ± 24.4	63.9 ± 12.6	13.1 ± 8.8	10.0 ± 2.4

[†] All patients were taking maximal doses of inhaled corticosteroids (≥500 µg beclomethasone equivalent daily) and long-acting bronchodilator therapy; summary values are mean ± SD.

ACT, asthma control test; BD, bronchodilator response; BMI, body mass index; BP+, positive bronchoprovocation testing; BUD, budesonide; CIC, ciclesonide; FORM, formoterol; FP, fluticasone propionate; H, typical asthma history + doctor diagnosis of asthma; ND, not done.

review after 1 and 3 months and by patient self-reporting in the period between reviews.

Univariate and multivariate analysis of variance (ANOVA) were done to compare the primary outcomes before and after injection. For analysis of ACT scores, ANOVA (with patient as a random factor) was first conducted to ascertain whether repeat injections acted as a confounding variable. It did not influence outcomes ($P = 0.667$). CT repeated in 10 patients after treatment was used to compare changes in inspiration plus expiration (20 epochs) as well as inspiration (10 epochs) and expiration (10 epochs) separately. Correlation between % time under LLN and ACT was done using the Kendall rank correlation coefficient (tau). Significance was achieved if $P < 0.05$.

RESULTS

Eleven patients received a total of 24 botulinum toxin injections (Supporting Information Table S1). Eleven injections were done initially and on 13 subsequent occasions patients were eligible for repeat injections.

Table 2 details outcomes 1 month after botulinum toxin administration. Improvements in ACT after 24 botulinum toxin injections were noted (9.1 ± 2.4 before and 13.5 ± 4.5 after treatment; difference 4.4 ± 4.2 ; $P < 0.001$, Fig. 2; $n = 24$). Increases in ACT scores ≥ 3 were noted after 14/24 (58%) injections (see also Supporting Information Fig. S1). There was no difference in ACT scores comparing methods of injection ($P = 0.39$; data not shown).

CT larynx was conducted before and four weeks after treatment ($n = 10$ patients). Overall assessment (% time below LLN for both inspiratory and expiratory epochs, $n = 20$) ascertained that mean time under LLN before injection was $39.4 \pm 37.63\%$ and improved to $17.6 \pm 25.6\%$ after botulinum injection

(Fig. 3; $P = 0.032$; $n = 10$). Inspiratory epochs were not significantly better ($P = 0.122$) but improvements were noted during expiration ($P = 0.019$, not shown). Changes on CT were not correlated with improved ACT scores (inspiration $r = -0.11$, $P = 0.62$ and expiration $r = 0.43$, $P = 0.07$; not shown).

Spirometry was conducted before, 1 and 3 months after injections. There were no significant improvements noted in FEV₁, FEV₁/FVC ratio or bronchodilator responses (Table 2 and Supporting Information Fig. S3). Inspection of flow-volume curves in individual cases did not show evidence of middle airway obstruction. Other secondary outcomes were also unchanged.

Side-effects were noted in 18/24 injections (68%) and associated with improved ACT scores (change in ACT score -0.4 ± 0.7 if no side-effects reported versus 6.4 ± 3.5 ; $P = 0.0004$; Supporting Information Fig. S4). Dysphonia was noted in 17/24 patients and dysphagia in 6/24 cases, categorised as mild in all cases. Partial loss of voice was prolonged for up to 6 weeks in 5/17 cases with dysphonia (30%); however, all patients were able to conduct normal conversation and work activities. One patient with severe asthma (P5) required hospital admission and a course of oral corticosteroids following GA with botulinum toxin injection.

DISCUSSION

This report provides proof-of-concept evidence for a novel method to treat asthma resistant to optimised treatment. Botulinum toxin injection of one vocal cord improved asthma control and reduced narrowing of the upper airway. Overall, the procedure was safe and side-effects were mild.

The link between asthma symptoms and coexisting middle airway obstruction has been difficult to

Table 2 Outcomes in 11 patients treated with botulinum toxin (24 injections) 1 month after injection

Patient	Method of injection [†]	ACT (score; change)	FEV ₁ (change % predicted) (n = 20)	CT larynx (change in % time below LLN) Insp/Exp (n = 10)	Side-effects
P1	EMG	9	ND	49/54	V
	EMG	0	ND	ND	none
P2	EMG	0	-2	ND	V
	GA	-1	6	ND	none
	GA	3	0	0/26	V, D x 6w
	Endoscopy	9	-2	ND	V, D
P3	EMG	4	4	ND	V
	EMG	9	6	0/18	V
	GA	6	0	ND	V, D x 6w
	GA	8	ND	ND	V
P4	EMG	2	0	0/45	V
	EMG	6	-13	ND	V
P5	GA	12	20	43/0	V, D x 6w, AEA
	GA	0	14	ND	none
	Endoscopy	10	ND	ND	V
P6	EMG	0	0	ND	none
	EMG	4	0	ND	V
	Endoscopy	8	2	ND	V x 6w
P7	Endoscopy	-2	12	ND	none
	Endoscopy	11	2	0/-21	V x 6w
P8	Endoscopy	3	3	-17/61	V, D
P9	Endoscopy	0	3	10/2	none
P10	Endoscopy	7	19	45/78	D
P11	Endoscopy	0	0	-26/89	none
Total	n = 24	4.4 ± 4.2*	3.2 ± 7.4	17.4 ± 31.9/33.2 ± 36.0**	17/24

[†] Methods used for botulinum toxin injection: (i) EMG—transcutaneous, injection with EMG guidance; (ii) GA—injection under general anaesthetic; (iii) Endoscopy—transcutaneous injection under endoscopic guidance.

* $P < 0.001$; ** $P = 0.032$.

ACT, Asthma control test; AEA, acute exacerbation asthma; D, dysphagia; Insp/Exp, Inspiration/Expiration; ND, not done; V, voice changes and dysphonia.

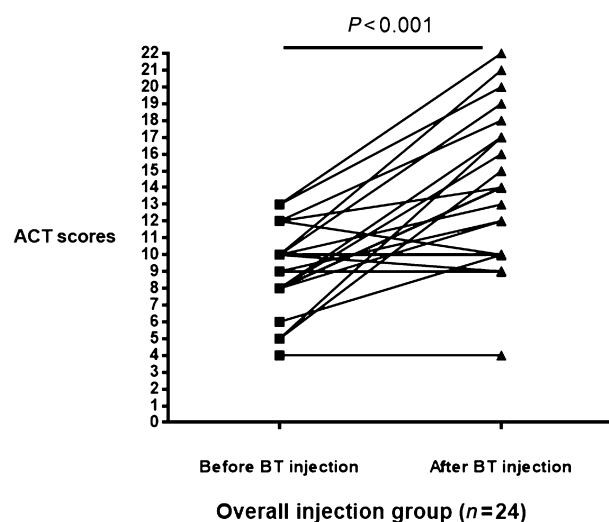


Figure 2 Asthma control test (ACT) scores before and after botulinum toxin (BT) injection in 11 patients (total 24 injections). There were significant improvements in ACT scores after treatment ($P < 0.001$).

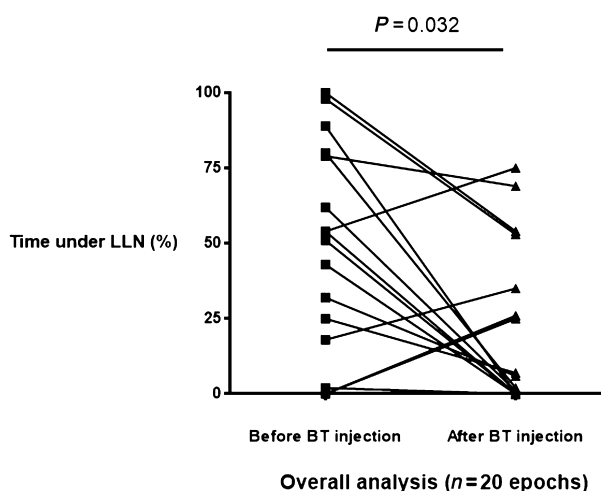


Figure 3 Measurements of % time under lower limit of normal (LLN) on computerised tomography (CT) larynx during either inspiration or expiration were compared in 10 patients (10 inspiration and 10 expiration, total 20 epochs). Comparisons were made between CT images before and after botulinum toxin (BT) injection. Significant improvements in middle airway size could be demonstrated following treatment ($P = 0.032$).

establish. However, it has long been suspected that middle airway obstruction could contribute to resistant asthma symptoms and seemingly poor asthma control.¹ Botulinum toxin, an established neurotoxin with limited duration of action,²¹ may reduce airflow obstruction and a number of case reports have illustrated dramatic benefits.^{9,11,12} We assessed the benefits of botulinum toxin injection in a selected group of asthmatics with abnormal vocal cord movement having postulated that vocal cord dystonia culminates in obstruction and poorly controlled disease resistant to optimised treatment. All patients had failed initial speech therapy and diagnosis of abnormal vocal cord movement was based on a novel methodology using dynamic CT with virtual endoscopy.⁵

ACT has been validated as a measure of asthma control over the preceding four weeks—the time of expected maximal benefit following botulinum toxin administration.²¹ Treatment overall was effective as judged by ACT scores with improvements (median change approximately 4.5 points) greater than the minimally clinically important difference of 3 points.²⁰ In about a third of patients ACT was changed <3 points suggesting that injection may have been inaccurate and in support of potential injection accuracy issues affecting treatment success, we documented a link between the side-effect of dysphonia and improvements in ACT. This suggests the more muscle paralysis achieved, the greater the asthma symptom benefit.

Findings on CT larynx indicated that botulinum toxin treatment reduced airway narrowing. CT larynx was done four weeks after injection and demonstrated a significant improvement in the time vocal cord function was normalised. This finding provides objective evidence that this novel therapy may improve laryngeal behaviour, at least in the short term. Radiation doses may in future be reduced to <1 mSv per CT larynx and this technology retains considerable potential to provide real-time middle airway information.

Although upper/middle airway obstruction measured by CT larynx improved, this did not correlate with higher ACT scores. We may have failed to demonstrate such an association since CT imaging captures vocal cord activity as a single breath snapshot whereas ACT scores reflect asthma control over a month.

Improvements in ACT and on CT larynx following botulinum toxin were not accompanied by increases in FEV₁. Intuitively this may seem surprising but numerous studies have found spirometry to be ineffective to detect middle airway obstruction of this nature.^{2,7,10,12,22,23} We have previously shown that patients with abnormal vocal cord movement on CT larynx had no evident abnormality on spirometry conducted immediately following CT.⁵ Other methodologies such as impulse oscillometry may improve detection of middle airway obstruction.

Published case reports of patients with intractable asthma have generally detailed use of botulinum toxin by injection of the vocal cords under GA.^{9,11,12} We used this method in conjunction with other approaches that aim to avoid the need for GA.

Although EMG guided injection has been successful to treat spasmodic dysphonia,^{19,24} it is technically difficult and cannot provide unequivocal verification of accuracy. In contrast, endoscopy guided injection permits exact placement to be verified by photography. It enables the surgeon to direct botulinum toxin injection to the thyro-arytenoid muscle with precision, an aspect judged to be crucial for successful treatment in other conditions.²⁵ A particular advantage of the endoscopy technique is that injection can be done with minimal sedation as part of a routine bronchoscopy list.

Given the experimental nature of botulinum toxin treatment a high level of care was taken to ensure patient safety and to monitor adverse effects. One patient with severe asthma required hospital admission and a short course of oral corticosteroids the day after treatment under GA had been administered. The anaesthetic with intubation may have contributed to this outcome but caution should be exercised, particularly in patients with severe asthma. Dysphonia occurred frequently with patients reporting a softer, 'breathy' voice; in all cases, they were able to communicate without problems. When dysphagia occurred, it was mild and transient and no patients had symptoms suggesting aspiration.

The current study has important limitations. Although dystonia was postulated, there is no EMG or other evidence that this is indeed present. Treatment was not blinded and a large placebo effect associated with procedural therapies cannot be excluded.²⁶ ACT does not give information about changes in vocal cord function and thus abnormal vocal cord movement may be an epiphenomenon with improvements in ACT the result of better control of asthma rather than botulinum toxin itself. Future studies should include additional methods to assess vocal cord function independently from asthma control. Finally, subjects were only assessed for one to three months after treatment and the study does not provide information about how long benefit was maintained, an aspect that should be assessed in future studies.

In conclusion, obstruction at the level of the vocal cords may play a role in asthma resistant to optimised management; a possibility reinforced by the benefits of botulinum toxin treatment noted in this report. Our findings suggest that a double-blind randomised controlled trial can be justified to evaluate the putative benefits of botulinum toxin in asthma.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Flow diagram to clarify botulinum toxin injections administered to 11 patients. Repeat injections were given depending on clinical responses until target enrolment was reached (n = 24). Patients who did not have repeat injections only became eligible after target enrolment had been achieved.

Figure S2 A,B,C. Botulinum toxin injection under endoscopic guidance showing visualisation of needle in the airway (left panel), angulation and injection into the thyro-arytenoid muscle (middle panel) with retraction of the needle after injection (right panel). The procedure caused minimal bleeding.

Figure S3 FEV₁ measurements are shown before and after botulinum toxin injections in 11 patients before and after 20 botulinum toxin injections. There were no significant changes noted.

Figure S4 Comparison of change in asthma control test scores between patients experiencing side-effects and those with none reported.

Table S1 Botulinum toxin—methods used to administer 24 injections in 11 patients.

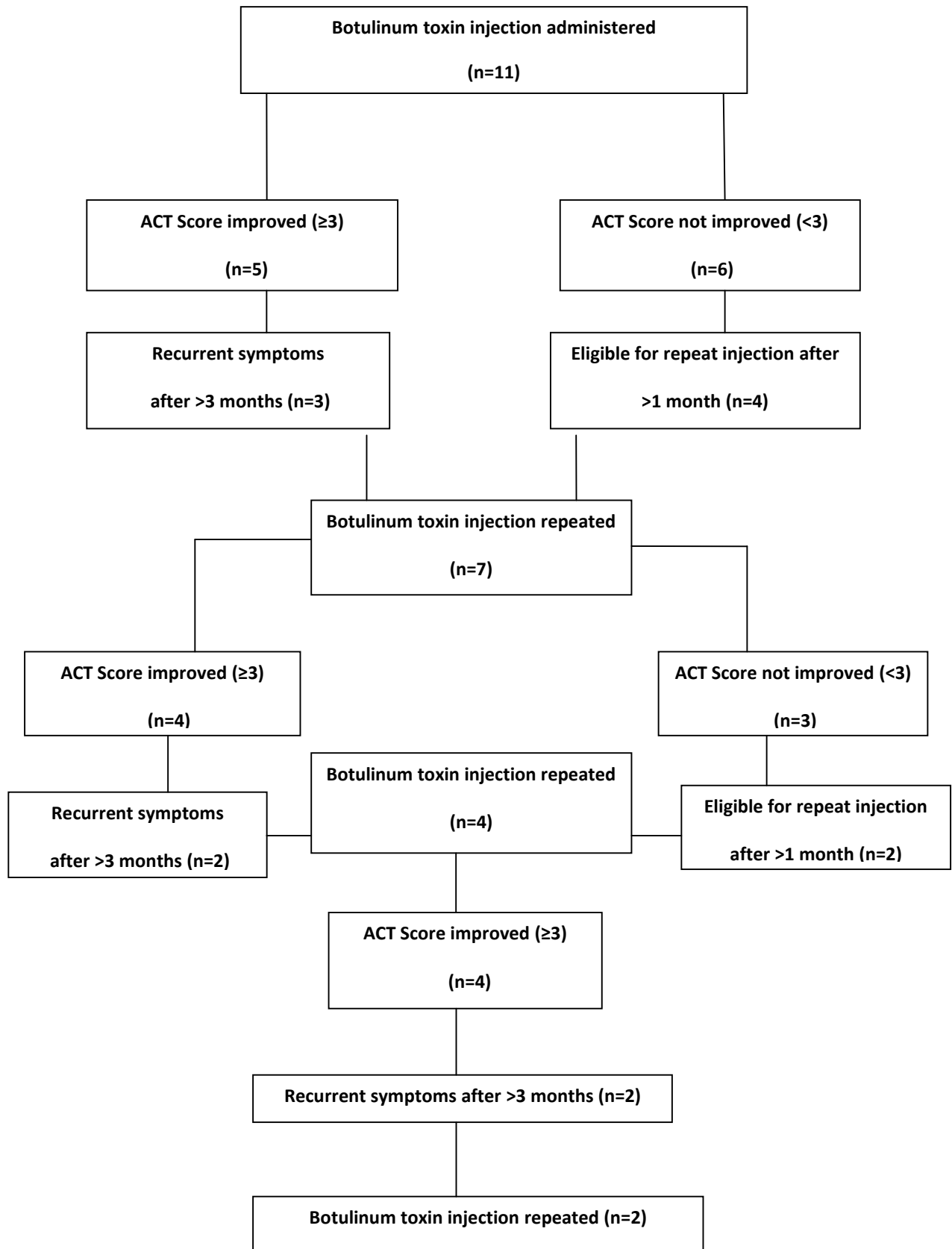


Figure E1 Online Repository

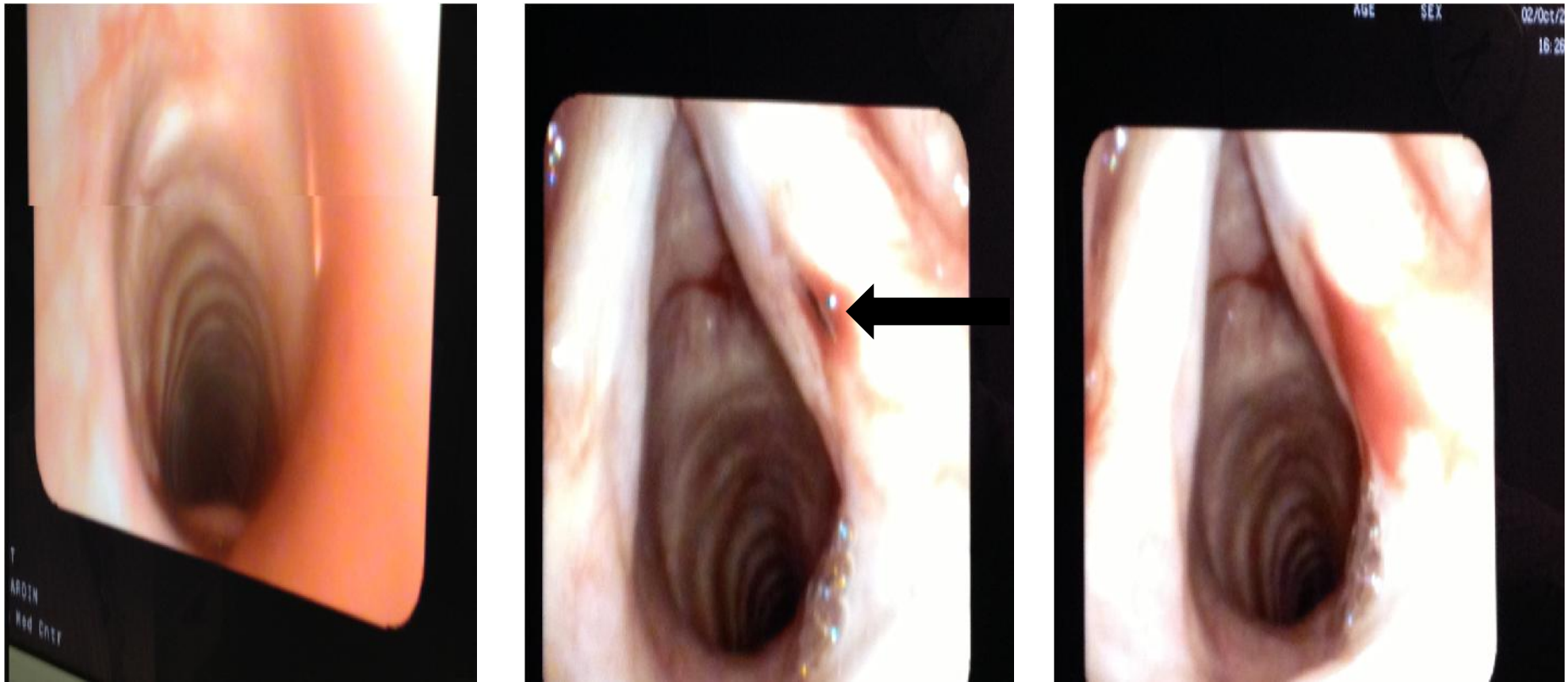


Figure E2 Online Repository

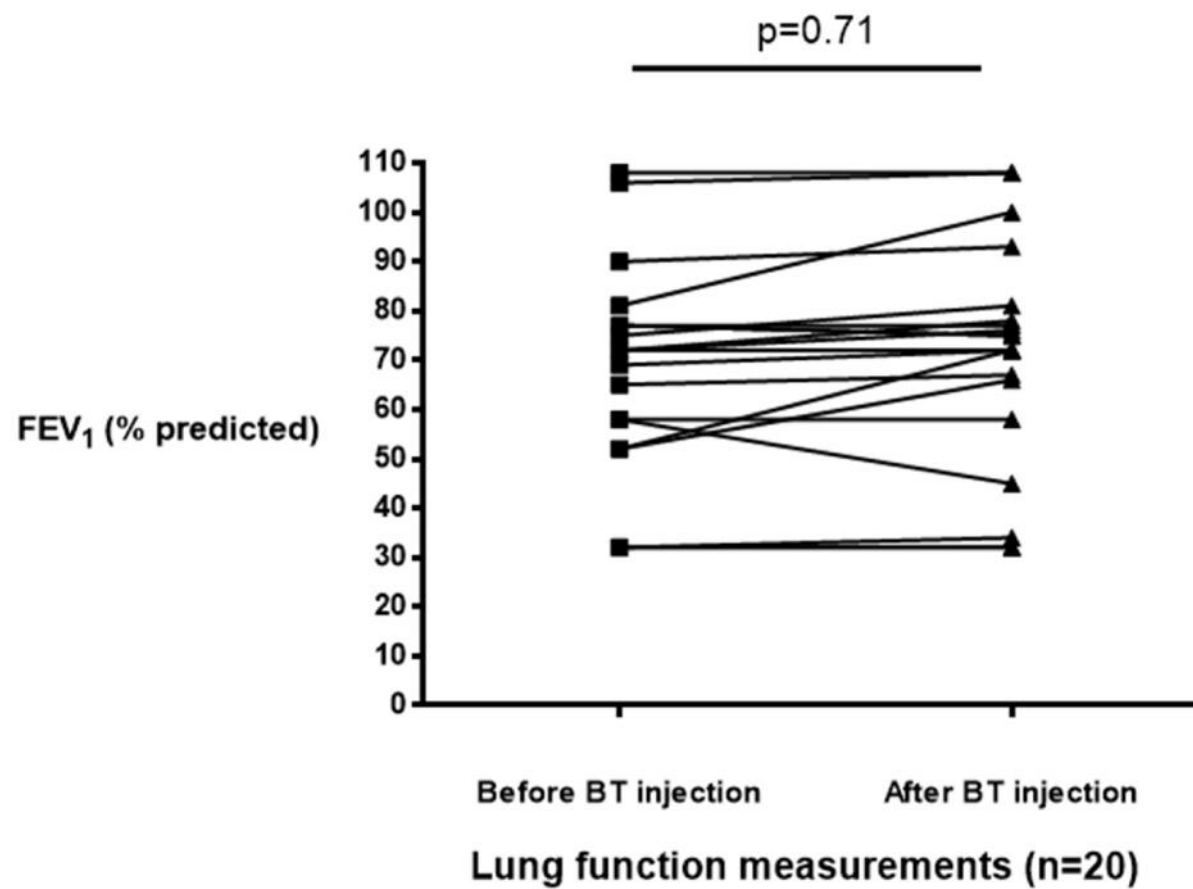


Figure E3 Online Repository

Table E1 Online Repository. Botulinum toxin - methods used to administer 24 injections in 11 patients

Patient	Method of injection		
	EMG (number)	GA (number)	Endoscopy (number)
P1	2	-	-
P2	1	2	1
P3	2	2	-
P4	2	-	-
P5	-	2	1
P6	2	-	1
P7	-	-	2
P8	-	-	1
P9	-	-	1
P10	-	-	1
P11	-	-	1
Total: n=24	9	6	9

Electromyography, EMG; GA, general anaesthesia; Endoscopy, injection under endoscopic guidance