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Aaron Jamison , Maribel Favor , Raman Malhotra

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Patient-reported outcomes following a break in ophthalmic botulinum toxin therapy during the COVID-19 pandemic

Aaron Jamison[1,*], Maribel Favor[1], Raman Malhotra[1]

[1]Corneoplastic Unit, Queen Victoria Hospital NHS Foundation Trust, East Grinstead, UK

[*]**Corresponding Author:** Mr Aaron Jamison, Corneoplastic Unit, Corneoplastic Unit,Queen Victoria Hospital NHS Foundation Trust, RH19 3DZ, United Kingdom, Phone: +44 (0) 7921 438031, E-mail: aaronjamison@gmail.com

Declaration of Competing Interest

We, the authors of "Patient-reported outcomes following a break in ophthalmic botulinum toxin therapy during the COVID-19 pandemic" (Aaron Jamison, Maribel Favor and Raman Malhotra) have no conflicts of interest to report.

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Abstract

Background: Study to evaluate the impact of a break in botulinum toxin treatment, necessitated by the COVID-19 pandemic, on patients' quality of life.

Methods: Prospective cohort study of all patients undergoing incobotulinumtoxinA treatment in our department - for benign essential blepharospasm (BEB), hemifacial spasm (HFS), aberrant facial regeneration (AFR) or crocodile tears - who were affected by the break in service (18/3/2020-17/6/2020). All patients who received treatment both before and after the break in service were included. Data gathered included subjective patient-reported measure of "time-till-treatment-failure", and disease rating scale scores: Blepharospasm-Dystonia Functional Disability Assessment Scale (BDFDAS) (for BEB/HFS/AFR); Jankovic Rating Scale (JRS) (for BEB/HFS); TEARS Epiphora Grading Scale (for crocodile tears).

Results: Across 72 patients there was mean treatment delay of 3.9 (0-9.8) months. After a period of effect, treatment failed in all patients,

with mean "time-to-treatment-failure" of 3.9 (0.5-12.0) months. All patient-reported outcome measurements increased, with greatest effect seen in AFR (178% increase in BDFDAS) and BEB (41% increase in JRS). At least two patients sought and underwent re-treatment elsewhere in the private sector due to their symptom severity.

Conclusions: Patients with AFR and BEB are likely to tolerate a break in service least, while patients with crocodile tears appear to be less affected. This "real-world" snapshot allows quantification of the harm caused by a break in botulinum toxin service or treatment delay. This study provides valuable information should further breaks in service or treatment delay be considered in future, due to a further wave of COVID-19 or other reasons.

Keywords: botulinum toxin, botox, COVID-19, pandemic, cessation, break, blepharospasm, hemifacial spasm, synkinesis

Introduction

The impact that the COVID-19 pandemic has had on every conceivable part of the healthcare services, not just the acute care setting, is now well recognised. One example, which has affected

countless patients across the UK and abroad, has been the impaired provision of elective and outpatient procedures, which for the most part have been postponed in order to decrease numbers of patients attending hospitals, reduce transmission rates, and re-direct workforces, workspaces, and personal protective equipment (PPE) to more acute, essential, services.

Botulinum toxin was first approved for medical use as an injection into the extraocular muscles for the treatment of strabismus, but has since proven useful in the management of a variety of medical conditions.[1-2] The Corneoplastic Unit at the Queen Victoria Hospital (QVH) offers botulinum toxin treatment for benign essential blepharospasm (BEB), hemifacial spasm (HFS), and aberrant facial regeneration (AFR, or synkinesis) (often collectively referred to as facial movements disorders), and also in the management of crocodile tears.[3-6] During the first wave of the COVID-19 pandemic, all botulinum toxin treatments were considered "non-essential" and postponed. At QVH, botulinum toxin treatments were halted from March and only reintroduced gradually, for facial movement disorders in June 2020, and later in 2020 for crocodile tears and epiphora.

Anecdotally, this negatively impacted many long-term patients. Having been spotlighted by a recent UK press article, this experience has clearly been shared by many others.[7]

This sudden, unexpected and undesirable cessation of botulinum toxin treatment across an entire service has provided an opportunity to answer questions that cannot, ethically, be studied under normal circumstances. We undertook this prospective audit to evaluate the impact that this recent break in treatment had on patients' quality of life, as assessed using various patient-recorded outcome measures / disease rating scales.

Methods

The QVH botulinum toxin service offers incobotulinumtoxinA (Xeomin) injections to patients with BEB, HFS, AFR or crocodile tears, injected at flexible treatment intervals, based on the patient's reported response to previous treatments. Quantitative measures of patient-reported response to treatment were chosen based on the condition being treated: the Blepharospasm-Dystonia Functional Disability Assessment Scale (BDFDAS) (for BEB/HFS/AFR); the Jankovic Rating Scale (JRS) (for BEB/HFS); or the TEARS Epiphora

Grading Scale (for crocodile tears).[8-11] The TEARS Epiphora Grading Scale is a new tool for the monitoring and grading of epiphora, which has been designed by our author (RM) and has been accepted for publication in the European Journal of Ophthalmology (*Schulz CB, Malhotra R. The 'TEARS' Score: A Tool for Monitoring and Grading the Clinical Severity of Epiphora.*). The TEARS scale combines the pre-existing Munk scale (which constitutes the 'T') with measurements of the effect of epiphora on the patient's quality of life ('EA'), indicators of a reflex tearing component ('R') and response to treatment ('S').[12]

All patient-reported disease rating scales were completed with a single clinician (MF). All treatments, except for treatments to the lacrimal gland, were performed by the same clinician (MF).

The authors undertook a review of a prospective audit of all patients undergoing incobotulinumtoxinA treatment at the Corneoplastic Unit at QVH who were affected by the break in service (18/3/2020 - 17/6/2020) during the COVID-19 pandemic. All patients who received treatment in the six months prior to the break in service (i.e., from September 2019) were identified and, of these patients, all those

who have re-attended the clinic since the recommencement of service were included in the study. Data gathered included basic demographic data, dates and dosages of incobotulinumtoxinA treatments, disease rating scale scores (BDFDAS, JRS, TEARS), and a subjective patient-reported measure of how long the effects of botulinum toxin treatment took to completely wear off. This information was recorded in the clinical records at every visit, as per normal clinical practice.

Disease rating scale scores recorded at both timepoints were compared using parametric paired t-tests. The "delay" in follow-up was calculated by taking the difference between the clinician's requested follow-up, made prior to the first wave of the pandemic, and their actual achieved follow-up. "Time to treatment failure" was also recorded, based on patients' self-reporting of symptoms. Comparative statistical analyses have not been performed for such results as they are likely insufficiently powered to be considered valid and add to the presented summary statistics.

This audit was approved by the Queen Victoria Hospital NHS Foundation Trust R&D Department, who deemed that ethical

approval was not required. This audit adhered to the Tenets of the Declaration of Helsinki.

Results

One hundred and eight patients underwent botulinum toxin treatment in the six months prior to the break in service, and of these, 72 received treatments both before and after the break. The mean age of this cohort was 67.9 years (Table 1). 38.9% (n=28) received treatment for BEB; 19.4% (n=14) for epiphora; 18.1% (n=13) for HFS; 9.7% (n=7) for AFR; 12.5% (n=9) for more than one indication; and 1.4% (n=1) for the treatment of entropion.

During the study period, the mean (range) follow-up "delay" was 3.9 (0-9.8) months. Treatment had, after a period of effect, failed for all of our patients, with a mean "time to treatment failure" of 3.9 (0.5-12.0) months. The follow-up that was arranged following each patient's post-break visit was a mean 0.4 (-6.0 to +6.0) months greater than had been requested at their last visit prior to the break.

The mean total treatment dose at pre-break visits was 15.1 (2.5-60) units. The mean total dose at the first post-break visit was 15.6 (2.5-60) units (breakdown by condition available in Table 1). This

represents an increased dose in just four patients (6%, with a mean dose increase in this group of 44%), whilst the dose remained unchanged in the remaining 68 patients (94%).

Table 1. Changes in treatment dose and planned follow-up duration by condition category

	All	**BEB**	**HFS**	**AFR**	**Epiphora**
n	72	28 (38.9%)	13 (18.1%)	7 (9.7%)	14 (19.4%)
Age (years, mean(range))	67.9 (36.8 - 90.4)	70.9 (43.7 - 90.4)	66.5 (36.8 - 89.9)	71.2 (51.7 - 83.6)	56.5 (37.6 - 81.3)
Time Till Treatment Failed (months,	3.9 (0.5 - 12.0)	3.7 (0.5 - 9.0)	3.9 (1.5 - 9.0)	4.0 (2.5 - 6.0)	4.9 (3.0 - 6.0)

mean(range))					
Treatment Dose (IU, mean(range))					
- before break in service	15.1 (2.5 - 60.0)	25.0 (2.5 - 60.0)	13.4 (5.0 - 37.5)	6.8 (2.5 - 12.0)	3.0 (2.5 - 5.0)
- after break in service	15.6 (2.5 - 60.0)	26.0 (2.5 - 60.0)	13.6 (5.0 - 37.5)	6.8 (2.5 - 12.0)	3.0 (2.5 - 5.0)
- change in dose between visits	**+0.5 (0.0 - 25.0)**	**+1.0 (0.0 - 25.0)**	**+0.2 (0.0 - 2.5)**	**0.0 (0.0 - 0.0)**	**0.0 (0.0 - 0.0)**
Appointment Timings (months, mean(range))					
- follow-up	4.0	3.8	3.7	3.9	4.8

planned at pre-break visit		(2.5 - 12.0)		(2.5 - 12.0)		(3.0 - 5.0)		(3.0 - 6.0)		(3.0 - 6.0)
- follow-up delay ("actual" - "planned")		**3.9 (0.0 - 9.8)**		**4.0 (0.0 - 9.8)**		**3.1 (0.6 - 7.2)**		**3.0 (0.3 - 5.4)**		**5.2 (2.0 - 8.1)**
- follow-up planned at post-break visit		4.4 (3.0 - 9.0)		4.3 (3.0 - 9.0)		3.9 (3.0 - 5.0)		4.3 (3.0 - 6.0)		5.3 (3.0 - 6.0)
- change in planned follow-up		**+0.4 ((-6.0) - (+6.0))**		**+0.5 ((-6.0) - (+6.0))**		**+0.2 ((-1.0) - (+1.0))**		**+0.4 ((-0.5) - (+2.0))**		**+0.5 ((-2.0) - (+2.5))**

There was increase in all patient-reported outcome measurements from the pre-break appointment to the post-break appointment, indicating a greater level of symptoms and impact on quality of life. This effect was seen across conditions, as detailed in Table 2. When considering the BDFDAS scores in isolation, the greatest impact of a break in service was seen in AFR patients. An increase in score from

9.2% to 25.6% (a 178% relative increase) effectively represents a global worsening of function across most, or all, of the defined activities (reading, watching TV, driving, cleaning etc.).

Table 2. Changes in patient-reported disease rating scales by condition category. (Numbers in brackets indicate the maximum score for each scale)

		BEB	**HFS**	**AFR**	**Epiphora**
BDFDAS score (mean(range))					
- Pre-break visit (100)		35.5 (0 - 80)	9.3 (0 - 25)	9.2 (0 - 44)	-
- Post-break visit (100)		38.4 (0 - 88)	10.6 (0 - 38)	25.6 (0 - 67)	-
- Change in score (i.e., percentage point change)		+2.9 ((-42) - (+37))	+1.3 ((-10) - (+29))	+16.4 (0 - 50)	-
- Percentage change		**8.2% ↑**	**14.0% ↑**	**178.3**	-

				% ↑	
- p-value		*0.1533*	*0.3231*	*0.0235*	-
Jankovic Rating Scale (mean(range))					
- Pre-break visit (8)		2.7 (0 - 5)	1.8 (0 - 4)	-	-
- Post-break visit (8)		4.6 (2 - 8)	2.3 (0 - 6)	-	-
- Change in score		+1.9 ((-2) - (+7))	+0.5 ((-4) - (+4))	-	-
- Percentage change		**41.3% ↑**	**27.8% ↑**	-	-
- p-value		*0.00002*	*0.1784*	-	-
TEARS score (sum of T/E/A/R scores, mean(range))					
- Pre-break visit (22)		-	-	-	8.4 (4 -

					14)
- Post-break visit (22)		-	-	-	8.6 (4 - 15)
- Change in score		-	-	-	+0.2 ((-3) - (+2))
- Percentage change		-	-	-	**2.4% ↑**
- p-value		-	-	-	*0.3099*
Patient-reported "symptom improvement" (mean(range))					
- Pre-break visit (%)		81.8 (0 - 100)	89.9 (70 - 100)	86.4 (80 - 100)	74.8 (50 - 100)
- Post-break visit (%)		84.2 (70 - 100)	89.5 (75 - 100)	86.3 (80 - 95)	76.8 (45 - 100)
- Change in score (i.e., percentage point		+2.4 ((-10) -	-0.4 ((-10) -	-0.1 ((-5) -	+2.0 ((-25) -

change)		(+70))	(+10))	(+5))	(+20))
- Percentage change		**2.9% ↑**	**0.4% ↓**	**0.1% ↓**	**2.7% ↑**
- p-value		*0.2330*	*0.4096*	*0.4612*	*0.2873*

Considering the Jankovic ratings, in patients with BEB there was a significant increase in severity and frequency of blepharospasm due to the delay in treatment (mean increase in score of 1.9 points, or a 41.3% increase). This increase was greater than that noted in the HFS group (27.8%).

Finally, of the 108 patients that underwent treatment in the six months prior to the break in service, two are known to have sought and obtained repeat treatments elsewhere, within the private health sector, due to the severity of their symptoms. The first, a patient with HFS, underwent treatment in February 2020 (when BDFDAS was 1, Jankovic 0). In the midst of the break in service, patients were telephoned on the day of their previously planned re-treatment appointments. During this patient's telephone consultation in June their BDFDAS was 4 (Jankovic unknown), and the patient proceeded to receive repeat treatment at a private clinic elsewhere in August.

The second patient, with BEB, received treatment in February 2020 (BDFDAS 8, Jankovic 2). At their telephone consultation in May they had a BDFDAS of 3, and in June 2020, they also sought and underwent re-treatment in a private clinic elsewhere.

Discussion

The COVID-19 pandemic has had an unprecedented impact on the provision of elective healthcare which, in our practice, included the need for a break in botulinum toxin treatment service for patients with involuntary facial movement disorders and epiphora. Whilst this break has unfortunately had detrimental effects on patients, it has provided a unique opportunity to study the effects of stopping treatment across an entire service. This study demonstrates the effects of a sudden cessation of treatment within a botulinum toxin service and a delay in treatment. Of note, it has allowed quantification of the effect that this has on the patient and their quality of life. All patient-reported outcome measures showed a worsening of symptoms and effect on quality of life after the break in service, although patients with AFR appear to have been the worst affected. Patients with HFS started with similar BDFDAS scores to those with AFR, but their

scores rose much less following the break in service, suggesting that those with AFR are a more sensitive group, and more susceptible to disability due to their synkinesis when treatment is not performed on time.

Patient-reported "symptom improvement" was recorded at both the pre- and post-break visits, and in both cases relate to the improvement gained from the *previous* visit. Increased symptom improvement was noted between the two visits in both the BEB and epiphora groups (2.9% and 2.7% increases respectively). This may have occurred as a result of the break in treatment giving patient's a truer sense of their baseline, untreated, symptom severity, and therefore, the full effectiveness of their treatment.

Over the course of this break in service, treatments were delayed a mean 3.9 (0-9.8) months, although it should be noted that not all delays will have been due to the pandemic. As all patients were left long enough between appointments for their incobotulinumtoxinA treatment effect to wear off, "time to treatment failure" could be reliably measured across the entire cohort: BEB, 3.7 months; HFS, 3.9 months; AFR, 4.0 months; epiphora, 4.9 months. In each of these

groups, duration of treatment effect was greater than those reported in the literature (as follows).

Duration of treatment effect has been presented in numerous previous reports, most commonly for BEB: onabotulinumtoxinA (Botox), 1.7–3.9 months;[13-20] incobotulinumtoxinA (Xeomin), 2.6-3.0 months;[19,21] and abobotulinumtoxinA (Dysport), 1.7-2.0 months.[17-18] Nussgens et al separated their patients into two easily identifiable groups: "good responders", whose effect lasted 3.7 months; and "poor responders", whose effect lasted a mean 1.7 months.[14] Duration of effect in HFS has been reported to be: Botox, 2.3-3.2 months;[15,18-20,22] Xeomin, 3.0 months;[19] and Dysport, 1.5-2.0 months.[18-22] In AFR: Botox, 3.3-4.0 months;[19,23] and Xeomin, 3.3 months.[19]

The follow-up arranged after each patient's post-break visit was 0.4 months greater than that requested at their pre-break appointment. The authors believe that this slight elongation in follow-up interval was due, at least in part, to the patient and clinician now knowing the patient's "time to treatment failure", specific to their own condition and to them as an individual. Prior to this break in service, many of these decisions of treatment intervals would be based on when the

effect decreased noticeably, rather than when effect wore off completely.

The findings of this study suggest that if a further break in service were ever required, patients with AFR should be prioritised to receive treatment where possible, due to the potential impact on their quality of life caused by stopping treatment. At the other end of the spectrum, patients undergoing treatment for crocodile tears / epiphora are likely to tolerate a break in treatment better given that treatment effect lasted the longest (4.9 months) in this group and the change in TEARS score caused by a delay in treatment was comparatively low.

All of the presented patient-reported disease rating scales are collected prospectively for all patients, which means that this retrospectively-designed study benefits from many of the characteristics normally associated with a prospective study – in particular, consistency of data recording. A further strength of this study is that all disease rating scales and all treatments, except treatment to the lacrimal gland, were administered by the same clinician. Limitations of this study include low sample size in a couple of the sub-groups, particularly AFR (n=7). Furthermore, given

sufficient staff/time resource, it would have been useful to complete the disease rating scales via telephone consultation, in the week of each patient's "planned" follow-up / re-treatment, although this was not possible at our centre during the first wave of the pandemic.

These findings suggest that patients with AFR are likely to tolerate a break in service least, while patients with crocodile tears may not be so greatly affected. Separate to this, patients with BEB and HFS for whom the ability to drive is essential (for example, for work or caring responsibilities) should also be prioritised, and this information should be recorded pre-emptively. This "real-world" snapshot, made possible by a global pandemic, has allowed quantification of the harm caused by a break in botulinum toxin service. It provides valuable information should further breaks in service or any delay in treatment be required in future, whether due to COVID-19, or otherwise.

Reference

1. Ross AH, Elston JS, Marion MH, Malhotra R. Review and update of involuntary facial movement disorders presenting in the ophthalmological setting. *Surv Ophthalmol.* 2011;56(1):54-67.

2. Miller NR. Reply to: review and update of involuntary facial movement disorders presenting in the ophthalmological setting, "Eyelid Myokymia". *Surv Ophthalmol.* 2011;56(3):277-8.
3. Keegan DJ, Geerling G, Lee JP, Blake G, Collin JR, Plant GT. Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. *Br J Ophthalmol.* 2002;86:43-6.
4. Montoya FJ, Riddell CE, Caeser R, Hague S. Treatment of gustatory hyperlacrimation (crocodile tears) with injection of botulinum toxin into the lacrimal gland. *Eye.* 2002;16:705-9.
5. Whittaker KW, Matthews BN, Fitt AW, Sandramouli S. The use of botulinum toxin A in the treatment of functional epiphora. *Orbit.* 2003;22(3):193-8.
6. Ziahosseini K, Al-Abbadi Z, Malhotra R. Botulinum toxin injection for the treatment of epiphora in lacrimal outflow obstruction. *Eye.* 2015;29:656-61.
7. Calman B / Daily Mail. Lockdown Botox ban that's been torture for facial palsy patients after treatment for condition is deemed cosmetic and non-essential. *Daily Mail*.

https://www.dailymail.co.uk/health/article-9358471/Lockdown-Botox-ban-thats-torture-facial-palsy-patients.html [accessed 12 June 2021].

8. Jankovic J, Orman J. Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. *Neurology*. 1987;37:616–23.
9. Brin MF, Jankovic J, Comella C, Blitzer A, Tsui J, Pullman SL. Treatment of dystonia using botulinum toxin. In: Kurlan R (ed). *Treatment of movement disorders*. USA: Lippincott Company; 1995, p. 183-230.
10. Thussu A, Barman CR, Prabhakar S. Botulinum toxin treatment of hemifacial spasm and blepharospasm: objective response evaluation. *Neurol India*. 1999;47:206–9.
11. Grivet D, Robert P-Y, Thuret G, et al. Assessment of blepharospasm surgery using an improved disability scale: study of 138 patients. *Ophthalmic Plast Reconstr Surg*. 2005;21(3):230-4.
12. Munk PL, Lin DT, Morris DC. Epiphora: treatment by means of dacryocystoplasty with balloon dilation of the nasolacrimal drainage apparatus. *Radiology*. 1990;177(3):687-90.

13. Mauriello JA Jr, Dhillon S, Leone T, Pakeman B, Mostafavi R, Yepez MC. Treatment selections of 239 patients with blepharospasm and Meige syndrome over 11 years. *Br J Ophthalmol.* 1996;80:1073–6.

14. Nussgens Z, Roggenkamper P. Long-term treatment of blepharospasm with botulinum toxin type A. *Ger J Ophthalmol.* 1995;4:363–7.

15. Quagliato EM, Carelli EF, Viana MA. Prospective, randomized, double-blind study, comparing botulinum toxins type A Botox and Prosigne for blepharospasm and hemifacial spasm treatment. *Clin Neuropharmacol.* 2010;33:27–31.

16. Roggenkamper P, Jost WH, Bihari K, Comes G, Grafe S, NT 201 Blepharospasm Study Team. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. *J Neural Transm (Vienna).* 2006;113(3):303-12.

17. Nussgens Z, Roggenkamper P. Comparison of two botulinum-toxin preparations in the treatment of essential blepharospasm. *Graefes Arch Clin Exp Ophthalmol.* 1997;235:197–9.

18. Bihari K. Safety, effectiveness, and duration of effect of BOTOX after switching from Dysport for blepharospasm, cervical dystonia, and hemifacial spasm dystonia, and hemifacial spasm. *Curr Med Res Opin.* 2005;21:433–8.

19. Bladen JC, Favor M, Litwin A, Malhotra R. Switchover study of onabotulinumtoxinA to incobotulinumtoxinA for facial dystonia. *Clin Exp Ophthalmol.* 2020;48(9):1145-51.

20. Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin A injections to treat blepharospasm and hemifacial spasm. *Clin Exp Ophthalmol.* 2014;42:254–61.

21. Jankovic J, Comella C, Hanschmann A, Grafe S. Efficacy and safety of incobotulinumtoxinA (NT 201, Xeomin) in the treatment of blepharospasm—a randomized trial. *Mov Disord.* 2011;26(8):1521-8.

22. Sampaio C, Ferreira JJ, Simoes F, et al. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—assuming a ratio of 4:1. *Mov Disord.* 1997;12:1013–8.

23. Toffola ED, Furini F, Redaelli C, Prestifilippo E, Bejor M. Evaluation and treatment of synkinesis with botulinum toxin following facial nerve palsy. *Disabil Rehabil.* 2010;32:1414–8.