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CLINICAL STUDY

Validation of a new photogrammetric technique to monitor the treatment effect of Botulinum toxin in synkinesis

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Abstract

Aims **To validate a new photogrammetric technique for quantifying eye surface area and using this to quantify the degree of improvement in symmetry in patients with oral–ocular synkinesis following Botulinum toxin injection.**

Study design **Feasibility study and retrospective outcomes analysis**

Methods **Ten patients' photographs were chosen from a photographic database. Their eye surface areas were measured independently by two raters using a graphics tablet. One rater repeated the procedure after 15 days. Bland–Altman plots were computed, ascertaining inter-rater and intra-rater variability. The eye surface areas of 19 patients were then derived from photographs taken before and after Botulinum toxin injections. Paired *t*-tests were used to analyse the significance of the difference in pre- and post-treatment symmetry.**

Results **Ninety per cent of eye surface areas derived from the two raters were within a coefficient of variation of 0.1 (95% CI: 0.05–0.15). Similarly, 90% of eye surface areas derived from one rater had a coefficient of variation of 0.08 (95% CI: 0.04–0.12). Botulinum toxin significantly reduced synkinesis resulting from lip puckering, Mona Lisa smiling and Hollywood smiling ($P<0.05$).**

Conclusions **We have proposed a clinically valid tool for quantifying the effects of Botulinum toxin treatment for oral–ocular synkinesis. We recommend this method be used to monitor the response of such patients when receiving Botulinum toxin treatment.**

Level of evidence **2c.**

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Keywords: synkinesis; botulinum toxin; facial palsy; photogrammetric

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Introduction

Patients with facial nerve injuries are frequently afflicted by synkinesis, a movement disorder principally attributed to aberrant nerve regeneration.[1] The incidence of synkinesis in patients recovering from facial paralysis is between 15–50% depending on the series.[2,3] Synkinesis specifically refers to the involuntary contraction of a muscle or muscle group, in addition to that required for a desired expression or movement; for example, a patient's eye may involuntarily close when smiling due to inappropriate innervation of the obicularis oculi muscle. Synkinetic movements affecting facial muscle groups may not only result in the impairment of normal facial functions, such as eating or eye closing, but may also result in difficulties in conveying appropriate or desired facial expressions. Synkinesis, therefore, frequently has a negative effect on a patient's quality of life.[4,5]

Since the early 1990s, directed Botulinum toxin injection to affected muscles has been the mainstay of treatment of synkinetic movement disorders.[6,7] The Botulinum toxin inhibits the release of acetylcholine from the presynaptic nerve terminal at the neuromuscular junction, preventing the propagation of the action potential and contraction of the targeted muscle. The resulting (temporary) paralysis of synkinetic muscles has been demonstrated to improve the quality of life in affected individuals.[5] However, the optimal dosing range of Botulinum toxin for treating synkinesis has not yet been established. It is frequently administered on an *ad hoc* basis, exposing patients to the possibility of under- or overtreatment.

One of the problems faced when establishing an efficacious Botulinum toxin treatment dose is that there is no universally accepted technique within the literature for objectively measuring the effects of treatment. Studies have attempted to address this issue; one such study used patient-reported perceptions of improvement after treatment,[8] and although the accuracy of such objective data cannot be guaranteed, the data is useful as it reflects patient satisfaction with treatment.[9] Clinician-based scales such as the House–Brackmann, Facial Grading and the Sunnybrook systems are also widely used, but also are subjective and subject to wide inter-rater variability.[10] Furthermore, these scales do not precisely quantify the degree of synkinesis present. Therefore, there has been a concerted effort to develop computer-based systems in order to provide objective measures of facial motion.[11–16] Although largely improving the objectivity of facial assessment, the cost of these specialised systems likely limits the widespread uptake of these systems, especially in these fiscal times. Thus, there is a clear need to continue investigating alternative, cheaper and more reliable techniques.

Eye closure resulting from voluntary mouth movements (oral–ocular synkinesis) is the most common synkinetic movement resulting from volitional mouth movements.[4] Techniques such as the Maximal Static Response assay have been used in attempts to quantify the degree of ocular-oral synkinesis,[14] but no methods have quantified oral–ocular synkinesis enough to guarantee wide uptake. At our unit, patients are routinely photographed before and after Botulinum toxin treatment. From these photographs, improvements in symmetry and position of the peri-ocular tissues are subjectively obvious, but like other institutions, we have struggled to accurately quantify the clinically obvious response to treatment.

In the current study, we propose to validate a novel photogrammetric method of assessing the synkinetic peri-ocular region and to accurately quantify the effects of Botulinum toxin therapy in the treatment of oral–ocular synkinesis through direct comparisons before and after treatment.

Materials and methods

Hardware and software

All photographs included in the present study were taken using either a Nikon D700 or a Nikon D300 camera (both Nikon, Tokyo, Japan). The photographs included were all frontal photographs taken with either a 2128 × 1416 pixel (D300) or a 1296 × 1936 pixel (D700) setting. For image analysis, ImageJ software (http://rsbweb.nih.gov/ij/) was used. The perimeter of the eye was traced using a graphics tablet (Bamboo, Wacom, Vancouver, WA, USA) and the number of pixels covered by the perimeter derived from ImageJ. Starting at the endocanthion, a line was drawn following the border of the sclera and conjunctiva to the exocanthion and back to the endocanthion (Figure 1).

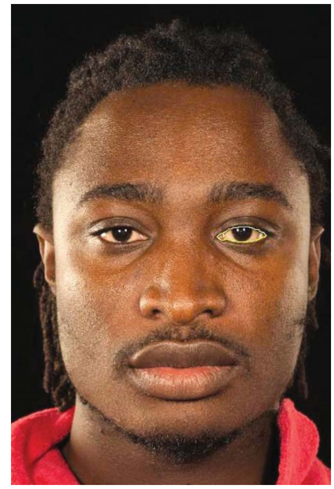

Figure 1 Example of a tracing line drawn to determine the eye surface area. The line starts at the endocanthion, and follows the border of the sclera and conjunctiva to the exocanthion around the eye.

Validation study

For validation purposes, 10 subjects (5 male, 5 female) were randomly selected from the hospital's database of facial photographs. Two raters (NTM and MJH) independently measured the area of the right and left eyes for each subject to derive inter-rater variability of the measurements. Additionally, NTM repeated the measurements on the same subjects after 15 days, without referring to the record of the first measurements, to derive intra-rater variability.

Photogrammetric analysis

A database of 246 patients, treated by the senior author for facial palsy at a tertiary referral centre between 2007 and 2011, was retrospectively searched for patients with oral–ocular synkinesis and a full set of standardised photos taken in a studio before and after Botulinum toxin treatment by a professional medical photographer. Nineteen suitable candidates (16 female, 3 male) were retrospectively identified. A full set of standardised photos was taken to mean photographs taken with the

Nikon D700/D300 with either a 105 mm lens (FX format) or 60 mm lens (DX format) at 1/160 s and f22, under constant lighting using four Bowens lights (Bowens, Clacton on Sea, UK, two backlights and two front lights), on a black background, demonstrating the following poses at maximal intensity under and distance: repose, smiling with (canine/ Hollywood smile) and without showing teeth (Mona Lisa smile),[17] lip puckering, blowing out cheeks and showing the lower teeth. All images were stored on the hospital's secure online database where they are kept for a period of 10 years before deletion. For each patient, the specific volitional movement(s) resulting in eye closure was recorded. The ratio of the area of the synkinetic eye to that of the normal eye, during specific volitional movements, was calculated both before and after treatment.

Statistical analysis

Bland–Altman plots[18] were constructed to illustrate trends in the area measurements and to visually depict inter- and intra-rater repeatability of our technique. Repeatability coefficients and 95% confidence intervals thereof were also determined. For all photogrammetric analyses, ratios of the area of the synkinetic eye to that of the normal eye were used. The difference in the pre- and post-treatment ratios for each patient were analysed using paired *t*-tests, with significance regarded as $P<0.05$.

Results

Inter-rater reproducibility

Table 1 shows the areas of the eyes as measured by the two raters independently. The mean difference between the ratios derived from the two raters was 0.03. The Bland–Altman graph for these differences (Figure 2a) shows that 90% of the ratios of eye areas derived from measurements made by the two independent raters were acceptably similar. The coefficient of the inter-rater variation was 0.1 (95% CI: 0.05–0.15).

Intra-rater repeatability

Table 2 shows the areas of the eyes as measured by NTM at two time points15 days apart. The mean difference between the ratios derived at the two different times was also 0.03. The Bland–Altman graph for these differences (Figure 2b) shows that 90% of the ratios of eye areas derived from measurements made by NTM 15 days apart were acceptably similar. The coefficient of variation for test–retest reliability was 0.08 (95% CI: 0.04–0.12).

Photogrammetric analysis

Botulinum toxin injection did not result in a statistically significant difference in the symmetry of eyes before and after treatment where patients were in repose ($P=0.35$; Table 3). Where Botulinum toxin was injected in patients with eye closure resulting from lip puckering, Mona Lisa smiling and Hollywood smiling, a statistically significant improvement in symmetry was seen ($P<0.05$; Table 3). Symmetry was not statistically significantly improved following injection in patient with synkinesis resulting from blowing out cheeks and using lip depressors to show lower teeth ($P=0.08$ and 0.07, respectively; Table 3).

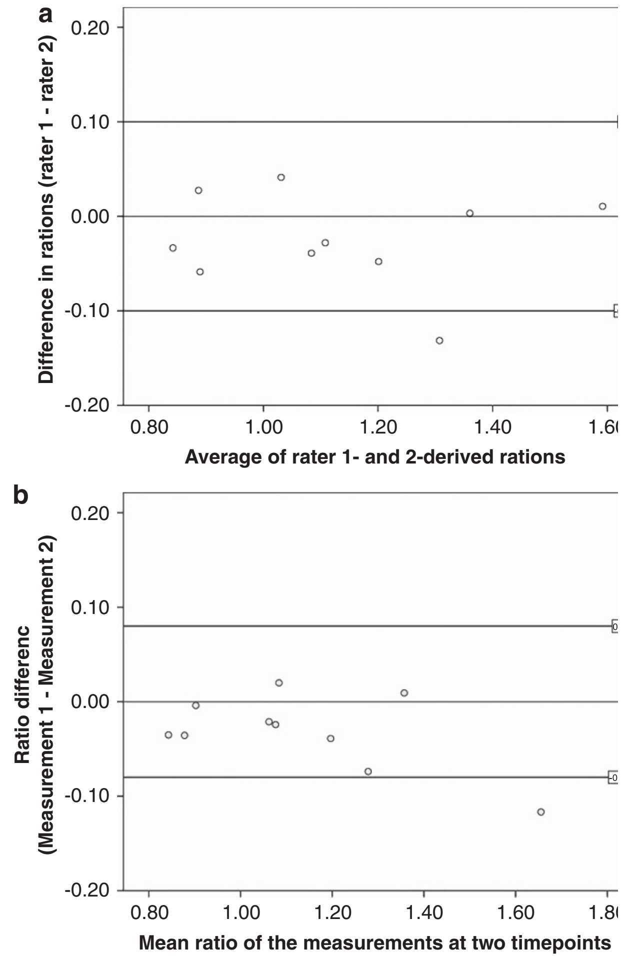

Figure 2 (**a**) Bland–Altman plot of the inter-rater variation in eye surface area measurements. Ninety per cent (9/10) of the areas measured by the two raters are within the coefficient of variation limits of ±0.1. (**b**) Bland–Altman plot of the test–retest reliability in measurements. Ninety per cent (9/10) of the areas measured by one rater were within the coefficient of variation limits of ±0.08.

Discussion

The first aim of this study was to validate the use of a graphics tablet and ImageJ to calculate the area of the eyes. The limits of agreement set for the Bland–Altman plot (Figure 2a) showed that the two independent raters

Table 1 Eye surface areas derived by two independent raters

Subject	Rater 1 Area (pixels) R	Rater 1 Area (pixels) L	Rater 1 Ratio (R:L)	Rater 2 Area (pixels) R	Rater 2 Area (pixels) L	Rater 2 Ratio (R:L)	Ratio difference
1	7105	6495	1.09	7353	6554	1.12	−0.03
2	8295	9211	0.90	8158	9343	0.87	0.03
3	12 734	9351	1.36	12 606	9279	1.36	0.00
4	14 245	13 548	1.05	13 898	13 757	1.01	0.04
5	5304	6167	0.86	5712	6217	0.92	−0.06
6	9252	7860	1.18	9279	7575	1.22	−0.04
7	5860	7100	0.83	6064	7061	0.86	−0.03
8	14 509	9085	1.60	14 269	8994	1.59	0.01
9	11 411	9191	1.24	11 754	8561	1.37	−0.13
10	10 003	9398	1.06	10 144	9194	1.10	−0.04

Abbreviations: R, right; L, left.

scored within two scale points of each other on 90% of measurements. There was no systematic bias between the raters. A coefficient of variation of 0.1 means that two ratios derived from area measurements made by two different raters are likely to differ by at most 0.1. This difference is small enough to make the level of inter-rater variation clinically acceptable and useful. Similarly, clinically acceptable test–retest reliability was demonstrated (Figure 2b), supported by a coefficient of variation of 0.08. Figure 2b also shows that the majority of the second area measurements are slightly smaller than the first measurements perhaps due to the rater becoming more comfortable with using the graphics tablet. These results show that this technique is a reliable method of measuring the area of an eye on a patient photograph.

Aside from its reliability, this method is also cost-effective. Clinicians in the developed world, certainly in UK, all have access to computers and the internet, from which ImageJ can be downloaded free of charge. Therefore, the only new hardware to be bought when using this method is a graphics tablet, although it is hoped that the photography departments of most hospitals will have these. Indeed, it is certainly possible to trace the borders of the eyes using a normal computer mouse. However, our experience has shown that this task is much simplified and expedited by using a graphics tablet that can be purchased for ∼£50.

The second part of this study aimed to perform a photogrammetric analysis on the images of patients treated with Botulinum toxin for oral–ocular synkinesis, using the technique validated above. Botulinum toxin treatment did not make a statistically significant difference to the symmetry of patients' eyes in repose (Table 1). This is to be expected as synkinesis, by definition, is produced following a volitional movement, and therefore, reasonable symmetry will normally be

Table 2 Eye surface areas as measured by one rater 15 days apart

Subject	First measurement Area (pixels) R	First measurement Area (pixels) L	First measurement Ratio (R:L)	Second measurement Area (pixels) R	Second measurement Area (pixels) L	Second measurement Ratio (R:L)	Ratio difference
1	7105	6495	1.09	7501	6984	1.07	0.02
2	8295	9211	0.90	8375	9259	0.90	0.00
3	12 734	9351	1.36	13 034	9637	1.35	0.01
4	14245	13 548	1.05	14 280	13 313	1.07	−0.02
5	5304	6167	0.86	5463	6099	0.90	−0.04
6	9252	7860	1.18	9293	7642	1.22	−0.04
7	5860	7100	0.83	5842	6789	0.86	−0.03
8	14 509	9085	1.60	15 180	8858	1.71	−0.11
9	11 411	9191	1.24	11 639	8848	1.32	−0.08
10	10 003	9398	1.06	9647	8862	1.09	−0.03

Abbreviations: R, right; L, left.

Table 3 Eye surface area ratios before and after Botulinum toxin treatment

Volitional movement	Number of patients	Prebotox s:n ratio (mean)	Postbotox s:n ratio (mean)	P-value
Repose	19	0.932322109	0.959508251	0.35
Lip pucker	15	0.48819484	0.761099614	0.001
Mona Lisa smile	13	0.539256903	0.838414757	0.001
Canine/ Hollywood smile	15	0.615228332	0.819504053	0.01
Blowing out cheeks	17	0.484640603	0.577822105	0.08
Showing bottom teeth	17	0.612998249	0.761525562	0.07

Abbreviation: s:n,ratio of area of synkinetic eye (s) to the normal eye (n).

seen in repose. The effect of Botulinum toxin treatment of ocular synkinesis resulting from the volitional oral movements of blowing out the cheeks and using the lip depressors to show the bottom teeth approached statistical significance, $P = 0.08$ and 0.07, respectively. However, because the mean eye area ratios before and after treatment clearly show increased symmetry (Table 3), that is, the post-treatment ratio is closer to 1.0 than the pre-treatment ratio, it is likely that the marginal statistical insignificance would be rectified in a larger cohort. Also, while statistical significance may not have been achieved within this group, it is still useful for a clinician to know the eye area ratios pre- and post-treatment to monitor individual patient responses, to allow personalised tailoring of therapy. One may also infer this result to suggest that the treatment dose used in these cases was sub-optimal and further treatments may require a higher concentration of Botulinum toxin. One reason for this is that higher toxin doses were likely to cause lagopthalmos in some patients; therefore, the objective of treatment needed to be balanced by the desire to avoid adverse effects. We suggest, therefore, that our method is also a useful way of monitoring response to and directing future treatments.

Statistically significant improvements in symmetry following treatment were seen, however, with synkinesis resulting from lip puckering, smiling with lips closed (Mona Lisa smile) and smiling with teeth showing (Table 3). These results quantify the physical effect of Botulinum toxin, which other authors have previously shown to result in an improvement in patients' quality of life.[5] This quantification will be useful if comparisons of the efficacy of different Botulinum toxin preparations were to be made. However, a limitation of this method is that it is specific for quantifying oral–ocular synkinesis and cannot in its present form be used to quantify other types of facial synkinesis. We are currently conducting further research in this area in order to develop similar tools that may be used to assess other synkinetic movements with accuracy.

Conclusions

This paper establishes the validity of a new photogrammetric tool that can be used to monitor the treatment effect of Botulinum toxin in patients with oral–ocular synkinesis. We therefore recommend this method be used to monitor patients with oral–ocular synkinesis who are to receive Botulinum toxin treatment.

Summary

What was known before

- Synkinesis is a common problem in facial palsy. Botulinum toxin is frequently used for treatment. Treatment response is difficult to quantify.

What this study adds

- New photogrammetric technique for quantifying eye surface area. A method to quantify the degree of improvement in symmetry in patients with oral–ocular synkinesis following Botulinum toxin injection.

Conflict of interest

The authors declare no conflict of interest.

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