A trial of a mechanical device for the treatment of blepharospasm

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Received: 5 December 2018 / Revised: 2 May 2019 / Accepted: 14 May 2019 / Published online: 2 July 2019

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Abstract

Background Idiopathic blepharospasm (IB) is a rare but well-characterised adult onset focal dystonia that may cause severe visual disability. The most effective treatment is with periodic injections of botulinum toxin (BTX) into the pre-tarsal and/or pre-septal orbicularis oculi muscles bilaterally. However, even with treatment, practical visual function often remains compromised. A subset of IB sufferers find that eye opening improves with a focal unilateral digital pressure usually on a specific point on the temple. This is known as a ‘sensory trick’. We have developed a spectacle mounted device (‘Pressop’) to apply continuous individually localised focal pressure on the temple to mimic the effect of finger pressure. The aim of the study was to determine if the ‘sensory trick’ could be replicated by Pressop and if the interval between BTX treatments could thereby be extended.

Subjects/methods Study participants had three clinic visits—an initial screening assessment, a visit 2 weeks before the next injection was due when the device was fitted, and one 2 weeks later to assess the response to Pressop. A CDQ 24 and device-specific feedback questionnaire were completed and comparison photographs were taken. Repeat BTX injections were administered at the third visit.

Results Of 58 patients with typical IB recruited to the trial, 39 reported an effective focal finger pressure sensory trick. 56 completed the trial, more than 50% of whom reported some benefit using Pressop; 18% had substantial improvement, sustained for up to 5 years. Improvement could occur in those without an effective sensory trick, therefore there was no significant correlation between using a sensory trick and benefiting from ‘Pressop’. There was a trend towards the responders having greater improvement in CDQ24 total score than non-responders but this was not statistically significant.

Conclusions We recommend a trial of this simple safe device as a means of augmenting visual function in all IB patients.

Introduction

Idiopathic blepharospasm is a rare chronic neuro-ophthalmic disorder that causes substantial visual handicap and compromises the quality of life. It affects adults, women more than men, usually beginning in the 5th or 6th decade and consists of repeated forceful bilateral spasms of eye closure with photophobia and ocular surface discomfort. In up to a third of cases there are synchronous mid and/or lower facial spasms and the spectrum of disorder extends to cranial dystonia involving jaw and neck muscle spasms (e.g. antecollis or retrocollis). Practical visual function is variably affected but

most patients will have to stop driving, many cannot work, manage the house or even leave the house unaccompanied. Leisure activities such as reading and watching television are compromised or impossible, and secondary mood dysphoria and depression are common [1, 2].

In some cases, patients have discovered that applying focal finger pressure, usually to the temple, relieves or even abolishes the spasms for the duration of the application [3, 4]. It is, however, difficult for the patient to sustain the finger pressure and impossible to apply it during bimanual activities when eyesight is important, e.g. driving and typing. The phenomenon can be regarded as the equivalent of the sensory trick (ST or geste antagoniste) seen in some cases of spasmodic torticollis whereby fingertip pressure on the chin prevents or reduces the muscle spasms in the neck and allows the head to be held straight [5].

In this study, we explored the hypothesis that the benefit of the finger-tip pressure sensory trick can be replicated by a spectacle mounted device applying focal pressure to the temple. Following preliminary design trials from 2005 onwards, we commissioned a manufacturer to develop a

Supplementary information The online version of this article (<https://doi.org/10.1038/s41433-019-0495-y>) contains supplementary material, which is available to authorized users.

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Fig. 1 The Pressop device used in the trial is easy to attach to most spectacle frames

light, easily handled pressure device that could be fixed to the frame of most spectacles. The clinical trial for the ‘Pressop’ device, registered at <https://clinicaltrials.gov> (NCT 03269123), fulfils these criteria (see Fig. 1).

Patients and methods

This was a prospective interventional ethically approved study conducted with adherence to the tenets of the Declaration of Helsinki.

Recruitment of subjects

Potential subjects for the study were identified from three sources.

- (1) Patients attending the Botulinum Toxin blepharospasm treatment Clinic at the Oxford Eye Hospital and fulfilling the inclusion criteria.
- (2) Patients attending the Dystonia clinic in the Neurology Department of The John Radcliffe Hospital, Oxford for blepharospasm treatment and fulfilling the inclusion criteria.
- (3) The Dystonia Society, a UK-based charity, publicised the study to its membership base through the newsletter and website www.dystonia.org.uk, and potential participants expressing interest were contacted by the investigators.

Inclusion criteria

Adult patients with idiopathic blepharospasm who were currently receiving or had trialled BTX injections were eligible for the study.

Spectacle wear (having a refractive error) was not a criterion as the participants could be provided with prescription free (zero power) spectacles.

The presence of an effective ‘sensory trick’ was not an essential criterion for inclusion into the study.

Exclusion criteria

- (1) Patients with eyelid spasms caused by different pathologies e.g. hemifacial spasm and difficulty of eyelid opening caused by apraxia of eye opening and/or Parkinson’s disease were excluded.
- (2) Individuals with psychogenic blepharospasm [6].
- (3) Individuals who were unwilling to wear spectacles.

Methods

Participants attended for three study visits. IB patients typically attend BTX treatment clinics every 2–3 months for injections and the study visits were based around these.

Visit 1: pre-intervention screening visit

Potential participants underwent a baseline assessment between injection treatments with detailed exploration of the nature and severity of symptoms, any trigger or relieving factors, and a medical and medication history. They were shown the device and tried sample spectacle frames with mounted devices.

It was emphasised that using the device would not alter their current treatment, and they would continue to receive botulinum toxin injections. Patients who did not routinely wear spectacles were provided with zero power spectacles for the purpose of the trial. The device was attached to the patients’ spectacles with a demonstration and explanation to apply the pressure device as required. Subjects were advised to alter the position and try various contact points to see if they experience relief of the spasms, and to record which position was most effective. A device users’ guide (Appendix 1) was supplied. Informed consent regarding use of Pressop was obtained at this visit, but the test period for use did not start until several weeks after the next injection treatment.

At this visit, the subjects completed the Craniocervical Dystonia Questionnaire CDQ-24 [7] (Appendix 2) and were tested for sensory tricks.

Visit 2: intervention initiation

Study subjects were invited to attend for their second visit towards the end of the therapeutic cycle, i.e. 2–3 weeks before the next BTX injections were due.

Following this visit, a trial period of at least 15 days of use of Pressop was recommended. Any changes to the

participants' medication schedule were documented. The patient's evaluation included recording any benefit for specific tasks such as reading, watching television and when possible, driving during the 2 weeks prior to retreatment with BTX. This was recorded in a device-specific feedback questionnaire (Appendix 3). Photographs were taken with and without the device to record the difference in eye opening.

Visit 3: evaluation

The third and final visit was arranged 2 weeks later, to coincide with their botulinum injection appointment. Subjects completed the CDQ-24 questionnaire again to assess the efficacy of the device, as well as the device-specific questionnaire.

Those benefiting from the device could keep it and continue use. Registered participants at the study centre were retreated as required with botulinum toxin injections. Visiting participants returned to their own specialists for retreatment. Participants who lived far away from the study centre were given the option of a final telephone consultation in place of visit 3.

Subjects were able to opt out at any time during the study and could be offered botulinum injections if needed.

Outcome measures

The study assessed the subjective response to the use of the device during the 2–3-week trial period using the CDQ-24 quality of life questionnaire. Subjects also received a questionnaire specific to the device addressing aspects such as wearing time, discomfort, and feedback. Scores from the CDQ-24 assessment carried out before and while using the pressure device were used for analysis. The primary outcome measure was the response to the device (relief from spasms). Delaying or avoiding the need for botulinum injections was considered a strongly positive outcome measure. Subjects experiencing relief some or all the time were categorised as responders.

Statistical methods

Intention to treat analysis was performed, assuming that patients who were unable to use the device properly or withdrew from the study were non-responders.

As the changes in CDQ-24 scores from baseline to follow-up were normally distributed, the paired *t*-test was used for the analysis. Additionally, the change in scores was compared between responders and non-responders with the unpaired *t*-test.

The remaining outcomes were all binary in nature. Descriptive statistics were used to summarise the numbers

in each outcome category including 95% confidence intervals (CI).

Results

63 potential participants were screened for the study. 4 were excluded as they did not meet the criteria and 1 withdrew. 58 subjects entered the study, 46 of whom were receiving regular BTX treatment follow up regimes varying between 2 and 4 monthly. None were treatment naive as the remaining 12 had stopped receiving treatment. There were 5 males and 53 females with mean age of 65 years (range 60–70). Two patients were excluded from all analyses as they did not complete the questionnaires, and 56 subjects were included in the final analysis for the main outcome.

Co-morbidities recorded in the questionnaire include hypertension, arthritis involving the hands ($n = 16$), ischaemic heart disease and diabetes. Ocular co-morbidities included blepharitis ($n = 19$) and ocular surface disease ($n = 41$).

Treatment response

61% (CI: 47–74%) of patients showed a positive response to the intervention. Of the 34 responders, more than half ($n = 24$) had partial relief from symptoms, while 10 experienced relief from symptoms all the time the device was used (see Table 1, Fig. 2a, b and the video link). Lack of response to BTX treatment did not influence benefit from using Pressop.

CDQ24 scores

The paired *t*-test was used to examine the changes in CDQ-24 scores over the duration of the study for the group. There was a significant improvement ($p < 0.001$) in mean scores (−7.0 change) from 28.4 (SD 16.9) at baseline to 21.4 (SD 15.4) at follow-up.

The change in CDQ-24 total score from baseline to follow-up was compared for responders and non-responders (change for responders minus change for non-responders) using the unpaired *t*-test. The mean value for

Table 1 Responses to use of Pressop. Results data

Figure	ITT analysis
Number in analysis	56
Relief symptoms <i>N</i> (%)	
None	22 (39%)
Some	24 (43%)
All time	10 (18%)
Treatment response—% (95% CI)	61% (47%, 74%)

Fig. 2 a, b Two subjects demonstrating relief of spasm with the Pressop device. *Video link with subtitles:* Subject with cranial dystonia and blepharospasm partly relieved by a sensory trick of digital temple pressure. This is replicated with Pressop, with additional improvement in lower facial movements

Fig. 3 Comparison of change in scores between responders and non-responders

non-responders was -4.3 (SD 7.8) and for responders was -8.9 (SD 12.6) with a mean difference of -4.6 . This difference was not significant ($p = 0.14$) (Fig. 3).

Other observations

A number of other features were assessed by the device-specific questionnaire. These were binary variables, and data was available for all 56 respondents. A sensory trick was present in 68% ($n = 40$) of the subjects in this cohort. 70% of those who benefitted from using Pressop used a sensory trick while 30% did not. There was no statistically significant correlation between using a sensory trick and benefitting from Pressop (phi coefficient of correlation = 0.03).

Half the subjects ($n = 29$, CI: 37–63%) found the device easy to fit on spectacles, and 71% ($n = 41$, CI: 57–82%)

found it easy to adjust. Most subjects used the device intermittently, and only 7% ($n = 4$, CI: 2–17%) wore it all the time. In some cases, as well as eye opening, lower facial dystonia improved with the use of Pressop (see video). There was no consistent change in either the interval between BTX injections or the dose requirement in those benefitting from Pressop.

Of those recruited at the study centre, 7 have continued to benefit from using Pressop for the period up to 8 years.

Discussion

The diagnosis of idiopathic blepharospasm in the patients we studied had been made by experienced consultant neurologists and ophthalmologists in specialist centres throughout the UK. The demographics of the patient cohort were typical of that widely reported in IB in respect of age, severity and duration of the condition and response to botulinum toxin treatment. We excluded cases where the diagnosis was uncertain or secondary blepharospasm was suspected. There was a disproportionately larger than expected number of females than males recruited but on analysis this reflected the demographic of our local blepharospasm population. All the individuals on the trial were benefiting from regular botulinum toxin injection treatment but nevertheless remained visually compromised as indicated in the baseline CDQ 24 analysis.

At the screening visit, it became evident that many of the patients recruited used special tricks or sensory manoeuvres to help open their eyes; 68% used focal finger pressure as a trigeminal sensory trick. Some had themselves devised novel ways of mechanically applying the pressure, for example wearing a tightly fitting cap, a sports head band or tightly fitting glasses, often sunglasses. It was hoped that the Pressop device could be used in the same way to mimic the individual's sensory trick and that the beneficial effect would be sustained for the period of use. This often proved to be the case and in addition, the same proportion of patients who did not have an effective ST nevertheless benefited from using Pressop.

Most patients found Pressop easy to handle, adjust and use, and were not concerned about the appearance, particularly if their visual function improved. Arthritis in the fingers, which is common in the patient age group, was taken into account when designing the device. A simple clip with a broad base to grasp was used and proved easy to handle and position for most participants.

Of those who completed the trial, more than 60% reported at least some benefit. Most continue to use Pressop to maximise visual function towards the end of the BTX treatment cycle but did not find its use increased the interval between treatments. A minority (10 patients, 18%) reported

substantial and continuing benefit throughout the treatment cycle. This included resuming driving in 2 cases, while 1 returned to full-time work, and 1 to voluntary work. Of this subgroup, 9 subjects continued with their habitual BTX treatment regime augmented by the use of Pressop. One discontinued BTX treatment, relying on Pressop alone for near normal visual function. Of the 12 participants not on regular BTX treatment, 5 patients used Pressop as an effective control for day-to-day activities.

Participants trialled the device during the last 2–3 weeks of their BTX treatment cycle. This corresponds to the period when the benefit of the injections was reduced and symptoms were increasing. As well as a visual benefit, improvements in day-to-day functioning were reported with increased confidence, self-esteem, and reduced headaches.

Although the use of Pressop improved overall function as indicated by the change in CDQ-24 scores, this was not statistically significant. We think this reflects the design of the questionnaire and the continuing practical and social consequences of a diagnosis of blepharospasm.

The device feedback questionnaire indicated most benefit was felt when reading, walking, sewing, shopping, riding a bicycle or driving a car. The device was therefore often not worn all the time but rather when carrying out specific tasks and was particularly helpful when used for short periods. As with a sensory trick, the benefit of Pressop may not be sustained.

There is evidence that the primary pathology in focal dystonia involves the basal ganglia resulting in secondarily disordered cortical sensorimotor integration and an abnormal motor output to the affected area [8]. In blepharospasm, there is evidence that this causes inter-neuronal hyper-excitability involving the trigeminal sensory nuclear complex (TSNC) [9]. The clinical correlates, reflecting increased gain in the trigemino-facial reflexes, are a high spontaneous blink rate, spasms of eye closure and the characteristic ocular sensory symptoms of surface discomfort, tearing and photosensitivity.

Botulinum toxin injections are the most effective treatment for blepharospasm [10]. These not only reduce the forceful spasms of eye closure by weakening the orbicularis oculi, but also often normalise or reduce the high periodic blink rate and reduce the sensory symptomatology. This suggests TSNC hyper-excitability has been reduced. This benefit may be due to the weakening of the abnormally contracting peri-ocular muscles, thereby reducing proprioceptive and nociceptive sensory feedback. Likewise, an effective ST in blepharospasm not only temporarily moderates the defective motor programming (the spasms of eye closure) but also reduces the sensory symptoms.

A transcranial magnetic stimulator study of individuals with cervical dystonia and an effective ST suggested that an

inhibitory effect on motor cortex excitability may be responsible [11]. However, the reduced excitability could equally be driven by dampening effects of the ST elsewhere in the neuronal circuitry involved. The fact that some individuals with cervical dystonia and an effective ST can achieve temporary improvement by imagining performing the trick indicates that interoceptive inputs can also be recruited. The ST phenomenon therefore contributes to our understanding of the focal dystonias in terms of the pathophysiology of abnormal cranial nerve sensori-motor integration and potential ways in which this can be modified.

It is recognised that a range of non-specific interventions, such as hypnosis and acupuncture, can produce improvement or resolution of the symptoms and signs in focal dystonia including IB [12, 13]. This improvement is usually inconsistent and unpredictable. In contrast, although used intermittently, the responders in this study group were able to replicate the benefit every time the device was used. While most participants used the device intermittently, they reported consistent responses over time.

We have shown in this trial that mechanical simulation of a sensory trick with Pressop can be as effective as focal finger pressure in a sizeable proportion of IB sufferers including those unaware of having a ST.

Pressop is a simple, safe prosthesis capable of improving the practical visual function in many IB sufferers and in preventing the decline in function towards the end of the botulinum treatment cycle. It complements the efficacy of the botulinum toxin injections. For a minority of users, it gave a substantial, statistically significant and sustained improvement in quality of life. Seventeen patients studied were recruited from the study centre. Of these, 9 have been using Pressop for 7–8 years and report continued benefit over time. There is a long-term benefit in symptom control but the requirement and frequency of BTX treatment has not been consistently reduced.

Summary

What was known before

- Focal temple pressure (a sensory trick) improves eye opening in a proportion of idiopathic blepharospasm sufferers.

What this study adds

- This benefit can be replicated by a simple spectacle mounted device which is equally effective in those without a sensory trick.

Acknowledgements This study was sponsored by The Dystonia Society of the United Kingdom. Further funding was provided by Ipsen Pharmaceuticals Ltd. for ongoing development of the Pressop device. Globsource Ltd., Reading, provided the prototype design and manufacturing of Pressop for the purposes of the clinical trial. Photography and imaging for the clinical trial and this publication has been contributed by Jonathan Brett, Research Photographer and Graphics Designer, Eye Research Group Oxford. Paul Bassett, Statsconsultancy Ltd., provided the statistical report. Colm Andrews, Clinical Research Analyst for The Eye Research Group Oxford assisted with the final statistical data.

Author contributions Alexina Fantato contributed to the concept, organisation and execution of the project, design and review of the statistical analysis, and writing and reviewing the manuscript. Manoj Parulekar and John Elston contributed to the concept and organisation of the project, design and review of the statistical analysis, and writing and reviewing the manuscript.

Compliance with ethical standards

Conflict of interest Alexina Fantato—Applicant: Ipsen Pharmaceuticals. Further development of Pressop (blepharospasm device), Fantato A, Parulekar MV, Elston J, £3800. Manoj Parulekar and John (Elston)—Each of these authors was awarded a grant for research project by Ipsen Pharmaceuticals. The authors declare that they have no conflict of interest.

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