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ORIGINAL ARTICLE

The combined treatment with orbital and pretarsal botulinum toxin injections in the management of poorly responsive blepharospasm

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Abstract Blepharospasm (BS) is a focal dystonia involving involuntary contractions of muscles around the eyes. Botulinum toxin (BoNT) is the most effective treatment for BS and the technique of injection changes depending on the clinical picture. Usually typical BS benefits from the injection in the orbital part of the orbicularis oculi (OOc) muscle (orbital injection), while BoNT injection in the pretarsal part of OOc muscle is helpful especially for the atypical BS (opening eyelid apraxia). The aim of this study was to compare the efficacy of two injection techniques, the orbital versus the combined (injection in both orbital and pretarsal part of OOc) in BS patients with unsatisfactory response to BoNT. Nineteen patients with typical BS not having a satisfactory response from BoNT treatment with the orbital injection (primary and secondary resistant patients) were studied. After 3 months from the last orbital injection patients received the combined injection; they were assessed with the JRS and BSDI scales after 4 weeks from the last orbital and the first combined injection. Statistical analysis showed a significant reduction ($p < 0.05$) of the mean score of JRS and BSDI scales comparing the combined with orbital injection. This study shows that the treatment of typical BS can have better results when BoNT is injected with the combined technique in primary and secondary resistant patients.

Keywords Botulinum toxin · Blepharospasm · Pretarsal · Orbital · Resistant

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Introduction

Blepharospasm (BS) is a focal dystonia characterized by involuntary and sustained contractions of muscles around the eyes. From a clinical perspective, BS can present with a repetitive or sustained contractions of the orbicularis oculi (OOc) muscles resulting in an increased blink rate, variably accompanied by more sustained spasms, eventually leading to a functional blindness due to eyes closure. When the involuntary muscle contraction mainly affects the pretarsal part of the OOc muscle, BS has an atypical presentation characterized by the levator palpebrae inhibition phenomenon, resembling sometimes the condition known as "opening eyelid apraxia" [1].

Botulinum neurotoxin (BoNT) injection is considered the first-choice treatment for BS, in light of its favourable efficacy/tolerability profile. The techniques of injection depend on BS clinical presentation: typical BS benefits from injections in the orbital part of OOc muscle (orbital injection), localized mainly around eyes and just above the eyebrow. By contrast, when BS presents with the levator palpebrae inhibition phenomenon, BoNT is usually injected in the pretarsal part of the OOc muscle just above the edge of the upper eyelids [2].

Since the effect of BoNT is self-limiting, patients regularly undergo injection sessions every 3 months, on average. Patients display a sustained response to BoNT injections for decades [3]. However, in some cases BoNT

efficacy decreases after repetitive injections even in patients who initially had a very good response (secondary resistant BS) [4]. More rarely, patients never experience an improvement after BoNT injections (primary resistant BS).

The injection in both the orbital and pretarsal parts of OOc muscle (combined injection) was proven to improve the response to BoNT therapy in BS patients regardless of their clinical presentation and previous response to orbital injection [5]. The aim of this study was to compare the efficacy of two injection techniques (orbital versus combined) in BS patients with unsatisfactory response to BoNT.

Methods

From September 2011 to December 2012 we enrolled 19 consecutive patients (5 males, 14 females; mean age 65.0 ± 8.0 years; mean disease duration 6.6 ± 5.7 years) affected by primary BS with typical presentation, treated with BoNT type A (BoNT-A) injections in the orbital part of OOc muscle and not having a satisfactory response. Patients were treated mostly with one brand of BoNT-A (from 40 to 60 U of onabotulinumtoxinA or from 120 to 180 U of abobotulinumtoxinA for both eyes) but experienced at least once the other brand. Resistance to BoNT-A was confirmed by a score higher than 4 at the Jankovic rating scale (JRS) after at least three injection sessions. Secondary resistant patients were those patients who had benefit from the orbital injection for at least three consecutive treatments (JRS <4) before experiencing an unsatisfactory response; primary resistant patients were patients who never had a satisfactory response from the orbital injection (JRS >4) (Table 1). All these resistant patients formed 28 % of the total number of people (66 subjects) with blepharospasm treated in the same period with botulinum toxin in our clinic.

Three months since the last orbital injection, these patients underwent a combined scheme of injection including the pretarsal part in addition to the orbital part of the OOc muscle (Fig. 1). Each patient was treated with a fixed total dose of 60U of onabotulinumtoxinA (Botox®; Allergan, USA) or 180U of abobotulinumtoxinA (Dysport®; Ipsen, UK) for both eyes, depending on the brand mainly used in previous treatment. Clinical outcome following BoNT therapy was assessed by the use of JRS and BS Disability Index (BSDI) [6]. JRS evaluates the severity of BS with a score ranging from 0 to 8 (maximum severity). BSDI determines the disability due to BS with six items scoring each one from 0 to 4.

JRS and BSDI were performed in each patient 4 weeks after the last orbital injection and 4 weeks after the combined injection. The mean score of these scales were analyzed with the Mann–Whitney U test comparing the outcome of the two methods of injection. The significance level was set at $p < 0.05$.

Each patient gave informed consent for participation to the study and no ethics board was needed as the combined injection represents a well-tested technique widely performed in common medical practice.

Table 1 Demographic and clinical data of the enrolled patients

	All pts	Primary resistant	Secondary resistant
Gender (M/F)	5/14	2/5	2/10
Age	65.0 ± 8.0	65.2 ± 7.3	64.9 ± 8.8
Disease duration	6.6 ± 5.7	7.25 ± 4.4	6.3 ± 6.3

There are no significant differences

Results

Twelve patients were secondary resistant after 9.4 ± 6.8 injections (mean doses 55.7 ± 7.3 and 163.8 ± 25.0 for onabotulinumtoxinA and abobotulinumtoxinA, respectively). Seven subjects never reported a good response (primary resistant) after three injections (mean doses 65.0 ± 13.3 and 175.2 ± 22.0 for onabotulinumtoxinA and abobotulinumtoxinA, respectively). Each patient was treated mainly with one brand of BoNTA but experienced at least once the other one.

At baseline, four weeks after the orbital injection JRS and BSDI mean scores were 6.2 ± 0.9 and 13.7 ± 4.6, respectively. Four weeks after the combined injection, JRS and BSDI mean scores were 4.5 ± 1.4 (−28 %) and 7.3 ± 4.8 (−47 %), respectively. Table 2 details treatment outcome in patients with primary or secondary resistant BS. Statistical analysis showed a significant difference ($p < 0.05$) favouring combined over orbital injection technique (Fig. 2).

As for side effects, three subjects (15 %) reported eyelid hematoma after the injection in the pretalsal part of OOc

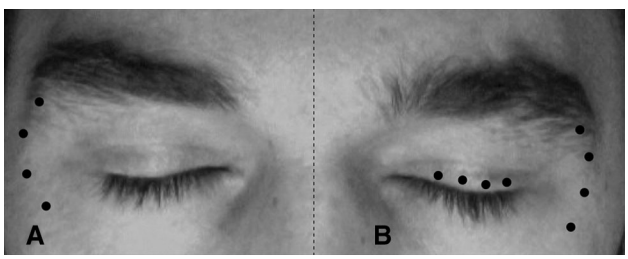

Fig. 1 Scheme of BoNT injection. **a** orbital injection; **b** combined injection. Injections were performed on both sides

Table 2 JRS and BSDI scores for orbital and combined injection

	JRS			BSDI		
	Orbital	Combined	% of change	Orbital	Combined	% of change
All patients	6.2 ± 0.9	4.5 ± 1.4	28	13.7 ± 4.6	7.3 ± 4.8	47
Primary resistant	6.3 ± 0.8	4.6 ± 1.3	27	13.1 ± 4.2	6.6 ± 3.3	50
Secondary resistant	6.2 ± 1.0	4.5 ± 1.6	28	14.3 ± 4.9	7.6 ± 5.6	47

See Fig. 2 for statistical significances

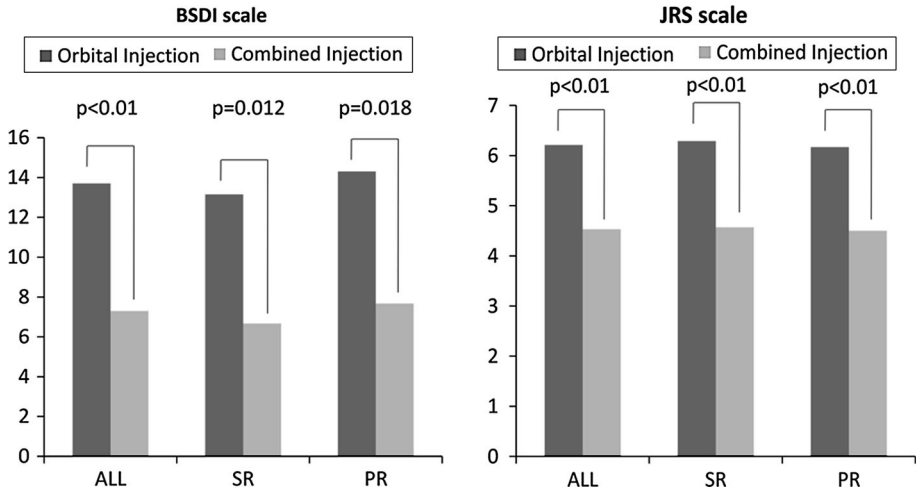

Fig. 2 JRS and BSDI scores for orbital and combined injection. *PR* primary resistant, *SR* secondary resistant

muscle. No other adverse event (including ptosis) was reported.

Discussion

Blepharospasm is one of the most frequent forms of focal dystonia and the efficacy of the treatment with BoNT is well documented by several studies [7]. Injections into the orbital part of OOc muscle is the most widely used technique, especially for typical BS phenotype. This technique is usually very effective in most of the patients but some of them do not respond or have an unsatisfactory response during disease course. For this group of patients we specifically investigated whether the effect of BoNT injection in the pretarsal part combined with the orbital part of OOc muscle is a suitable strategy in terms of both efficacy and tolerability. Almost all patients who underwent the combined injection reported a clinical improvement, with a marked reduction of the JRS and BSDI scores. This benefit should result only from the new scheme of injection, as there was no change of BoNT dose between orbital and combined injection. Clinical improvement was confirmed in both subgroups of primary or secondary resistant BS, thus suggesting that efficacy of the combined injection is not depending on the length of the treatment. However, two primary resistant patients did not show any improvement with the combined injection even with the use of BoNT-Type B, suggesting that resistance to the treatment was not related to the presence of specific antibodies against BoNT-A. Actually biological responsiveness to BoNT-A was also confirmed in these cases with the "extensor digitorum brevis test" [8].

The efficacy of the combined injection technique in BS was already proven by Aramideh et al. [5] in a group of patients with typical presentation and with the levator palpebrae inhibition phenomenon and including responders and not responders to the conventional treatment. This study showed that injecting the pretarsal site in addition to the orbital one was effective in the treatment of BS regardless of clinical features. However, it did not enrol patients with secondary resistant BS. Few other studies were conducted later, comparing the efficacy of BoNT injected in the orbital versus the pretarsal part of the OOc muscle in BS patients poorly responsive to the orbital injection [9, 10]. In particular, Albanese et al. [9] found a greater efficacy of the sole pretarsal injection than the orbital one in a group of patients with BS (clinical features were not described) not adequately responding to the previous treatment. This comparison was not assessed in our study because all patients were injected also in the orbital part of OOc muscle as they presented a typical BS always showing the spasm of the orbital part of the muscle.

Our study expands these notions as it found that a benefit might be gained without increasing the dose and combining both techniques in patients with either primary or secondary resistance to the conventional orbital injection. This efficacy has been confirmed using clinical and disability rating scales. As for the side effects, eyelid hematoma is the main risk related to the combined injection while ptosis seems to be not frequent when BoNT is properly injected in pretarsal area: in our scheme we used to treat the pretarsal part along the whole border of the eyelid injecting BoNT at least in four points and giving a very small volume of solution in each site to avoid the spread of toxin to the levator palpebrae superioris muscle. Then, as the pretarsal injection can be painful and may cause eyelid hematoma, especially in people taking antiplatelet drugs, the initial treatment of BS should be performed with the orbital injection. We suggest performing the combined scheme of BoNT injection for typical BS only when there is a weak response following repeated treatment with increasing doses injected in the orbital part of the OOc muscle.

The main limitations of our study are the small sample, the limited follow-up period and the lack of blind fashion as both raters and patients were aware of the study rationale. Future studies should focus on factors promoting the unresponsiveness to BoNT in BS to delay the occurrence of the secondary resistance to further optimise the treatment of this disorder.

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