TOPICAL NAPHAZOLINE IN THE TREATMENT OF MYASTHENIC BLEPHAROPTOSIS

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Accepted 10 December 2010

ABSTRACT: *Introduction*. When treating ocular myasthenia gravis (MG), the risk/benefit profile of corticosteroids is unclear, and acetylcholinesterase inhibitors are not very effective. We examined the efficacy of topical naphazoline in the treatment of myasthenic blepharoptosis. *Methods*. Sixty MG patients with blepharoptosis (32 with ocular symptoms only and 28 with mild generalized symptoms) were enrolled in a multicenter open trial of topical naphazoline. The effects were reported by patients via a questionnaire and were also confirmed for each patient at the clinic. *Results*. Among 70 eyes of 60 patients, 20 eyes (28.6%) of 17 patients (28.3%) exhibited a marked response (full eye opening), and 24 eyes (34.3%) of 20 patients (33.3%) showed a good response (adequate but incomplete eye opening). Topical naphazoline was evaluated as useful in the treatment of myasthenic blepharoptosis by >70% of the patients. *Conclusions*. Topical naphazoline was found to be an effective supplementary symptomatic treatment for myasthenic blepharoptosis.

Muscle Nerve **44:** 41–44, 2011

The clinical manifestations of myasthenia gravis (MG) are variable, ranging from limited ocular involvement to respiratory failure. The optimal treatment for purely ocular MG (OMG) and residual ocular symptoms after generalized MG (GMG) is unclear.[1–3] Corticosteroids appear to be more effective than the acetylcholinesterase (AChE) inhibitors for OMG[1,3], however, there is not clear evidence for the risk/benefit ratio of corticosteroids or other immunosuppressive agents for OMG patients.[2] Accordingly, we do not know whether the side effects of long-term corticosteroids can be justified in an individual with only ocular symptoms.[4] Hence, particularly for patients with blepharoptosis only and those in whom blepharoptosis remains after GMG, we hesitate to use corticosteroids or increase the dosage. As AChE inhibitors are not very effective,[1,3] supplementary symptomatic treatments would be useful.

An eyewash containing naphazoline, a sympathomimetic drug with preferential α_2 activity, is reported to selectively increase the tone of the Müller muscle, widen the palpebral fissure, and have cosmetic and functional effects for mild to moderate myopathic ptosis or partial Horner syndrome.[5,6] In this study, we examined the efficacy of topical naphazoline in the treatment of myasthenic blepharoptosis in a multicenter open trial.

METHODS

Sixty-eight MG patients with blepharoptosis were enrolled in this multicenter open trial for topical naphazoline from December 2008 until June 2010. They were treated at Hanamaki General Hospital, Keio University Hospital, Tokyo Medical University Hospital, or Tokyo Women's Medical University Hospital. All patients provided informed consent and were followed monthly (range 1–18 months). Among 68 patients, 8 were excluded from analysis due to dosage increases in other treatments. Finally, 60 (32 with only ocular symptoms and 28 with mild generalized symptoms) were subjected to analysis. Clinical background data for the 60 MG patients are shown in Table 1. Topical naphazoline was also administered to 10 non-MG healthy volunteers without blepharoptosis (controls 40–60 years old), with informed consent.

The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with reductions in symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli, or the presence of antibodies against the acetylcholine receptor of skeletal muscle (AChR-Abs). Single-fiber electromyography (EMG) was not systematically examined. Twenty-five patients were negative for AChR-Abs. There were no muscle specific tyrosine kinase (MuSK) antibody-positive patients among the 25 AChR-Ab–negative cases. Magnetic resonance imaging examinations of the brain were normal in all patients.

Eyewash containing 0.05% naphazoline nitrate (Privina; Novartis) was used (instillation into the conjunctival sac of one drop) for 70 eyes of the 60 MG patients with frequency as needed per day (duration 1–18 months) and for 20 eyes of 10 controls

Abbreviations: AChE, acetylcholinesterase; AChR, acetylcholine receptor; GMG, generalized MG; MG, myasthenia gravis; OMG, ocular MG; MGFA, Myasthenia Gravis Foundation of America; QMG score, quantitative MG score

Key words: blepharoptosis, eyewash, myasthenia gravis, naphazoline, open trial

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Published online 13 April 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.22002

Table 1. Patient background.

Age (years)	56.8 ± 17.8	
Gender (M/F)	17/43	
Age at onset (years)	51.0 ± 19.3	
Time since onset (years)	6.3 ± 6.7	
Duration of untreated disease (years)	1.2 ± 1.4	
MGFA clinical classification[8]	Worst condition	Study entry
I	31.7% (19/60)	53.3% (32/60)
Blepharoptosis only	42.1% (8/19)	81.3% (26/32)
II	38.3% (23/60)	46.7% (28/60)
III	18.3% (11/60)	0% (0/60)
IV	6.7% (4/60)	0% (0/60)
V	5.0% (3/60)	0% (0/60)
Ocular QMG score[8] (range)	Worst condition	Study entry
	3.6 ± 1.5 (1–6)	2.0 ± 1.5 (0–6)
Duration of naphazoline [months (range)], $n = 50$	7.2 ± 6.2 (1–18)	
AChR-Ab–positive cases	58.3% (35/60)	
Thymectomy	60.0% (36/60)	
Histology (remnant/hyperplasia/thymoma)	6/5/25	
Corticosteroids (%)	75.0 (45/60)	
	Maximum dose (mg/day)	Study entry(mg/day)
Dose of prednisolone (range), $n = 45$	25.0 ± 19.9 (5–60)	4.6 ± 4.8 (0–20)
Calcineurin inhibitors	50.0% (30/60)	
AChE inhibitors (60 or 120 mg/day of pyridostigmine bromide)	53.3% (32/60)	

AChE, acetylcholinesterase; AChR-Ab, antibodies against the acetylcholine receptor; MGFA, Myasthenia Gravis Foundation of America; QMG score, MGFA quantitative MG score.[8]

two times per day (duration 1 month). As for MG, the effects were reported by patients via a questionnaire regarding degree of ptosis at naphazoline instillation and response to naphazoline. Participating physicians also examined the effects of naphazoline in each patient at the clinic (the self-reported results were revised for 3 patients) (Table 2). All patients also answered a questionnaire item regarding final evaluation of overall efficacy (Table 3). Items answered by subgroups of patients concerned: time to attain maximum response; duration of action after instillation; frequency of use and reduction of the effects with long-term or frequent use (for 50 patients with some response); difference in response between right and left eyes (for 10 patients who had bilateral treatment); and effects on photophobia (for 22 patients with photophobia in ptotic eye) (Table 3). The patients were given a questionnaire at the start of naphazoline, and they completed and presented it to the

Table 2. Degree of ptosis at instillation and response levels to naphazoline in a total of 70 ptotic eyes of 60 patients.

	Degree of ptosis at naphazoline instillation			
	Slight ptosis (recognizable with careful observation; 23 eyes of 20 patients)	Moderate ptosis (evident ptosis, visual field not limited; 34 eyes of 30 patients)	Severe ptosis (visual field limited; 10 eyes of 7 patients)	Most severe ptosis (vision completely interrupted; 3 eyes of 3 patients)
Marked response (eye completely open; 28.6%, 20/70)	9	9	2	0
Good response (eye not completely open but satisfactory response; 34.3%, 24/70)	7	13	3	1
Modest response (unsatisfactory response, obvious residual ptosis; 22.8%, 16/70)	3	7	5	1
No response (14.3%, 10/70)	4	5	0	1

Table 3. Evaluation of overall effects of naphazoline.

Time to attain maximum response ($n = 50$, excluding 10 with no response)	<5 min 52.0% (26/50)	5–15 min 38.0% (19/50)	15–60 min 10.0% (5/50)	≥60 min 0% (0/50)
Duration of action ($n = 50$, excluding 10 with no response)	<1 h (%) 10.0% (5/50)	1–2 h (%) 14.0% (7/50)	2–3 h (%) 48.0% (24/50)	≥3 h (%) 28.0% (14/50)
Frequency of use (times/day) ($n = 50$, excluding 10 with no response)	≤1 12.0% (6/50)	2–3 44.0% (22/50)	4–6 34.0% (17/50)	≥7 10.0% (5/50)
Reduction of the effects with long-term or frequent use ($n = 50$, excluding 10 with no response)	Occurred		Did not occur	
	14.0% (7/50; mean duration of use 7.0 ± 5.5 months)		86.0% (43/50; mean duration of use 7.4 ± 6.3 months)	
Difference in response between the two eyes (for patients having bilateral treatment, $n = 10$)	Yes		No	
	30.0% (3/10)		70.0% (7/10)	
Effects on photophobia (for patients with photophobia, $n = 22$)	Adequate		None/inadequate	
	81.8% (18/22)		18.2% (4/22)	
Evaluation for overall efficacy ($n = 60$)	Useful for MG therapy		Not useful for MG therapy	
	71.7% (43/60)		28.3% (17/60)	

treating neurologists at 1 month after the start (all patients) and at the last follow-up visit (50 patients with some response).

The ice-pack test[7] was performed by applying an ice pack for 5 min on both eyelids for diagnostic confirmation of myasthenic blepharoptosis and for comparison of the effects to those of naphazoline.

To determine whether any clinical factors were associated with the effects of naphazoline, correlations between response levels to naphazoline and clinical factors (degree of ptosis at naphazoline instillation and all factors described in Table 1) were initially calculated using univariate analysis (Spearman rank correlation, with categorical variables converted to continuous variables). Factors displaying a value of $P < 0.05$ were then entered into a multivariate regression analysis to identify those associated with the effects of naphazoline. $P < 0.05$ was considered statistically significant. All continuous data are expressed as mean ± standard deviation. Statistical analysis was performed using StatView (version 5.0) statistical software (SAS Institute, Cary, North Carolina).

The protocol for this study was approved by the ethics committees of each institution. Written informed consent was obtained from all patients and controls participating in the study.

RESULTS

Among 70 eyes of 60 patients, 20 eyes (28.6%) of 17 patients (28.3%) exhibited a marked response (eye completely open) equivalent to the response to the ice-pack test, and 24 eyes (34.3%) of 20 patients (33.3%) showed a good response (eye not completely open but satisfactory response) to naphazoline (Table 2). Naphazoline was used for less severe conditions (slight or moderate ptosis without visual field limitation) in 57 eyes (81.4%) of 50 patients (83.3%) and showed marked or good response in 66.7% (38 of 57) eyes of 64.0% (32 of 50) of these patients (Table 2). When used for more severe conditions [ptosis with visual field limitation or complete interruption: 13 eyes (18.6%) of 10 patients (16.7%)], marked or good response was somewhat less frequent [46.2% (6 of 13) eyes of 40.0% (4 of 10) patients] (Table 2).

Twenty eyes of 10 non-MG controls without ptosis showed neither response nor adverse effect to naphazoline.

With regard to the 50 patients with some response, the maximum response to naphazoline was attained within 15 minutes in 90%, and the duration of action was over 2 hours in 76% (Table 3). Frequency of use was two to six times per day in 78% of patients, and 86% reported no reduction of the effects with long-term or frequent use (Table 3). There was no difference in duration of naphazoline use between patients with and without reduction of effects (Table 3).

Among 10 patients using naphazoline for both eyes, although responses of two eyelids showed a correlation ($P = 0.02$; Spearman rank correlation), 3 (30.0%) reported a difference in response

between the two eyes (Table 3). Effects on photophobia were reported by 18 of 22 (81.8%) patients with photophobia in the ptotic eye (Table 3). No overt mydriasis occurred, with a modest increase ($\leq$0.5 mm) in pupil size observed in only 4 patients.

In terms of final evaluation for overall efficacy, 43 of 60 (71.7%) patients reported naphazoline to be useful as MG therapy (Table 3).

Multivariate regression analysis revealed the ocular QMG score [the Myasthenia Gravis Foundation of America (MGFA) quantitative MG score[8]] at study entry as the only factor negatively correlated with the response to naphazoline ($r = -0.36$, $P < 0.001$). Age, gender, and AChR positivity showed no correlation with response levels to naphazoline (Spearman rank correlation).

DISCUSSION

Topical naphazoline was evaluated to be useful in the treatment of myasthenic blepharoptosis by >70% of the patients. Most of them attained rapid effects lasting >2 hours and used this eyewash habitually without significant adverse effects. Although the response to naphazoline was variable (from full eye opening to no response) among individual patients or between the two eyes in some patients, it was considered to be an effective supplementary symptomatic treatment.

The eyelid elevator muscles include the levator palpebrae muscle for voluntary opening and Müller smooth muscle for tonic control.[6,9] The former receives cholinergic motor innervation (by the third cranial nerve), and the latter receives adrenergic sympathetic innervation from the superior cervical ganglion.[6,9] Antibodies against AChE (AChE-Abs) are often present in MG and are more frequently detected in OMG than in GMG.[9] AChE-Abs induce myasthenic blepharoptosis via a selective loss of preganglionic sympathetic neuron terminals but produce no evident motor dysfunction.[9,10] At the neuromuscular junctions of striated muscle, AChE is stored in the synaptic cleft and may be spared from AChE-Abs.[9,10] Myasthenic blepharoptosis probably arises from a combined impairment of voluntary levator palpebrae and preganglionic sympathetic function (the latter decreases the tonus of the Müller muscle).[9]

The Müller muscle contracts via α-adrenergic receptors and is reported to respond dramatically to topical phenylephrine, a selective α_1-agonist.[6] However, phenylephrine has the drawback of producing mydriasis and associated glare due to stimulation of the iris dilator muscle.[6] Naphazoline, a primarily α_2-agonist, selectively increases the tone of the Müller muscle without mydriasis[5,6] and successfully reduces myopathic blepharoptosis.[6] In this study, the responses to naphazoline negatively correlated with severity of ptosis (ocular QMG score) at study entry, and marked response with full eyelid opening was infrequent. Naphazoline probably increased the tone of the Müller muscle and improved the component of myasthenic ptosis caused by its impairment. Given that the response to naphazoline was variable, it is possible that either there was variation in the relative contributions to ptosis caused by Müller muscle and levator palpebrae muscles, or expression levels of α_2-adrenergic receptors in the Müller muscle differed considerably.

The favorable effects of naphazoline on photophobia prompt the hypothesis that it might have some effects on miosis or light adaptation, but these mechanisms could not be addressed in this study.

In conclusion, topical naphazoline appears to be an effective supplementary symptomatic treatment for myasthenic blepharoptosis. Although this study has limitations due to its unblinded design, somewhat subjective assessment methods, and the relatively small number of patients, we did obtain information useful for planning treatment of OMG and GMG patients with blepharoptosis. Larger scale, double-blinded, and placebo-controlled trials are required to confirm the efficacy of topical naphazoline for myasthenic ptosis.

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