The Phenylephrine Test Revisited

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Purpose: To characterize the phenylephrine test in ptotic patients to help clinicians perform the test more efficiently.

Methods: Adults with involutional ptosis (n = 24, 30 eyes) were assessed with digital photographs for response to topical 2.5% phenylephrine drop instillation. Patient characteristics (age, gender, iris color, dermatochalasis, brow ptosis, and baseline marginal reflex distance-1 [MRD-1] height) were recorded. From the photographs, change in (MRD-1), presence of conjunctival blanching, pupillary dilation, and Hering effect were recorded at specified time intervals, 1 minute to 1 hour after drop placement. Correlations between patient characteristics and measured outcomes were evaluated using analysis of variance, Pearson coefficient, or chi-square tests.

Results: The authors found that 73% of eyes had eyelid elevation with phenylephrine. Of these, 50% reached maximal eyelid elevation by 5 minutes, and 86% by 10 minutes after drop placement, but 14% did not reach maximal MRD-1 until 30 minutes. There is a negative correlation between the maximum MRD-1 and the baseline MRD-1 eyelid height ($r = -0.5330$, $p < 0.01$). There is no significant relationship between time to pupillary dilation with either time to max eyelid elevation or max eyelid elevation. No patient characteristic studied affected the likelihood of eyelid response to phenylephrine or presence of Hering effect.

Conclusions: Although most ptotic eyelids demonstrate a response to 2.5% phenylephrine within 10 minutes, there is a subset of patients that respond much later. More ptotic eyelids had greater eyelid elevation with phenylephrine. Pupillary dilation and conjunctival blanching are neither predictive of nor temporally associated with eyelid height elevation. The authors did not identify any patient factors (e.g., dermatochalasis, brow ptosis) that can predict the likelihood of response to phenylephrine.

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The phenylephrine test is commonly used in the evaluation of ptotic patients and their suitability for internal ptosis repair.[1] In 1961, Fasanella and Servat[2] described a simplified posterior approach to treat mild ptosis that provides good cosmetic results. Putterman and Urist[3] modified this procedure to avoid partial tarsectomy. Furthermore, they were able to predict the success of this surgery with the application of topical 10% phenylephrine. The eyelid elevation after the phenylephrine test was within 0.5 mm of the final postoperative upper eyelid height.[3,4]

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Subsequently, 2.5% phenylephrine was compared with 10% phenylephrine. While eyelids receiving 10% phenylephrine rose an average of 0.2 mm higher than the same eyelids tested with 2.5% phenylephrine, the small magnitude of the difference was deemed clinically insignificant given the higher risk of adverse systemic side effects, such as subarachnoid hemorrhage, ventricular arrhythmia, and severe hypertension.[5]

In several later studies, an elevation in eyelid height to phenylephrine was assessed after 5 to 10 minutes.[5–8] Although this time frame is consistent with standard clinical practice, there does not seem to be evidence about the ideal amount of time to wait for a phenylephrine response in ptotic patients. Furthermore, the authors could not find studies that examine patient variables that may influence the response to phenylephrine. In addition, phenylephrine is also commonly used as a mydriatic, but the temporal relationship between pupillary dilation and eyelid elevation in ptotic patients has not been studied.[9]

This study aims to better characterize the phenylephrine test in ptotic patients to help clinicians perform the test more efficiently. Specifically, the authors investigate 1) the onset and duration of eyelid elevation; 2) the temporal relationship between eyelid elevation and pupillary dilation; and 3) patient factors that may affect response to phenylephrine.

METHODS

Patient Selection. Patients were recruited for the study from the Oculoplastics clinic at the New York Eye and Ear Infirmary of Mount Sinai. Inclusion criteria were patients between the ages of 18 to 90 years with a diagnosis of acquired involutional ptosis. Exclusion criteria included congenital or traumatic ptosis or a history of intraocular/oculoplastic surgery. Patients were also excluded if they were at risk of adverse events from phenylephrine, e.g., history of anatomical narrow angles, cerebral aneurysms, and severe atherosclerotic disease, or who were pregnant. Finally, photophobic patients or those unable to tolerate a camera flash were excluded.

Data Collection. Patients were instructed to look upward, and 1 drop of 2.5% phenylephrine was instilled directly on the surface of the ptotic eye. Photographs were taken using a digital single-lens-reflex Nikon camera (NikonUSA, Melville, NY) with a 105-mm lens per established protocols.[10] The photographic frame was centered on the eyes and extended from the midphiltrum to the midforehead. Patients were instructed to relax their brows in all photos. A predrop photo was taken. After instillation of 2.5% phenylephrine in the ptotic eye(s), photographs were taken at 1, 3, 5, 7, 10, 20, 30, 45, and 60 minutes. Data were deidentified and the following variables were recorded from each digital image: severity of dermatochalasis and brow ptosis (0–3 scale: absent/mild/moderate/severe), iris color, presence/absence of conjunctival blanching, and Hering effect in the contralateral eye of unilateral ptosis patients. Marginal reflex distance-1 (MRD-1, millimeters) and pupil size (millimeters) were measured via ImageJ software (NIH ImageJ, National Institutes of Health, Bethesda, MD, U.S.A.) using a digital caliper set to a corneal diameter of 11.8 mm per established protocols[11,12] (Fig. 1). Digital measurements of MRD-1 have been shown to have similar reliability as clinical measurements.[13]

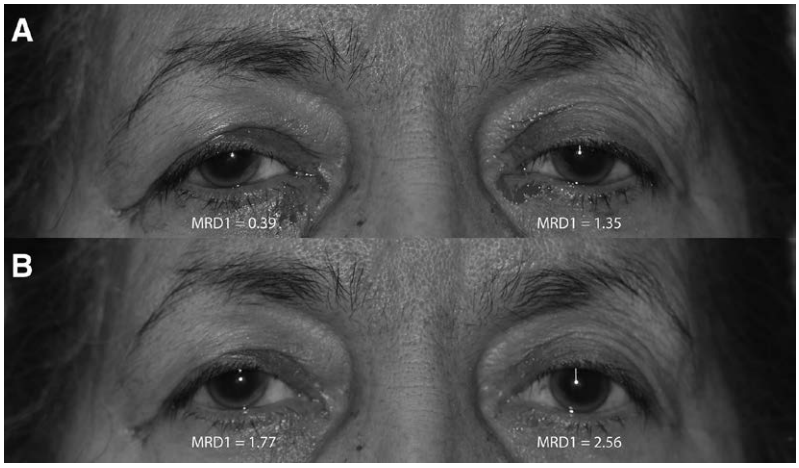

FIG. 1. A 71-year-old female with bilateral ptosis showing a clear response to 2.5% topical phenylephrine.

Data Interpretation. Response to phenylephrine was defined as >1 mm change in MRD-1 from baseline. The earliest time point at which the MRD-1 was within 0.5 mm of the maximal MRD-1 was noted as "time to maximal eyelid elevation." The duration of eyelid elevation was defined as the time point from when the eyelid elevated to within 0.5 mm of max MRD-1 until the time point that it returned to within 0.5 mm of the baseline MRD-1 height. This definition of the maximum MRD-1 was chosen rather than the absolute maximum MRD-1 because there are small physiologic fluctuations in eyelid height over time. Clinically significant pupil dilation was defined as >1 mm change from the predrop pupil size. Statistical analysis was conducted using STATA software version 14.2. The analysis of variance test and chi-square contingency table were used to evaluate the correlations between patient characteristics and the likelihood of response to phenylephrine and the likelihood of observing Hering effect. The analysis of variance test and the Pearson correlation coefficient were used to evaluate correlations between patient characteristics and the maximum eyelid height.

The institutional review board of the Mount Sinai School of Medicine approved this study, and this research was in compliance with Health Insurance Portability and Accountability Act requirements and adhered to the tenets of the Declaration of Helsinki.

RESULTS

Twenty-four patients (30 eyes) met the inclusion/exclusion criteria for this study; 6 patients had bilateral ptosis, and 18 had unilateral ptosis. Mean age was 68.4±9.2 years and 67% were female. All patients had brown irides. Seventy-three percent of the eyes had eyelid elevation with the phenylephrine test. Of eyes that had a response to

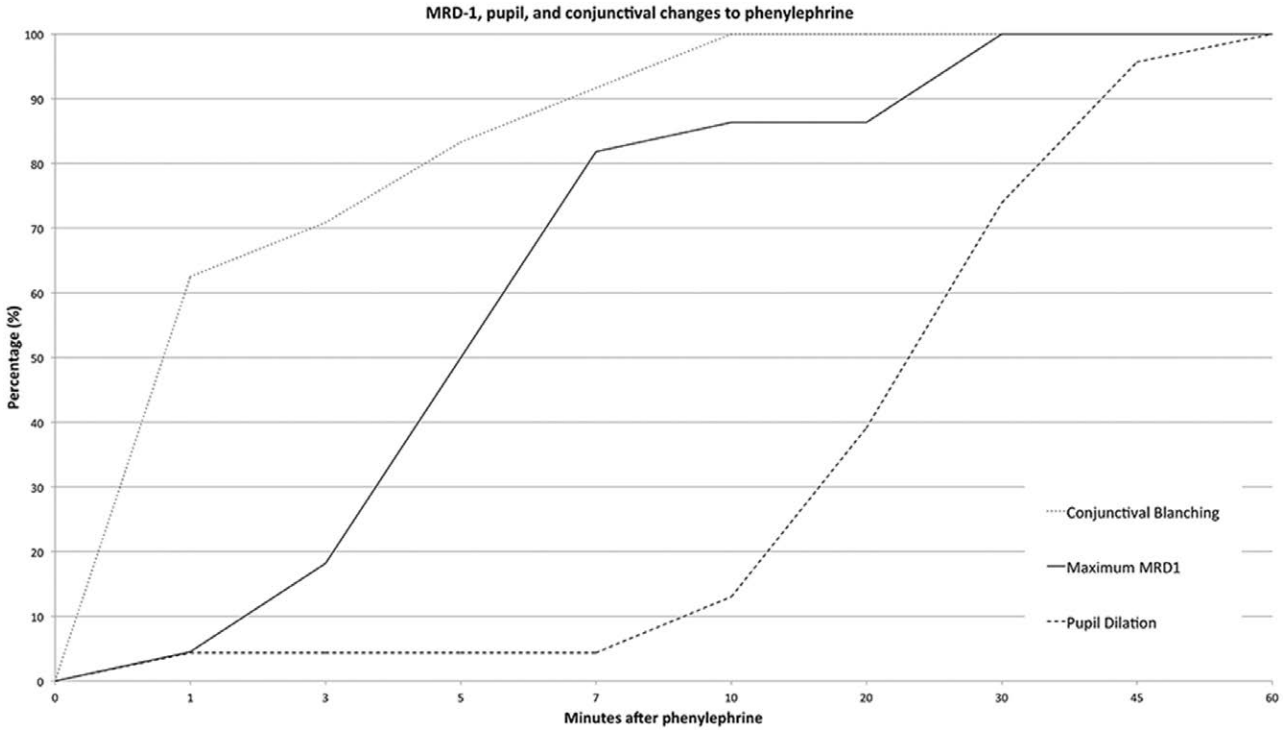

FIG. 2. Cumulative percentage of phenylephrine-responding eyes that reached maximum MRD-1, demonstrated pupillary dilation, and showed conjunctival blanching over time. MRD-1, marginal reflex distance-1.

TABLE. Relationship between patient variables and maximum eyelid height elevation (ΔMRD-1).

Variable	Type of test	Statistic	*p*
Gender	One-way analysis of variance	F = 2.93	$p = 0.1023$
Dermatochalasis	Pearson product-moment correlation coefficient (2 tailed)	r = −0.0712	$p > 0.10$
Brow ptosis	Pearson product-moment correlation coefficient (2 tailed)	r = 0.1894	$p > 0.10$
Baseline MRD-1	Pearson product-moment correlation coefficient (2 tailed)	r = −0.5330	$p < 0.01$

MRD-1, marginal reflex distance-1.

phenylephrine, 50% reached maximal eyelid elevation at 5 minutes and 86% at 10 minutes after phenylephrine drop placement. However, another 14% of eyes did not reach maximal MRD-1 until 30 minutes after drop placement (Fig. 2). The average time to maximum eyelid elevation was 9 minutes and the duration of eyelid elevation was at least 27.1 minutes. In 4 of the 6 patients with bilateral ptosis, the maximum MRD-1 height was reached within 2 minutes of the fellow eye. Of the remaining 2 patients with bilateral ptosis, one of them had no elevation in either eye, and in the other patient, only one eye demonstrated eyelid elevation.

Predrop MRD-1 was inversely correlated with maximal eyelid height elevation ($p < 0.01$). Patient characteristics such as age, gender, dermatochalasis, or brow ptosis did not show any correlation with the maximum change in MRD-1. Clinically significant pupillary dilation was present in 88% of patient with use of 2.5% phenylephrine. At 5 and 10 minutes, only 4% and 12% of patients' pupils were dilated, respectively. By 30 and 45 minutes, however, 65% and 85% had clinically significant pupil dilation. The mean time to dilation was 29 minutes (Fig. 2). Eighty percent of the patients exhibited conjunctival blanching. Among these patients, 63% and 100% had blanching by 1 minute and 10 minutes, respectively. Dermatochalasis was absent in 27% of the patients. Forty-three percent had mild, 17% moderate, and 13% severe dermatochalasis. Thirty-three percent of patients had no brow ptosis, while 37% had mild, 20% moderate, and 10% severe brow ptosis.

The authors found no relationship between time to pupillary dilation and time to maximal MRD-1 height ($r = -0.2408$, $p > 0.10$). Furthermore, there was no relationship between time to pupillary dilation and maximal MRD-1 ($r = -0.2585$, $p > 0.10$, 2-tailed test). None of the patient characteristics studied (age, gender, dermatochalasis, and prephenylephrine MRD-1) affected the likelihood of eyelid response to phenylephrine. The authors did find a negative correlation between the change in MRD-1 and the baseline MRD-1 height ($r = -0.5330$, $p < 0.01$). However, no other patient characteristics studied showed a correlation with the maximum change in eyelid height (Table). There were 6 patients in the study who could not be evaluated for Hering effect because they had bilateral ptosis. Of the remaining 18 patients, 50% demonstrated Hering effect. There were no significant differences among the variables studied between patients who demonstrated a Hering effect compared with those who did not.

DISCUSSION

This study sought to further characterize the 2.5% phenylephrine test in ptotic patients. A number of previous studies have improved the authors' understanding of the phenylephrine test since Putterman and Urist[3] first popularized its use. These studies have focused on mitigating adverse effects of phenylephrine and on utilizing the results of the phenylephrine test to refine the approach to ptosis repair.[5–8] This study aims to help clinicians perform the test more efficiently and investigate patient factors that may affect response to topical phenylephrine.

The authors found that 73% of the patients had a positive phenylephrine test, but there were no reliable factors, including age and baseline MRD-1 that predicted who would respond to phenylephrine. The maximal MRD-1, which the authors defined as MRD-1 within 0.5 mm of the maximal MRD-1 to account for subtle differences in digital measurement, was reached in 86% of responders by 10 minutes. However, only 50% reached maximal MRD-1 by 5 minutes. Therefore, the authors advocate a testing protocol that includes waiting at least 10 minutes before assessing response to phenylephrine test. Some prior studies have noted a quicker response to phenylephrine than this study. This difference may be partly explained by use of a higher concentration of phenylephrine, multiple doses, or instilling drops directly into the superior conjunctival fornix.[5]

Interestingly, this study found a subset of "late responders" who may have been characterized as nonresponders in most clinical settings. Fourteen percent of the patients had eyelid elevation only 30 minutes after drop instillation. These results differ from a recent paper by Ramesh and Mancini[14] that showed eyelid elevation within 2 minutes. This difference may be due to their study including predominantly nonptotic patients while this study focused exclusively on patients with ptosis. The duration of eyelid elevation among responders was at least 27 minutes and in 3 cases persisted beyond the 1-hour study period.

The authors found that age, gender, dermatochalasis, and brow ptosis do not have a statistically significant relationship with maximum eyelid elevation or time to maximum eyelid elevation. Additionally, there is no relationship between baseline MRD-1 and time to maximum eyelid elevation. There is a statistically significant negative correlation between the maximum MRD-1 and the baseline MRD-1 ($p < 0.01$). Perhaps this is not surprising because more ptotic eyelids have more room to increase. However, one may also have predicted that more ptotic eyelids would be less responsive to phenylephrine because of levator dehiscence or other factors—indeed, some surgeons do not perform internal ptosis repair or the phenylephrine test in severely ptotic eyelids.

Despite phenylephrine's well-known effect on pupil size, there have not been any studies to the authors' knowledge that investigate the temporal relationship between pupil dilation and eyelid elevation.[9,15] The authors found that in individual patients, eyelid height elevation and pupil dilation are not correlated, i.e., those whose pupils dilate faster may not have had early eyelid elevation or vice versa. However, in general, pupil dilation occurs much later (on average, 29 minutes after drop placement) than eyelid elevation. In addition, all the patients in this study had brown irides—dilation in lighter irides would presumably occur sooner.[16] Conjunctival blanching occurs within one minute of drop placement and this blanching is useful to confirm that the drop reaches the ocular surface, but it is not predictive of eyelid elevation. None of the patients volunteered symptoms of photophobia or eye pain after phenylephrine drop administration.

The predictability of Hering effect (contralateral upper eyelid lowering) continues to be elusive. The authors defined Hering effect as ≥1 mm lowering of the contralateral eyelid in unilateral ptosis. Fifty percent of the patients demonstrated such an effect, but none of the variables the authors studied predicted which patients would show a Hering reaction. Accordingly, in unilateral ptosis patients, clinicians should still carefully

examine the contralateral eyelid as part of phenylephrine testing—photographs may identify more subtle cases that may be missed on casual examination.

Bilateral ptosis patients showed a similar rate of response to phenylephrine as compared with unilateral ptosis patients (75%, 9/12 eyes); interestingly, one patient showed a response in one eye but not the other. A subgroup analysis of patients with bilateral ptosis did not show a higher amount of eyelid elevation than in unilateral patients ($p = 0.973$). This study was not designed to study "bilateral Hering" phenomenon, in which presumably, the eyelid elevation of either eyelid alone (i.e., when phenylephrine is only placed in that eye) is less than the elevation of that eyelid when phenylephrine is placed in OU—this would be a novel and clinically relevant direction of future inquiry.

There are several limitations to this study. First, the sample size is relatively small, owing to the difficulty of having patients undergo a testing protocol for 1 hour after drop placement in a busy clinic setting. Second, despite attempts to standardize the photographic protocol and exclusion of photos that were clearly affected by blinking, there is variability in voluntary eyelid elevation/brow elevation between photographs for an individual patient. Third, while the digital measurement software is the most quantitative method available, there is some subjectivity in the placement of calipers for the measured parameters. In addition, the subjects only had brown irides meaning the results may not be applicable to patients with lighter colored irides. The authors only evaluated patients with involutional ptosis so the results are not generalizable to other categories of ptosis. Finally, no prior studies allowed the authors to adequately estimate an effect size, and the authors could not properly perform a power analysis in this study—the lack of correlation between the patient characteristics the authors studied and the phenylephrine test may be due to the study not being adequately powered. This pilot study could be used to better power future studies.

This study further elucidates the widely used 2.5% phenylephrine test in ptotic patients. Neither patient characteristics (e.g., age, gender, dermatochalasis) nor phenylephrine's other effects (pupil dilation, conjunctival blanching) predicted eyelid elevation to topical phenylephrine, but more ptotic eyelids showed greater eyelid elevation. While most patients (73%) showed eyelid elevation, only 50% of responders reached maximum MRD-1 at 5 minutes after drop placement. The authors suggest monitoring a patient for 10 minutes, at which point 80% of the responders have reached maximal MRD-1. Finally, the authors found a subset (14%) of "late responders" (>30 minutes)—patients who did not show a response to phenylephrine during the office visit could be instructed to self-monitor for delayed eyelid elevation. The surgical response of this group to internal ptosis repair would be an interesting avenue of future study.

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