Assessing the utility of 2.5% phenylephrine for diagnostic pupillary dilation

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ABSTRACT • RÉSUMÉ

Objective: To evaluate whether the addition of phenylephrine to tropicamide produces any clinically significant change in pupil size during diagnostic eye examination.

Methods: Twenty healthy adults at the Washington University School of Medicine Eye Clinic were enrolled in this prospective, nonrandomized, crossover trial. Each had 3 dilating eye drop regimens administered to the left eye on separate days. Tropicamide (T) + proparacaine (PP) + phenylephrine (PE) (T+PP+PE) was considered the standard therapy, to which tropicamide alone (T alone) and tropicamide + proparacaine (T+PP) were compared against. Main outcome measures were postdilation pupil size and proportion of pupils able to achieve adequate clinical pupil dilation of >7 mm. Comparisons were made using Wilcoxon signed-ranked tests and McNemar's test.

Results: Mean postdilation pupil size was 7.94 ± 0.78 mm, 7.64 ± 0.78 mm, and 7.48 ± 0.77 mm for T+PP+PE, T+PP, and T alone, respectively. T+PP+PE was statistically superior to T+PP ($p = 0.004$) and T alone ($p < 0.001$) with respect to postdilation pupil size. The proportion of pupils able to achieve adequate pupil dilation of >7 mm was 90%, 80%, and 70% for T+PP+PE, T+PP, and T alone, respectively. No statistical difference was observed in each regimen's ability to achieve adequate pupil dilation of >7 mm (T+PP+PE and T+PP: $p = 0.47$; T+PP+PE and T alone: $p = 0.13$).

Conclusion: The addition of phenylephrine eye drops to tropicamide produced larger pupil dilation, but the magnitude of benefit was marginal and clinically insignificant in this young, healthy cohort. A single-dilating-agent regimen using tropicamide could be considered in routine clinical practice.

Objet : Évaluer si l'ajout de phényléphrine au tropicamide entraîne une variation cliniquement significative de la taille de la pupille durant l'examen diagnostique des yeux.

Méthodes : Vingt adultes en bonne santé ont été admis à cette étude prospective non randomisée menée en mode croisé, tenue à la Washington University School of Medicine Eye Clinic. Chacun devait s'administrer, lors de 3 jours distincts, 3 schémas de dilatation médicamenteuse de la pupille dans l'œil gauche. On a comparé le tropicamide seul (T seul) et l'association tropicamide + proparacaïne (T+PP) à l'association tropicamide (T) + proparacaïne (PP) + phényléphrine (PE; T+PP+PE). Les principaux paramètres mesurés étaient la taille de la pupille après dilatation et la proportion de pupilles dont la dilatation était adéquate sur le plan clinique (> 7 mm). Les comparaisons ont été effectuées à l'aide du test de Wilcoxon pour observations appariées et du test McNemar.

Résultats : La taille moyenne des pupilles post-dilatation s'est chiffrée à 7,94 ± 0,78 mm, à 7,64 ± 0,78 mm et à 7,48 ± 0,77 mm avec les schémas T+PP+PE, T+PP et T seul, respectivement. Le schéma T+PP+PE s'est révélé statistiquement supérieur aux schémas T+PP (p = 0,004) et T seul (p < 0,001) en ce qui a trait à la taille de la pupille après dilatation. La proportion de pupilles dont la dilatation était adéquate (> 7 mm) était de 90 %, de 80 % et de 70 % sous T+PP+PE, T+PP et T seul, respectivement. On n'a pas relevé de différence statistiquement significative entre les 3 schémas pour ce qui est de l'obtention d'une dilatation adéquate (> 7 mm) de la pupille (T+PP+PE vs T+PP : p = 0,47; T+PP+PE vs T seul : p = 0,13).

Conclusions : L'ajout de phényléphrine au tropicamide a procuré une plus forte dilatation de la pupille, mais l'ampleur du bienfait était négligeable et sans portée clinique dans cette cohorte de jeunes adultes en bonne santé. Dans la pratique clinique courante, la dilatation médicamenteuse de la pupille peut se faire à l'aide du tropicamide seul.

Diagnostic pupillary dilation is essential for comprehensive evaluation of the eye. The American Academy of Ophthalmology recommends comprehensive eye examinations to screen for vision-threatening conditions at least every 2–4 years in adults aged above 40 years, with even more frequent examinations in patients with systemic and ocular diseases such as diabetes mellitus, glaucoma, and macular degeneration.[1,2] To achieve the pupillary dilation necessary to effectively evaluate the structures in the back of the eye, it is common practice to use a dual-dilating-agent regimen with phenylephrine and tropicamide, as the 2 medications dilate the pupil by different mechanisms (i.e., tropicamide inhibits the iris sphincter via parasympathetic control, whereas phenylephrine activates the iris dilator via sympathetic control).[3] Because of the unique mechanisms by which tropicamide and phenylephrine work, one would assume a pharmacologic synergism to their use in combination. Yet few studies have evaluated the degree to which this expected synergism translates into standard clinical practice.

The question of how much clinical benefit there is in a dual-dilating-agent regimen has become an increasingly salient one in light of the recent rise in phenylephrine prices. At Washington University Eye Clinic, the cost of tropicamide has remained relatively stable, with a current price of $6.50 per 15-mL bottle. In contrast, the cost of

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phenylephrine peaked at $140 per 15-mL bottle over the last 2 years. This represents more than a 50-fold increase from just a few years earlier, when the price per bottle was as low as $2.75. The price increase comes largely as a result of a single pharmaceutical manufacturer winning formal FDA approval for ophthalmic phenylephrine hydrochloride as a "new" drug, in effect ending the generic status of the medication and pushing other large manufacturers without FDA approval out of the market.[4]

This development comes at a time when the frequency of recommended ophthalmic screening examination already falls well short of adequate. For example, only about 50% of patients with diabetes in the United States are receiving comprehensive annual eye examinations for early detection and treatment of diabetic retinopathy.[5] In this setting, where convincing patients to adhere to recommended screening guidelines is already an uphill battle, the sizable increase in the price of phenylephrine may further affect eye examination accessibility and quality. Additionally, the growing emphasis on efficient resource allocation and reduction of medical waste places a needed pressure to scrutinize any outdated medical practices that increases cost without adding clinical value.

Given these recent escalations in phenylephrine prices, there is growing consideration for alternative dilating regimens that preclude the use of phenylephrine altogether. Yet there is a paucity of published data regarding the viability of these alternatives. In particular, hardly any studies have compared combination therapy to single-dilating-agent regimen using tropicamide alone. One study compared the efficacy of 1% tropicamide alone, 2.5% phenylephrine alone, and a combination therapy of the 2 medications.[6] In that study, 50 patients were divided into 3 treatment groups based on the aforementioned dilating regimens and maximal pupil size was compared. The therapies were not repeated on the same patients, thereby introducing variability among individual responses to dilating drops. The study demonstrated that 2 drops of tropicamide produced a larger pupil size compared to 1 drop each of tropicamide and phenylephrine, though the results were not statistically significant and the difference in pupil sizes was not quantified. Interestingly, the authors suggested that combination therapy might still be more effective, despite their own evidence to the contrary.

A second study evaluated the efficacy of 10% phenylephrine alone against 10% phenylephrine plus 1% tropicamide.[7] The authors' conclusion also supported combination therapy, as it produced a mean pupil size of 8.0 mm compared to 6.9 mm with single-agent therapy. However, there was no statistical difference in either regimen's ability to achieve >6-mm dilation, a generally accepted size of adequate pupil dilation for diagnostic examination.[8] Additionally, tropicamide alone was not evaluated in this study despite evidence that it has a shorter latency period to dilation and produces a larger amount of dilation compared to phenylephrine alone.[9]

The current state of phenylephrine pricing has necessitated a critical eye in regard to its routine use. The present study evaluates the clinical benefit of including phenylephrine eye drops under typical dilated eye examination conditions and compares it to dilating regimens that preclude its use altogether.

Methods

This prospective, nonrandomized, crossover study was conducted at the Washington University School of Medicine with 20 healthy students and faculty affiliated with the institution. All study participants were free from any ocular disease other than refractive error. None were taking any medications known to affect pupil size. A minimum corrected vision of better than 20/40 for all participants was required and verified by an initial screening eye examination. The Institutional Review Board of the aforementioned medical centre approved the study before participants were recruited. The study was compliant with the Health Insurance Portability and Accountability Act, and informed consent was obtained from all participants.

Dilating Regimens

One of 3 eye drop regimens was instilled into the left eye only (intervention eye). T+PP+PE consisted of 1% tropicamide [Akorn Inc, Lake Forest, IL] + 0.5% proparacaine hydrochloride [Akorn Inc] + 2.5% phenylephrine hydrochloride [Akorn Inc]. This triple-drop therapy is considered the standard therapy at the Washington University Eye Center and was the "gold standard" to which statistical comparisons were made. T+PP consisted of 1% tropicamide + 0.5% proparacaine hydrochloride, and T alone consisted of 1% tropicamide.

A single drop of each agent was used in the prescribed regimen and delivered into the conjunctival sac of the left lower eyelid. Proparacaine was administered first if indicated by the prescribed dilating regimen (T+PP+PE and T+PP). For these multidrop regimens, an interval of approximately 15 seconds was used between each eye drop. Although previous studies have recommended longer intervals for optimal pharmacologic effect of these medications,[10,11] we chose a time interval that closely resembles the clinical experience seen at Washington University Eye Clinic. Our priority was evaluation under typical clinical conditions, potentially at the expense of optimal pharmacology. Subjects were instructed to refrain from squinting and to tilt the head backward in order to avoid unintended loss of medications. The right eye (control eye) did not receive any drops and served as an internal control for possible environmental and systemic influences.

Measurements

Study participants were asked to sit in a darkened examination room for 5 minutes to allow pupils to dark-adapt.