

Pupil dilation using drops vs gel: a comparative study

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CLINICAL STUDY

Abstract

Purpose To compare the efficacy in pupil dilation and degree of discomfort between topical instillation of mydriatic drops and gel.

Methods The study included 60 patients with no previous ocular history of trauma and surgery. One eye was dilated with two drops (tropicamide 0.5% and phenylephrine 10%), and the other with one drop of gel (tropicamide 0.5% + phenylephrine 5%). Pupil size was measured by a Colvard pupillometer at baseline and 5, 15, 30, and 45 min following instillation. Pain upon instillation was measured by visual analog scale (VAS).

Results There was no difference in pupil size at baseline. Use of the gel achieved greater mydriasis than drops ($P = 0.01$), and was also associated with lower pain scores ($P = 0.003$). In diabetic patients, pupil size was smaller at baseline and following instillation of drops and gel. Use of the gel achieved an even greater degree of pupil dilation in this subset of patients than drops ($P = 0.019$).

Conclusions Gel formulation achieved significantly greater pupil dilation than drops, despite a lower concentration of phenylephrine, and was also associated with significantly lower patient discomfort. This study is the first report of improved mydriatic efficacy in diabetic patients.

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Introduction

Cataract is the leading cause of age-related blindness worldwide,¹ and cataract extraction is the most commonly performed ophthalmic surgery.² An adequately dilated pupil is a prerequisite for safe cataract extraction surgery, and small pupil size has been shown to be associated with increased risk for intraoperative and early postoperative complications.^{3–5}

Preoperative pupil dilation is commonly achieved by repeated administration of mydriatic drops. This process is time consuming,

and it has also been shown that repeated instillation of drops may damage the corneal epithelium, which may cause patient discomfort and interfere with the visibility during surgery.⁶ Therefore, additional methods for pupil dilation have been explored. Intracameral injection of mydriatic agents has been shown to be safe and effective,^{7,8} but was reported to be inferior to conventional topical mydriasis in several studies.^{9,10} Use of wicks saturated in mydriatic agents has been shown to be comparable to use of drops, but has been associated with an increased risk of conjunctival and corneal abrasions.^{6,11,12} One recent study has reported the topical use of a gel containing phenylephrine, tropicamide, diclofenac, and lidocaine for topical anesthesia and mydriasis, which was found to achieve greater and more rapid pupil dilation compared with drops. It has been suggested that the greater efficacy is owing to the fact that the gel was retained in close proximity to the eye while the drops were cleared by the lacrimal system, and that the gel formulation provided additional permeability through the cornea.¹³

The purpose of our study was to compare the efficacy in pupil dilation between topical instillation of mydriatic drops and gel, and to compare the degree of patient discomfort during both methods of mydriasis.

Material and methods

Patient selection

All patients in this study were 18 years or older, and were recruited during their visit at our clinic. Exclusion criteria included any prior ocular trauma or surgery, any ocular condition requiring treatment by intravitreal injections, any ocular condition that affects pupillary function (such as optic neuropathy, Adie's tonic pupil, oculomotor nerve palsy, and so on), and any use of drops or gels. Male patients were also specifically asked about current or previous use of α 1-adrenergic receptor antagonists (such as tamsulosin) for prostate problems, and were excluded if their

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history was positive for their use. Patients with pseudoexfoliation or anisocoria >0.5 mm at baseline were also excluded. Patients with known allergy to tropicamide or phenylephrine were not included. The study protocol was reviewed and approved by the Institutional Review Board, and a written informed consent was obtained from all participants. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Recorded parameters included demographic information and previous medical and ocular history. Specifically, patients were asked whether they had diabetes mellitus or not, and this was confirmed with their medical records.

Pupil dilation and measurement

Each participant received one drop of tropicamide 0.5% (Mydramide, Fischer Pharmaceutical Labs., Tel Aviv, Israel) and one drop of phenylephrine hydrochloride 10% (Efrin, Fischer Pharmaceutical Labs., Tel Aviv, Israel) in one eye, and one drop of a gel containing tropicamide 0.5% and phenylephrine 5% in the other. Drops were administered to both eyes within 30 s of each other, by a technician, in a single-masked manner.

We note that the gel was designed especially for this study, and is not a commercially available product. The gel was manufactured by a GMP approved pharmacy under sterile conditions (Concept pharmaceuticals, Kfar-Saba, Israel). After compounding, the gel was distributed into individual small tubes, for single use with each patient. Tubes were not reused in order to avoid any variation in the gel's efficacy due to different times after their opening. This study did not evaluate the gel's shelf life after its opening.

Horizontal pupil diameter was measured by a Colvard pupillometer (Oasis Medical, London, England), at baseline, and at 5, 15, 30, and 45 min following pupil dilation. All measurements were made by a single observer (DL), who was masked for the method of mydriasis used on all eyes, in the same room under photopic conditions (luminance of 5.0 candelas (cd/m^2)).

Pain measurement

Pain was measured by subjective grading on a visual analog scale (VAS), immediately following the instillation of pupil dilation drops and gel. The VAS is a horizontal line measuring exactly 10 cm (100 mm), as shown in Figure 1. Each patient was asked to mark a vertical line crossing the horizontal line, according to his or her subjective pain assessment during the drops and gel instillation, ranging from no pain at all to maximal pain. The distance between the left edge of the horizontal line and the vertical mark made by the patient was later measured and recorded

Please make a mark along the line according to the degree of pain you felt during the instillation of pupil dilation drops:



Figure 1 An example of the VAS graded by the participant at each time point in the study. All lines were exactly 10 cm in length.

in mm, and transformed into a score between 0 and 100. All VAS measurements were collected by the same observer (DL), after explaining this method to the patients. The VAS is a common tool for assessing pain and other symptoms, which has been shown to be a valid and reliable research method in previous clinical studies.^{14–17} It has been successfully used in ophthalmological studies evaluating pain associated with ocular surgery, intravitreal injections and topical therapies.^{18–25}

Statistical analysis

Correlations between continuous variables were analyzed using Pearson's correlation coefficient, and paired *t*-tests were used to analyze associations between categorical parameters. An analysis of variance (ANOVA) with repeated measure (over time) was performed in order to assess the change in pupil diameter over time. The statistical significance level was set at 0.05. Data were analyzed using SPSS for windows version 20. (SPSS Inc., Chicago, IL, USA).

Results

The study included 60 patients, 37 (61.7%) women and 23 (38.3%) men. Mean age was 66.6 ± 17.9 years (range 19–93 years). Seventeen (28.3%) patients were diabetic.

Comparison of pupil dilation between drops and gel

Pupil diameter at baseline was not significantly different between eyes that received drops and eyes that received gel. After instillation of the drops and gel, pupil diameter was enlarged. ANOVA with repeated measures over time comparing pupil diameter between eyes treated with drops and gel demonstrated a significantly larger pupil diameter in eyes that received gel for pupil dilation ($P=0.01$). The mean difference in final pupil diameter at 45 min was ~ 0.2 mm (Figure 2). Pupil size data at all time points is provided in Table 1.

Comparison of pain measurements between drops and gel

Mean pain scores in eyes that received drops were 33.6 ± 25.6 , and 23.5 ± 26.3 in eyes that received gel.

This difference was statistically significant between groups ($P=0.003$), with less pain associated with use of the gel.

Effect in diabetic patients

Pupil diameter at baseline was 3.6 ± 0.9 mm (median 3.75 mm) in diabetic patients, and 4.16 ± 0.9 mm (median 4 mm) in non-diabetics. This difference was statistically significant ($P=0.01$). Regardless of pupil dilation method, pupil diameter was significantly smaller in eyes of diabetic patients at all time points (Figure 3).

The effect of the drops and gel on pupil dilation were analyzed separately in diabetic patients. Significantly larger pupil diameter was achieved in eyes that received gel than in eyes that received drops ($P=0.019$). The mean difference in final pupil diameter at 45 min was ~ 0.3 mm (Figure 4). Pain scores were also significantly lower in eyes treated with gel in this subset of patients ($P=0.04$).

Discussion

Our results demonstrate that use of a gel containing tropicamide 0.5% and phenylephrine 5% achieved significantly greater pupil dilation than use of tropicamide 0.5% and phenylephrine 10% drops. These results support those of the previous study comparing gel and drops for pupil dilation.¹³ It should be noted that the previous study was smaller and included only 20 patients, and that it compared a gel containing

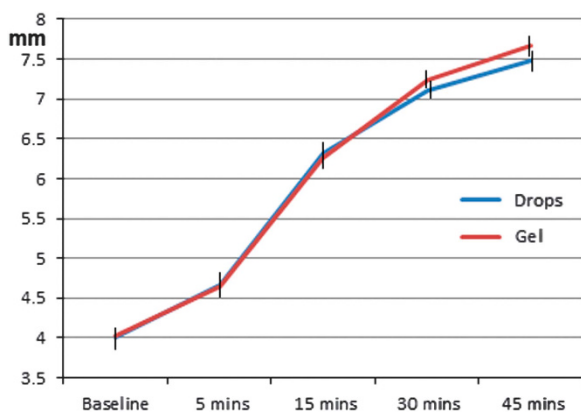


Figure 2 Comparison of pupil diameter (mean ± SE) between eyes that received drops and eyes that received gel for pupil dilation.

Table 1 Pupil size data at all time points of the study

Groups	Baseline	5 min	15 min	30 min	45 min
Drops	4.01 ± 0.91 (4)	4.66 ± 1.06 (5)	6.30 ± 1.05 (6.25)	7.10 ± 1.02 (7)	7.47 ± 1.01 (7.5)
Gel	4.04 ± 0.93 (4)	4.64 ± 1.04 (4.75)	6.26 ± 1.04 (6.25)	7.25 ± 1.05 (7.5)	7.66 ± 1.02 (8)

Values are provided as mean ± SD (median), in mm.

tropicamide 1% and phenylephrine 10% with tropicamide 1%, phenylephrine 2.5%, and cyclopentolate 1% drops. This study included a larger cohort, and the fact that the phenylephrine concentration was lower in the gel than in the drops supports the hypothesis that using a gel formulation will achieve greater mydriasis. As previously mentioned, there are two possible explanations for this finding. First, the gel is more viscous than the drops and is not rapidly cleared by the lacrimal system, and therefore stays as a depot on the ocular surface and may have a longer duration of action. Second, the biochemical properties of the gel may give it improved corneal penetration and increase its efficacy.

In addition, this study is the first to compare the patients' perceived level of pain between instillation of drops and gel. Our results indicate that the gel was associated with significantly lower pain scores than drops. There are two possible explanations for this difference. First, eyes dilated with drops received two drops that contain a preservative (both Mydramide and Efrin drops contain benzalkonium chloride), whereas eyes dilated with gel received one drop of a preservative-free formulation. It has been shown that preservative-free formulations are associated with lower pain score than the equivalent preserved formulations.^{20,21,26} Second, it is possible that the difference resulted from the increased osmolality of the phenylephrine 10% drops (Osmolality values were for the tropicamide 0.5% drops, phenylephrine 10% drops and the gel were 308, 1000, and 590 mosmol, respectively). Increased osmolality has been associated with ocular discomfort, most notably in dry eye syndrome, and use of drops with lower osmolality has been correlated with improved tolerability.^{27–29}

A novel finding in this study is that significantly better mydriasis was achieved by the gel compared with the drops in diabetic patients. The difference in this subset of patients was larger and more significant than in non-diabetic patients. At baseline, pupil diameter was significantly smaller in diabetic patients ($P=0.01$), which is compatible with previous reports of smaller pupil size and reduced response to pharmacological mydriasis in diabetes.^{30–32} Our results indicate that use of the gel achieves greater pupil dilation than drops in diabetic patients. It is possible that the suggested mechanisms for the higher efficacy of the gel in general, the gel's longer duration of action on the ocular surface, and increased

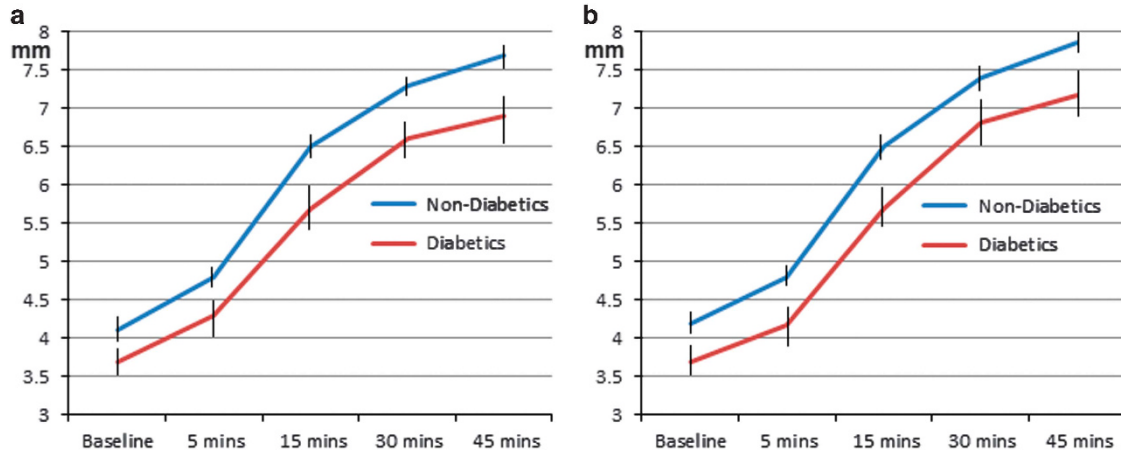


Figure 3 Comparison of pupil size (mean \pm SE) between diabetic and non-diabetic patients (a -eyes that received drops, b- eyes that received gel). Pupil diameter was significantly smaller in eyes of diabetic patients at all time points.

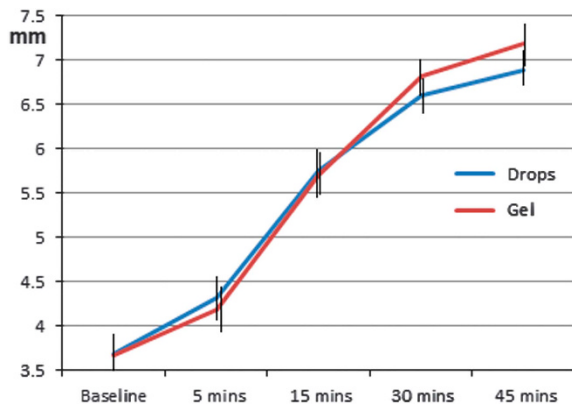


Figure 4 Comparison of pupil diameter (mean \pm SE) in diabetic patients between eyes that received drops and eyes that received gel for pupil dilation.

penetrance, are even more significant in eyes of diabetic patients who tend to have smaller pupils.

A limitation of this study is its relatively small sample size. However, we note that the series is much larger than that reported in the only previous study on pupil dilation using a gel, which included only 20 patients,¹³ and that its size was still sufficient to achieve statistically significant results. Another limitation is that patients' eyes were not examined for conjunctival and corneal irritation following instillation of the drops and gel. This parameter may have correlated with the VAS pain scores. In addition, the concentration of phenylephrine was different between the drops and gel (10% and 5%, respectively). However, it should be noted that the gel was found to have better efficacy despite the lower concentration, which supports that hypothesis that a gel formulation for pupil dilation will be advantageous over drops.

In conclusion, the use of gel was demonstrated to achieve greater mydriasis than drops, supporting the finding of the previous smaller study.¹³ The superior

efficacy was even more pronounced in eyes of diabetic patients, and this is the first report of a pharmacological delivery method that improves pupil dilation in these patients. In addition, use of the gel was also associated with lower pain scores, implying better patient tolerability to it than drops. A single instillation of the gel achieved greater pupil dilation with less discomfort, and appears to be a better alternative than the commonly used drops. This method may improve pupil dilation before cataract surgery, as well as other ocular procedures, dilated fundus examinations and imaging techniques such as fluorescein angiography and optical coherence tomography. Such a gel may have a widespread use in the current practice of ophthalmology.

Summary

What was known before

- Preoperative pupil dilation is most commonly achieved by repeated instillation of mydriatic drops.
- Only one small study had previously compared the efficacy of pupil dilation between drops and gel, and demonstrated that gel achieved greater mydriasis.

What this study adds

- This study includes a larger cohort of patients, and its results show that gel is more effective than drops in pupil dilation. This supports and strengthens the only previous study on this issue.
- A novel finding that gel is even more significantly effective in pupil dilation than drops in diabetic patients, who tend to have smaller pupils and be more resistant to dilation.
- A novel finding that use of a gel for pupil dilation is associated with lower pain scores (ie, better tolerability) than drops.
- The results of this study indicate that a pupil dilation gel may be a better alternative for preoperative preparation of patients, and may have an important place in the clinical practice of ophthalmology.

Conflict of interest

The authors declare no conflict of interest.

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