CLINICAL STUDY

Comparison of mydriatic efficacy of spray application and drop instillation of tropicamide 1%

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Abstract

Purpose **To determine whether the mydriatic efficacy of spray application of tropicamide 1% is comparable to drop instillation of tropicamide 1%, and to compare the ocular discomfort caused by these methods.**

Methods **Thirty-four healthy volunteers were randomly assigned to one of two groups, and received either a single drop of tropicamide 1% eye drops or a single puff of tropicamide 1% spray into open eyes. Pupil diameters were measured from anterior segment images taken using a Topcon Imagenet system at baseline and at the fifth, tenth and fifteenth minute after drug administration. Ocular discomfort experienced with each method was also compared.**

Results **Repeated measures analysis of variance revealed that a statistically significant increase in pupil diameter was achieved with both application methods over time ($p < 0.0001$), and that there were no statistically significant differences in pupil diameter between the two groups at each time point ($p = 0.409$). The mean ocular discomfort score for tropicamide 1% spray was 1.45 ± 0.56, and for tropicamide 1% eye drops was 2.71 ± 0.67. This difference was statistically significant ($p < 0.001$).**

Conclusions **The mydriatic efficacy of tropicamide 1% spray is similar to that of conventional tropicamide 1% eye drops, and spray application causes less ocular discomfort.**

Key words Mydriatics, Ocular drug delivery, Ocular spray, Tropicamide

Ophthalmic formulations can be classified as solutions, suspensions and ointments. Solutions and suspensions are administered in the form of eye drops.[1] Application of ophthalmic drugs as eye drops has advantages and disadvantages. Drop instillation is quite easy for adults, but is often an unpleasant procedure for young children and can be a difficult task for elderly persons with poor vision, hand tremors, or orthopaedic neck or hand problems. Furthermore, microbial contamination of eye drops causes significant morbidity.

As a result of these difficulties and the pharmacokinetic disadvantages of eye drops, new, controlled ocular drug delivery systems have been introduced.[1] In addition to these systems, spray application of ocular drugs is an alternative to classical eye drops. While studies on the spray method are few, the results seem promising.[2-5] We investigated the feasibility and effectiveness of spray application of tropicamide 1%.

Materials and methods

We conducted a prospective, randomised, examiner-masked, parallel group study in 34 healthy volunteers 25–42 years of age (mean 34.7 years). All subjects had dark irides. After routine anterior segment examination, subjects were randomly assigned to one of two groups, and received either a single drop of tropicamide 1% eye drops or a single puff of tropicamide 1% spray. There were 10 women and 7 men in the spray group and 9 women and 8 men in the eye drops group. Anterior segment images of both eyes were taken using a Topcon Imagenet system at baseline and at the fifth, tenth and fifteenth minute after drug administration.

The spray application technique was as follows: The eyelids were held open by two fingers, similar to the position for inserting a contact lens, and one puff of spray was instilled from a distance of 4 cm. An opaque plastic 10-ml spray bottle of the pump atomiser type, designed for aerosolisation of perfumes (Kimya Plastik, Ankara, Turkey), was used. Tropicamide 1% spray was prepared by transferring under sterile conditions 5 ml of tropicamide 1% eye drops (Tropamid forte, Bilim Ilaç, Istanbul, Turkey) into a spray bottle sterilised with ethylene oxide.

The volume in each spray and drop was measured by repeated application to dry filter paper.[3,5] We determined volume per drop or

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Table 1. *Changes in mean pupillary diameters (mean ± SD) at baseline and the fifth, tenth and fifteenth minute after application of tropicamide 1% spray and tropicamide 1% eye drops*

	Tropicamide 1% spray	Tropicamide 1% eye drops	*p* value
Diameter at baseline (mm)	1.66 ± 0.30	1.28 ± 0.29	0.491
Diameter at 5 min (mm)	2.24 ± 0.63	2.24 ± 0.59	0.617
Diameter at 10 min (mm)	3.09 ± 0.58	3.29 ± 0.64	0.344
Diameter at 15 min (mm)	3.49 ± 0.40	3.47 ± 0.40	0.904

spray by subtracting the dry weight of the filter paper from the wet weight, assuming the density of the solution was 1.0 g/ml. Our measurements showed that the spray bottle produced a consistent amount of mist only after three puffs. The study was performed on three consecutive days and the spray bottle was emptied and refilled with 5 ml tropicamide 1% every morning. Also, the amount of tropicamide delivered was checked using the above-mentioned method each morning before the start of applications. In order to deliver a consistent amount of tropicamide to each subject, the first three puffs of spray were directed into a plastic bag and the fourth puff was applied to the eye of the study subjects.

A second investigator, who was masked to the drug delivery method, recorded the pupil diameter measurements. To prevent errors due to magnification and illumination, we standardised the camera flash power, magnification and room illumination for all patients. Image measurement software of the Topcon Imagenet image analysis system was used for measuring pupil diameter.

After drug instillation, the subject was asked to respond to questions about burning, stinging and lacrimation. The responses were scored as follows: 0 for 'none', 1 for 'slight', 2 for 'moderate', 3 for 'severe' and 4 for 'very severe'. Mean scores for ocular discomfort were derived from the mean of the scores for individual symptoms.

Statistical analysis of the data was carried out using the Statistical Package for Social Sciences software. Two-tailed non-parametric tests (the Mann-Whitney *U*-test and the Wilcoxon matched pairs signed-ranks test) and repeated measures analysis of variance (ANOVA) were used, and a p value <0.05 was considered statistically significant. The study was carried out in accordance with the principles of the revised Declaration of Helsinki (Venice, 1993) and all patients gave their written, informed consent.

Results

The volume of tropicamide 1% delivered in a single spray puff was 24.90 ± 0.98 µl (mean ± SD) and the mean drop volume was 31.08 ± 0.81 µl (mean ± SD) for the tropicamide 1% eye drops used in the study.

The patients' mean pupil diameter changes over time are presented in Table 1, which indicates there were no statistically significant differences between the two application methods at any time point. Fig. 1 shows the change in the mean pupillary diameter throughout the study period for the two application methods. Repeated measures ANOVA revealed a statistically significant effect of time on pupil size for both application methods ($p < 0.0001$), but there was no statistically significant difference in pupil size between the two methods of drug administration over time ($p = 0.409$). These data show that both forms of application produced statistically significant pupil dilatation but that the rate of dilatation did not vary significantly between the two methods.

Table 2 lists the mean clinical scores for ocular irritation symptoms (burning, stinging and lacrimation) and the mean ocular discomfort scores, which represent the mean of the scores for individual symptoms with each application method. The mean ocular discomfort score for tropicamide application by spray was 1.45 ± 0.56, and by eye drops was 2.71 ± 0.67. This difference was statistically significant ($p < 0.001$).

Discussion

Our results indicate that spray and eye drop application of tropicamide have comparable mydriatic efficacy but that spray application causes less ocular discomfort.

Both methods produced significant mydriasis, and pupil diameters in the two groups did not differ statistically at any time point. The mydriasis achieved by either method after 15 min would be adequate for fundus examination; however, repeated applications or longer waiting periods might be required for maximal dilation.

Spray application of tropicamide 1% caused significantly less ocular discomfort than drop instillation. Smaller droplet size, and probably the smaller amount of drug reaching the eye surface with the spray method, might explain this result. It is well known that the drop size released from currently used eye drop bottles is much larger than required; only a fraction of the applied

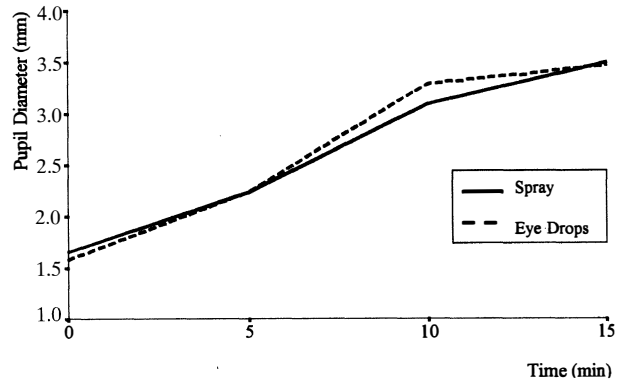

Fig. 1. *Changes in pupillary diameter relative to time after spray (continuous line) and eye drop (broken line) application of tropicamide 1%.*

Table 2. *Mean scores (mean ± SD) for ocular discomfort symptoms after application of tropicamide 1% spray and tropicamide 1% eye drops*

	Tropicamide 1% spray	Tropicamide 1% eye drops	*p* value
Burning	1.53 ± 0.62	2.82 ± 0.81	< 0.001
Stinging	1.41 ± 0.51	2.47 ± 0.62	< 0.001
Lacrimation	1.42 ± 0.58	2.86 ± 0.71	< 0.001
Mean ocular discomfort[a]	1.45 ± 0.56	2.71 ± 0.67	< 0.001

[a]Mean ocular discomfort values represent the mean of the scores for individual symptoms.

drug can be asborbed by ocular tissue and the remainder is eventually circulated in the body.[1,6,7] It is important to reduce drop size in order to minimise systemic side-effects, and spray application is an excellent way to achieve this goal.

Spray application of ophthalmic drugs can be a useful method of topical drug delivery and may solve many problems related to eye drop instillation of ophthalmic drugs to children, the elderly and patients with poor vision. Elderly people with hand tremors, poor vision or neck problems have difficulty in positioning eye drop bottles over the eye, and often miss when trying to use drops. Similar problems exist for small children, who often resist eye drop administration and refuse to lie back or extend their necks for proper drop delivery. People with poor vision also experience difficulty in instilling eye drops into the lower conjunctival cul-de-sac. Use of a spray does not require neck extension, exact positioning of an eye drop bottle or good vision. The eye drop administration problems mentioned above are eliminated, since a patient simply positions the spray bottle in front of the eye and presses the button. In order to prevent blinking, the eyelids are held open with the other hand. In the 1970s, some glaucoma medications were commercially available in mist-dispensing bottles but no articles have been published related to the use of these kinds of preparations and their effect on patient compliance.

Many types of spray bottles are available for medical use. The most commonly used systems are pressurised pharmaceutical preparations and atomiser-type spray bottles. According to the European Pharmacopoeia,[8] pressurised pharmaceutical preparations are presented in special containers under pressure, and contain one or more active ingredients. Upon actuation of a valve, the preparation is released from the container in aerosol form. The pressure for release is generated by propellant gas. To date there have been no studies published on the use of these types of sprays in ophthalmology. A second type of spray bottle, the pump atomiser, generates the pressure to release the preparation through air that is pumped into the bottle with a special pumping spray cap. With no need for propellant gas, this type of bottle is more suitable for ophthalmological use.

Antimicrobial preservatives are required in multiple-dose ophthalmic drugs, such as eye drops, in order to prevent bacterial contamination.[1,9] Although preservatives such as benzalkonium chloride and thiomerosal destroy most micro-organisms that contaminate eye drops, their cytotoxic effects frequently damage ocular tissue.[10,11] Also, microbial contamination can still occur and cause ocular morbidity despite these additives. Spray bottles are closed chambers in which the risk of bacterial contamination is small compared with open-chamber eye drop containers. Thus, sprays can be preservative-free, like unidose ophthalmic preparations.

To date, few studies have been published on spray application of ophthalmic eye drops.[2–5] The results of these investigations suggest that administering cycloplegics, mydriatics or miotics by spray to the closed eye is as effective as instilling eye drops to the open eye. In our study we chose to apply tropicamide spray to the open eye, and achieved a similar effect to that of eye drop instillation. We believe that spray application of other ophthalmic drugs, such as antibiotics, steroids and glaucoma medications, may be feasible, and might improve patient compliance with these agents. Future studies on the effectiveness and patient compliance of spray application of these medications are planned.

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