Shelf Life and Efficacy of Diagnostic Eye Drops

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SIGNIFICANCE: Pharmaceutical companies recommend discarding ophthalmic drugs 28 days after opening. This study shows that diagnostic eye drops have a low risk of contamination over a 7-month period in a controlled clinical setup. The diagnostic efficiency seems to be preserved over this period.

PURPOSE: The aim of this study was to evaluate the preservation period and the efficacy of ophthalmic preparations, such as 0.5% proparacaine hydrochloride, 1% tropicamide, 2.5% phenylephrine hydrochloride, and 1% cyclopentolate hydrochloride ophthalmic solution in a clinical and controlled setting.

METHODS: Thirty-eight primary eye care students were recruited to participate in the study. They used 25 bottles of each diagnostic drop at the Clinique Universitaire de la Vision for a 7-month period. An analysis of the bacterial contamination was repeated 10 times using both an agar plate and a nutrient broth at 0, 2, 4, 6, and 8 weeks and at 3, 4, 5, 6, and 7 months. The anesthetic, mydriatic, and cycloplegic effects were tested after 7 months of use and compared with nonopened ophthalmic bottles.

RESULTS: During the 7-month period, 4971 drops of proparacaine, 3219 drops of tropicamide and phenylephrine, and 1896 drops of cyclopentolate were administered to the patients. A total of 226 contacts between bottles and biological tissues were reported. After the 10 inoculation sessions on the agar medium at the predetermined times, no bacterial and fungal contamination was noted. No patient reported eye infections for 2 weeks after the drop instillation. Moreover, there was no difference in the efficacy when compared with new drops.

CONCLUSIONS: According to the results of the current study, diagnostic eye drops can be used with a low contamination risk beyond the recommendation date of 28 days up to 7 months, with the same efficacy, in a controlled clinical context.

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The administration of contaminated ocular preparations is a probable cause of eye infections. These preparations may be carriers of bacteria such as *Pseudomonas* species and *Serratia* species.[1] To limit such contamination, most topical medications contain a preservative with an antimicrobial action that increases their shelf life. Benzalkonium chloride has been used since 1935 as a preservative of choice in ophthalmic solutions and for nasal and otic medications. The mechanism of action of benzalkonium chloride is based essentially on the destruction of the cell membrane of microorganisms, thus preventing their propagation. The American College of Toxicology concluded that benzalkonium chloride can be used as an antimicrobial agent with a concentration of up to 0.1%.[2] Benzalkonium chloride reduces contamination of ophthalmic preparations especially in patients who have difficulty self-administering eye drops.[3] Furthermore, the use of benzalkonium chloride in some fluoroquinolone-containing ophthalmic solutions results in a greater reduction in the growth of the *Aspergillus niger* fungus compared with other unprotected fluoroquinolones. Benzalkonium chloride therefore has considerable antifungal activity in ophthalmic solutions.[4] However, it is important to note that some bacterial strains such as *Pseudomonas aeruginosa* are resistant to benzalkonium chloride and can multiply within the preservative itself.[3]

The Royal Pharmaceutical Society's guidance for the use of ophthalmic preparations in hospitals and care homes indicates that "If a fresh container of eye drops is supplied on discharge from hospital, this may be apportioned a 'user life' of 28 days."[5] However, this recommended period dates back to the British Pharmaceutical Codex of 1966, when drops were stored in glass bottles with a separate dropper. It goes without saying that the sterility of eye drops is paramount. However, user life (or "in-use shelf life") is difficult to apply in many clinics that use low-frequency ophthalmic preparations. In the literature, no studies seem to show evidence of contamination after this period. Although many studies have focused on microbial contamination of therapeutic preparations used by patients and hospital staff, few have focused on the microbial stability of ocular diagnostic preparations. For example, in hospitals, a 14-day use of therapeutic solutions did not result in contamination, whereas the recommendation was to replace them after 7 days.[6] Indeed, a direct relationship between in-use shelf life and contamination has not always been demonstrated.[7] Preservatives seem to play an essential role in the sterilization of topical medicines. On the other hand, in the literature, administration techniques seem to be much more significant in avoiding contamination. In fact, people trained to instill drops correctly do not cause contamination even with unpreserved drops.[8] The main sources of contamination are the eyelashes, eyelids, and eyes of patients and the hands of the person dispensing the drops. One of the few studies on the microbial stability of diagnostic drugs was carried out in private clinics by analyzing bacterial and fungal

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contamination regardless of in-use shelf life, and 11.7% of the bottles were contaminated.[8]

The bacteria most commonly found in eye drops are derived from normal skin flora, in particular coagulase-negative staphylococci and micrococci.[6] Other microorganisms present are those that can be found in the environment.

Several studies have reported low contamination rates for ophthalmic solutions; however, none of these have studied ophthalmic preparations for more than 28 days. In a study conducted in a veterinary clinic, no bacterial contamination was detected after 2 weeks of diagnostic eye-drop use.[9] Another study in Kenya found that, over a 2-week period, only 4 of the 77 eye drops tested were contaminated, whereas these were instilled by different people, increasing the risk of bacterial contamination.[10] Furthermore, a study by Hovding and Sjursen[11] showed that the frequency of contamination of ophthalmic preparations did not increase with in-use shelf life. The low contamination rates reported in these various studies lead us to question whether, with proper use, the bacterial sterility of eye drops can be extended beyond their recommended user life.

The first objective of this study was to evaluate the contamination rates of 4 classes of diagnostic ophthalmic drops in an eye clinic as a function of time, frequency of use, and frequency of contact with nonsterile surfaces. The second objective of the study was to evaluate diagnostic efficacy after a 7-month period.

METHODS

Phase 1: Contamination Rates

Ophthalmic Drops

The 4 types of ophthalmic drops analyzed in this study were Alcaine (0.5% proparacaine hydrochloride), Mydriacyl (1% tropicamide), Mydfrin (2.5% phenylephrine hydrochloride), and Cyclogyl (1% cyclopentolate hydrochloride), all from Novartis Pharmaceuticals, Camberley, UK. However, the company was not involved in the study and therefore did not sponsor the drops used. Table 1 summarizes the composition and format of the drops used.

Proparacaine hydrochloride is a topical anesthetic in the form of an aqueous ophthalmic solution. The main clinical uses of this pharmacological agent are tonometry, the removal of foreign bodies, and other procedures requiring anesthesia of the cornea and conjunctiva.[12] Tropicamide is an anticholinergic. This pharmacological agent blocks the cholinergic stimulation of the iris sphincter and ciliary muscle, causing mydriasis and paralysis of accommodation.[13] Phenylephrine hydrochloride is a sympathetic α-receptor agonist. It induces vasoconstriction and activates the dilating muscle of the iris, causing mydriasis. Tropicamide and phenylephrine are generally used together to perform dilated fundus examinations. Cyclopentolate hydrochloride is a muscarinic receptor antagonist that causes mydriasis and blockage of accommodation. Its use is mainly pediatric to measure refractive error by controlling accommodation. It can also be used for therapeutic usage in patients with uveitis, corneal abrasions, and others (i.e., cycloplegia to control for pain and prevent posterior synechia). These 4 ophthalmic eye drops contain 0.1% benzalkonium chloride as a preservative.

Participants

The study was carried out with the participation of optometry students from the University of Montreal during their internship at University Vision Clinic. The research followed the tenets of the Declaration of Helsinki and was approved by the institutional review board. Informed consent was obtained after the presentation of the project and before testing. Because students have varying internship periods, the study was divided into two major phases to ensure that each student involved was on-site for seven consecutive months. The first cohort of 25 students used bottles of 0.5% proparacaine and 1% tropicamide. A second cohort of 30 students used bottles of 2.5% phenylephrine and 1% cyclopentolate. Each student was given new bottles at the beginning of the study and had to keep using them for the 7-month study period. A total of 110 eye-drop bottles were thus analyzed. The students were solely instructed to use the diagnostic drops normally during their clinical internship. Drops were stored in students' instrument cases at room temperature for the duration of the study. Each participant had to complete a table to list the number of drops instilled and the number of contacts between the bottles and the eyelashes, the eyelids, or other biological tissues.

Agar Cultures

One drop from each bottle was collected and analyzed at 0, 2, 4, 6, and 8 weeks and at 3, 4, 5, 6, and 7 months. During the analysis, the presence of any positive microbial culture (bacterial or fungal) in a bottle resulted in its immediate removal from the study.

Analysis of the drops was carried out under a sterile hood in the neuropharmacology laboratory of J-FB at the University of Montreal. Each drop was mixed with a nutrient broth (1 mL) and spread on a regular nutrient agar plate composed of 3 $g \cdot L^{-1}$ of beef extract, 5 g of peptone, 8 g of sodium chloride, and 15 $g \cdot L^{-1}$ of agar. The agar plates were then incubated for 24 hours in a humidity-controlled oven at 37°C. The presence of microorganism colonies on the agar plates was then determined by the naked eye. Positive and negative controls were carried out during each inoculation. Positive controls were conducted with agar plates inoculated with oral specimens to verify that the agar plates were suitable for microorganism cultivation. Negative controls were conducted with sterile agar plates inoculated with sterile nutrient broth to confirm the sterility of the working environment.

The objective of the study was to assess the contamination rates of the eye drops without identifying the pathogens involved. For

TABLE 1. Summary of diagnostic drops used

Commercial name	Alcaine	Mydriacyl	Mydfrin	Cyclogyl
Active agent	0.5% Proparacaine HCl	1% Tropicamide	2.5% Phenylephrine HCl	1% Cyclopentolate HCl
Sample size (bottles)	25	25	30	30
Volume (mL)	15	15	5	15
Conservative	0.1% Benzalkonium chloride			

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TABLE 2. Dependent variables measured to compare the diagnostic effects of old and new drops

Diagnostic drops	Dependent variables
0.5% Proparacaine hydrochloride	Cornea sensitivity after 30 s and 5 and 10 min
1% Tropicamide/2.5% phenylephrine hydrochloride	Pupil dilation after 20 and 30 min
1% Cyclopentolate hydrochloride	Residual accommodation after 40 min

this reason, quantitative and qualitative measuring instruments were not used.

Phase 2: Diagnostic Efficacy

Methodology

At the end of the study, the efficacy of the diagnostic drops opened for 7 months was evaluated and compared with a sample of unopened "control" drops from the same batch. The control drops were conserved for 7 months according to the supplier's recommendations. For each diagnostic effect, a drop from a new bottle was instilled into one eye, whereas a drop from a bottle opened for 7 months was instilled into the other eye in a random order. The diagnostic effect of new and "old" drops was therefore compared between both eyes of each participant, thus eliminating interindividual variations. Measurements were performed in a double-blind manner, in which participants and the person responsible for making the measurements did not know which drops were instilled in which eye. Table 2 summarizes the dependent variables used to compare the diagnostic efficacy of the new bottles with that of those opened for 7 months.

Anesthetic and Mydriatic Effect

A first group of 10 participants recruited from the Université de Montreal School of Optometry received a drop of 0.5% proparacaine, 1% tropicamide, and 2.5% phenylephrine in each eye to compare the anesthetic and mydriatic effects. New opened drops were instilled in one eye, and old drops (opened 7 months ago) were instilled in the other eye. A digital lacrimal punctum occlusion was performed for a minimum of 10 seconds to help avoid the systemic absorption and optimize the topic absorption.

Corneal anesthesia was assessed by touching the cornea with a cotton swab. Participants reported their corneal sensitivity on a scale ranging from 0 (no sensation) to 10 (extreme pain) after 30 seconds and 5 and 10 minutes.

The relative pupillary dilatation of the new and old drops was measured by comparing the pupillary diameter before and after the instillation of the drops. Pupil diameters were objectively measured with a NeurOptics pupillometer VIP-300 (NeurOptics Inc., Irvine, CA) using an infrared camera and light-emitting diode light. NeurOptics uses a dynamic measurement system that captures 30 pupil positions over an approximate 2-second scanning period, thus producing the weighted average pupil size. According to the company brochure, the pupillometer does not require a calibration and can be used under various light conditions, independent of the examiner.[14] NeurOptics pupillometer is generally used under scotopic conditions because the device can change the background illumination and measure the pupillary diameter under different light conditions. In our protocol, we wanted to measure the pupillary dilatation after instilling mydriatic drops and when using a bright illumination (as for direct or indirect fundus ophthalmoscopy). The measurements were then performed under photopic light condition (320 cd/m^2) to be more relevant to the light condition of a fundus ophthalmoscopy. Before instilling drops, an evaluation of pupillary reflexes confirmed that no participant had an efferent or afferent pupillary defect or anisocoria.

According to the supplier's recommendations, the mydriatic effect required to perform the ophthalmoscopic examination occurs 15 to 30 minutes after the instillation of a drop of Mydriacyl or Mydfrin and persists for several hours. The relative pupillary dilatation of each eye was thus evaluated 20 and 30 minutes after the instillation of the drops.

Cycloplegic Effect

A second group of 10 participants recruited from the Université de Montreal School of Optometry received a 1% cyclopentolate drop in each eye to compare the cycloplegic effects of the old and new drops. Because measurement of the cycloplegic effect is more relevant in people with high amplitude of accommodation, participants had to be younger than 25 years and must have a monocular accommodative amplitude of at least 7 diopters in both eyes. Participants were also required to have a monocular visual acuity of 0.0 logMAR or more wearing their best visual correction and a difference of less than 0.06 logMAR between both eyes.

Studies have shown that the maximal cycloplegic effect is reached 30 to 40 minutes after the instillation of the first drop of 1% cyclopentolate.[15] In the present study, the refractive error was measured using an automatic refractometer 40 minutes after the instillation of 1% cyclopentolate drops. The residual accommodative amplitude of each eye was then measured using the Donders method, which consists of determining the distance at which vision becomes blurred when a text is brought progressively closer to the participant's eyes.

RESULTS

Contamination Rates

Participants reported 12,566 instillations of eye drops and 226 contacts with biological tissues. Table 3 summarizes the number of drops instilled and the contacts for each type of drop.

TABLE 3. Number of drops instilled and number of contacts with biological tissues for each kind of drop

Eye drops	0.5% Proparacaine HCl	1% Tropicamide	2.5% Phenylephrine HCl	1% Cyclopentolate HCl
No. drops used	4971	3219	2472	1904
Drops used per bottle (mean value)	198.8	128.8	82.4	63.5
Contact with biological tissues	80 (1.61%)	53 (1.65%)	58 (2.35%)	35 (1.84%)

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TABLE 4. Maximal risk of contamination of diagnostic ophthalmic drops as a function of sample size at a 95% confidence interval

	Eye drops	0.5% Proparacaine HCl	1% Tropicamide	2.5% Phenylephrine HCl	1% Cyclopentolate HCl
6 mo	Sample size	25	25	30	30
	Maximal risk of contamination (%)	11.29	11.29	9.50	9.50
			Overall: 2.69		
7 mo	Sample size	20	25	5	28
	Maximal risk of contamination (%)	13.91	11.29	45.07	10.15
			Overall: 3.77		

During the 7-month study period, no bacterial or fungal contamination was found in the agar inoculations at 0, 2, 4, 6, and 8 weeks and at 3, 4, 5, 6, and 7 months. In addition, no viral contamination was reported by patients who received eye drops at University Vision Clinic during the experimental period. The positive and negative controls were all conclusive and confirmed that the agar preparations were suitable for the growth of microbial colonies and that the experimental conditions were sterile.

Although none of the 110 bottles in our sample were contaminated in 7 months of use, it is impossible to affirm that the risk of contamination was zero. In the literature, there are numerous studies in which the event measured never actually occurred. Hanley and Lippman-Hand[16] showed that it is possible to calculate the maximal theoretical risk of an event even when it has not occurred in a given sample. The risk is expressed as a function of the sample size n and the α error threshold.

$$\text{Maximal risk} = 1-\sqrt[n]{0.05}.$$

Table 4 summarizes the maximal risk of contamination of the diagnostic drops calculated from the study sample. After 6 months of the study, all the bottles were still in use. According to our results, the theoretical maximal risk of contamination over a 6-month period was 11.29% for proparacaine and tropicamide and 9.50% for phenylephrine and cyclopentolate, with a 95% confidence interval. Between the sixth and seventh months of the study, 5 bottles of proparacaine and 24 bottles of phenylephrine (5 mL) were depleted. In addition, two bottles of cyclopentolate and one bottle of phenylephrine were accidentally discarded in the last month. The theoretical maximal contamination risk over a 7-month period was 13.91% for proparacaine, 11.29% for tropicamide, 45.07% for phenylephrine, and 10.15% for cyclopentolate. The high maximal contamination risk of phenylephrine resulted from the low number of bottles still available at 7 months. Because all the bottles contained the same preservative (benzalkonium chloride 0.1%), the maximal risk of contamination could be extrapolated to the entire sample of bottles in the study. The overall maximal risk of contamination was therefore 2.69% after 6 months and 3.77% after 7 months.

Diagnostic Efficacy

Fig. 1 shows the results of corneal sensitivity (scale from 0 to 10) for different time points (30 seconds and 5 and 10 minutes) after the instillation of one drop of 0.5% proparacaine from a new bottle in one eye and one drop from a bottle opened for 7 months in the other eye. A multivariate linear analysis of variance showed no difference in corneal sensitivity between new and old bottles at three time points: 30 seconds, $F_{1,18} = 0.000$ ($P > .99$); 5 minutes, $F_{1,18} = 1.552$ ($P = .23$); and 10 minutes, $F_{1,18} = 0.063$ ($P = .80$).

Fig. 2 shows the results of pupillary dilatation for different time points (20 and 30 minutes) after the instillation of one drop of 1% tropicamide and 2.5% phenylephrine from new bottles in one eye and one drop from bottles opened for 7 months in the other eye. A multivariate linear analysis of variance showed no difference in pupillary dilatation between new and old bottles at two time points: 20 minutes, $F_{1,18} = 0.013$ ($P = .91$), and 30 minutes, $F_{1,18} = 0.154$ ($P = .70$).

Finally, Fig. 3 shows the results of residual accommodative amplitude 40 minutes after the instillation of one drop of 1% cyclopentolate from a new bottle in one eye and one drop from a bottle opened for 7 months in the other eye. An univariate linear analysis of variance showed no difference in residual accommodation between new and old bottles ($F_{1,18} = 0.003$, $P = .95$). The large amplitude of the error bars was expected and arose from the low relative accommodation values after the instillation of cycloplegic drops.

DISCUSSION

Contamination Rates

Throughout the duration of the study, no contamination was detected among the 110 bottles analyzed, despite the contacts reported by the users. However, some bottles in our sample were depleted or discarded between the sixth and seventh months of

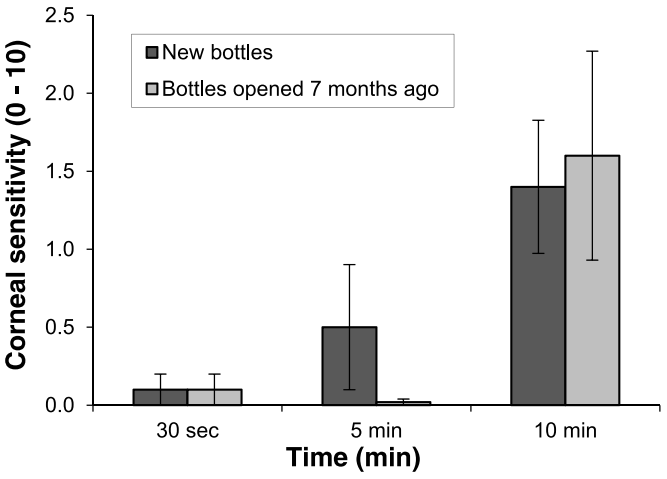

FIGURE 1. Corneal sensitivity after 30 seconds and 5 and 10 minutes. Anesthetic effect: corneal sensitivity (scale from 0 to 10) measured at different durations after the instillation of a drop of Alcaine of new bottles and those opened for 7 months. The error bars represent the SE.

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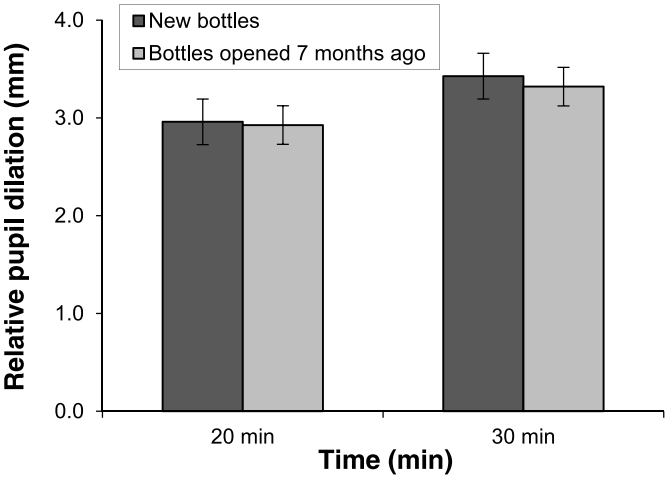

FIGURE 2. Relative pupillary dilation after 20 and 40 seconds. Mydriatic effect: relative pupillary dilatation (in millimeters) measured at different durations after the instillation of a drop of Mydriacyl and Mydfrin of new bottles and those opened for 7 months. The error bars represent the SE.

the study. The results indicate that the maximal contamination risks were 2.69% after 6 months and 3.77% after 7 months, with a 95% confidence interval for all bottles. In the absence of contamination, it was not possible to analyze contamination rates according to the frequency of use or contact with biological tissues.

Students were asked to report the number of occurrences of bottle tip and cap contact with biological tissues. They might skew the number of occurrences, knowing that these factors were monitored. Bottles were referenced as a number, and results were anonymized to minimize this effect. However, because no contamination was detected, the rate of bottle contamination could not be evaluated as a function of contact frequency with biological tissue.

The company's recommendation to store bottles of diagnostic drops for no longer than 28 days after opening applies to all ophthalmic solutions used by individuals and in uncontrolled environments. The results of this study were obtained in the controlled environment of a university clinic and would be difficult to apply to drops directly used by individuals and stored under different hygienic conditions and temperatures. Furthermore, the diagnostic drops analyzed in this study were only from Novartis Pharmaceuticals. Although the composition, containers, and preservation methods used by most companies are similar, it is not possible to affirm that our results would apply to diagnostic drops from other companies.

Inoculation of regular nutrient agar plates demonstrated a wide variety of bacterial and fungal cultures; however, it did not demonstrate the presence of viral strains, which can be implicated in certain types of ocular infections. Nevertheless, no bacterial, viral, or ocular fungal infections were reported by patients at University Vision Clinic who received diagnostic drops throughout the experimental period.

The study was performed in a university clinical setting with a low number of patients with a high risk of ocular infection such as post-operative patients (i.e., cataract and refractive surgery), patients with compromised cornea (i.e., trauma), or systemically or locally immunocompromised patients. Our results may not be applicable to these situations of special risk, and a conservative approach of not risking the use of diagnostics drops beyond the recommended time of approximately 1 month should be considered.

In-use shelf life of eye drops depends on the bottle volume and the frequency of use; it therefore varies from one practitioner to another but should rarely exceed 7 months. We were able to conduct our study over such a long period because the university setting is such that students examine fewer patients compared with regular practitioners. The frequency of use of anesthetic agents such as proparacaine is quite high in eye examinations, so it is unlikely that proparacaine drops are kept for as long as 7 months. This observation also applies to phenylephrine drops, which are stored in 5-mL bottles. This small volume means that the bottles are generally depleted before 7 months. Conversely, a full bottle of cyclopentolate (15 mL) can take several months to be completely used because cycloplegia examinations are not performed on a regular basis in most clinics. The results of this study therefore have a greater impact on this class of diagnostic drops.

Diagnostic Efficacy

During the implementation of the experimental design, it was envisaged to compare the effect of new and old diagnostic drops on the same group of participants at two different time points (1 week apart) and in a randomized order. However, it was preferred to evaluate the diagnostic effect between both eyes at the same time, as such a design was used in the literature.[17] Also, it was more reliable to compare the diagnostic effects of both new and old drops at the same time rather than a week apart, considering that dependent variables were subjective and can fluctuate on a day-to-day basis.

Our results show that the anesthetic, mydriatic, and cycloplegic efficacy of bottles opened for 7 months remains similar to that of newly opened eye drops. It should be noted that the dependent variables were used to measure diagnostic and nontherapeutic efficacy. These results can therefore not be applied to other therapeutic drops, which also are often generally stored in uncontrolled environments.

The anesthetic effect of 0.5% proparacaine bottles opened for 7 months was identical to that of new bottles after 30 seconds,

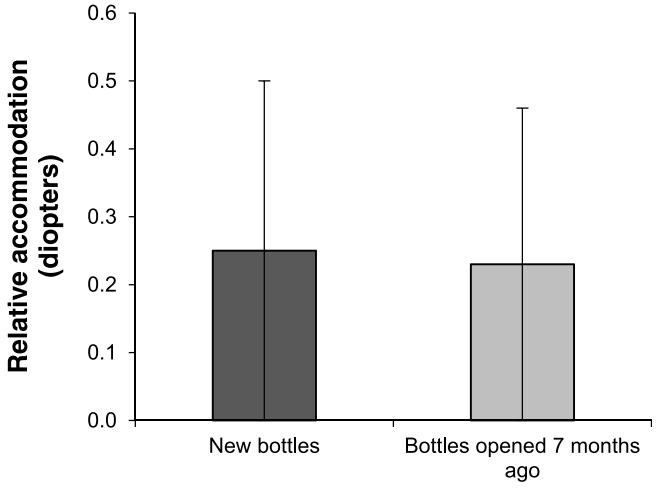

FIGURE 3. Relative accommodation after 40 minutes. Cycloplegic effect: residual accommodating amplitude (in diopters) measured 40 minutes after the instillation of Cyclogyl drops of new and those opened for 7 months. The error bars represent the SE.

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suggesting a comparable speed of action. Differences in corneal sensitivity at 5 and 10 minutes after the instillation were not significant, suggesting a comparable anesthetic effect between drops opened for 7 months and new ones. The maximal duration of the anesthetic effect of 0.5% proparacaine drops was 10.7 minutes; thus, corneal sensitivity was not measured after this time.[18]

A study by Steinmann et al.[19] found that 87% of persons dilated with a 1% tropicamide drop had a pupillary diameter of greater than 4 mm after 15 minutes. This diameter is sufficient, according to the authors, for an ocular fundus screening examination. However, the maximal effect is achieved after 30 minutes. Our results did not show a significant difference in relative pupillary dilatation between the old and new drops at 20 and 30 minutes after instillation. These results suggest that pupillary dilatation speed and mydriatic efficacy are comparable between new bottles of 1% tropicamide and 2.5% phenylephrine and those opened for 7 months.

A study conducted in 2016 by Laojaroenwanit et al.[20] showed that the maximal cycloplegic effect after the instillation of a drop of 1% cyclopentolate was obtained after 40 minutes for 90% of the patients. Our results do not show a significant difference in relative accommodation between the old and new drops 40 minutes after instillation, suggesting that 1% cyclopentolate retains its cycloplegic efficacy after 7 months of opening. This analysis was based on subjective measurements. Use of an open-field autorefractor would have provided objective measurements of relative accommodation. However, the drops were compared in a double-blind manner and between the right and left eyes of the participants, which allowed for the use of the same blurring criteria between both eyes.

CONCLUSIONS

This study shows that the risk of contamination of diagnostic eye drops remains low 7 months after opening and that their diagnostic efficacy is comparable with that of new drops. These findings apply to diagnostic drops used in a controlled clinical setting but cannot be applied to drops used by patients in an uncontrolled environment.

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REFERENCES

1. Kim MS, Choi CY, Kim JM, et al. Microbial Contamination of Multiply Used Preservative-free Artificial Tears Packed in Reclosable Containers. Br J Ophthalmol 2008;92:1518–21.

2. Marple B, Roland P, Benninger M. Safety Review of Benzalkonium Chloride Used as a Preservative in Intranasal Solutions: An Overview of Conflicting Data and Opinions. Otolaryngol Head Neck Surg 2004; 130:131–41.

3. Baudouin C, Labbe A, Liang H, et al. Preservatives in Eyedrops: The Good, the Bad and the Ugly. Prog Retin Eye Res 2010;29:312–34.

4. Kim MS, Kim HK, Kim JM, et al. Comparison of Contamination Rates between Preserved and Preservative-free Fluoroquinolone Eyedrops. Graefes Arch Clin Exp Ophthalmol 2013;251:817–24.

5. The Society: New Guidance on Use of Eye Preparations. Pharm J 2001. Available at: http://www.pharmaceutical-journal.com/the-society-new-guidance-on-use-of-eye-preparations/20004917.article. Accessed March 5, 2018.

6. Livingstone DJ, Hanlon GW, Dyke S. Evaluation of an Extended Period of Use for Preserved Eye Drops in Hospital Practice. Br J Ophthalmol 1998;82:473–5.

7. Feghhi M, Mahmoudabadi AZ, Mehdinejad M. Evaluation of Fungal and Bacterial Contaminations of Patient-used Ocular Drops. Med Mycol 2008;46:17–21.

8. Clark PJ, Ong B, Stanley CB. Contamination of Diagnostic Ophthalmic Solutions in Primary Eye Care Settings. Mil Med 1997;162:501–6.

9. Betbeze CM, Stiles J, Krohne SG. Assessment of Bacterial Contamination of Three Multidose Ophthalmic Solutions. Vet Ophthalmol 2007;10:81–3.

10. Nentwich MM, Kollmann KH, Meshack J, et al. Microbial Contamination of Multi-use Ophthalmic Solutions in Kenya. Br J Ophthalmol 2007;91:1265–8.

11. Hovding G, Sjursen H. Bacterial Contamination of Drops and Dropper Tips of In-use Multidose Eye Drop Bottles. Acta Ophthalmol 1982;60:213–22.

12. U.S. National Institutes of Health (NIH), National Library of Science, DAILYMED. Alcaine: Proparacaine Hydrochloride Solution/Drops. 2011. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?Setid=0c0fa0bf-977d-4539-b8dc-54c187c5b094. Accessed March 5, 2018.

13. Alcon. Mydriacyl Monography. 2004. Available at: http://ecatalog.alcon.com/PI/Mydriacyl_us_en.pdf. Accessed March 5, 2018.

14. NeurOptics. Vip-300 Pupillometer. 2016. Available at: https://neuroptics.com/wp-content/uploads/2017/08/VIP-300-IFU_Rev-C-v4-email.pdf. Accessed July 17, 2018.

15. Lovasik JV. Pharmacokinetics of Topically Applied Cyclopentolate HCl and Tropicamide. Am J Optom Physiol Opt 1986;63:787–803.

16. Hanley JA, Lippman-Hand A. If Nothing Goes Wrong, Is Everything all Right? Interpreting Zero Numerators. JAMA 1983;249:1743–5.

17. Moshirfar M, Mifflin MD, McCaughey MV, et al. Prospective, Randomized, Contralateral Eye Comparison of Tetracaine and Proparacaine for Pain Control in Laser in Situ Keratomileusis and Photorefractive Keratectomy. Clin Ophthalmol 2014;8:1213–9.

18. Bartfield JM, Holmes TJ, Raccio-Robak N. A Comparison of Proparacaine and Tetracaine Eye Anesthetics. Acad Emerg Med 1994;1:364–7.

19. Steinmann WC, Millstein ME, Sinclair SH. Pupillary Dilation with Tropicamide 1% for Funduscopic Screening. A Study of Duration of Action. Ann Intern Med 1987;107:181–4.

20. Laojaroenwanit S, Layanun V, Praneeprachachon P, et al. Time of Maximum Cycloplegia After Instillation of Cyclopentolate 1% in Children with Brown Irises. Clin Ophthalmol 2016;10:897–902.

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