Title

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Journal

Ophthalmology, 130(3)

ISSN

0161-6420

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Publication Date

2023-03-01

DOI

10.1016/j.ophtha.2022.10.016

Peer reviewed

HHS Public Access

Author manuscript

Ophthalmology. Author manuscript; available in PMC 2023 April 17.

Published in final edited form as:

Ophthalmology. 2023 March ; 130(3): 324–330. doi:10.1016/j.ophtha.2022.10.016.

Randomized Trial to Evaluate the Efficacy of the Nanodropper Device for Pupillary Dilation and Cycloplegia in Children

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Abstract

Purpose: We evaluated the noninferiority of 10.4 μl of eye drops eluted with a commercially available eye drop adapter, the Nanodropper (Nanodropper, Inc), on pupillary dilation and cycloplegia in children compared with the standard of care (SOC), 50 μl of eye drops.

Design: Prospective randomized trial.

Participants: Pediatric patients scheduled for routine pupillary dilation at the University of California, San Francisco, at the Pediatric Ophthalmology Clinic were enrolled. Each participant provided 1 eye for the intervention group (Nanodropper) and 1 eye for the control group (SOC).

Methods: Participants were randomized to receive small-volume dilating drops in 1 eye (Nanodropper) and SOC dilating drops in the other eye. Dilation was performed using 1 drop each of 1% cyclopentolate, 1% tropicamide, and 2.5% phenylephrine. Refraction and pupillometry were

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Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Presented at: American Association for Pediatric Ophthalmology and Strabismus Annual Meeting, March 2022, Scottsdale, Arizona.

HUMAN SUBJECTS: Human subjects were included in this study. This parallel-group randomized trial was approved by the University of California, San Francisco (UCSF) Institutional Review Board. Research protocols adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from parents and subject verbal assent was obtained.
No animal subjects were included in this study.

Supplemental material available at www.aaojournal.org.

obtained before and 30 minutes after dilation. A noninferiority analysis was performed to assess change from before to after dilation in spherical equivalent and in pupil constriction percentage and maximum pupil diameter after dilation.

Main Outcome Measures: Spherical equivalent, maximum pupil diameter, and pupil constriction percentage.

Results: One hundred eyes of 50 patients were included, with a mean ± standard deviation age of 9 ± 3 years. After controlling for baseline measurements, the spherical equivalent after dilation was 0.05 diopter (D) more (95% confidence interval [CI], −0.28 to 0.37 D) in the Nanodropper arm, which did not achieve noninferiority. Maximum pupil diameter after dilation was lower in the Nanodropper group (mean, −0.01 mm; 95% CI, −0.20 to −0.03), which did achieve noninferiority. Constriction percentage after dilation was 0.57 percentage points more (95% CI, −1.38 to 2.51 percentage points) in the Nanodropper group, which did not achieve noninferiority.

Conclusions: Administration of eye drops using a small-volume adaptor demonstrated similar efficacy to SOC in a pediatric population. Strict noninferiority was met only for pupillary dilation and not for cycloplegia or constriction percentage; however, the small differences in the effect of the Nanodropper versus SOC on all primary outcomes were not clinically significant. We conclude that small-volume eye drops have the potential to decrease unnecessary medical waste and medication toxicity while maintaining therapeutic effect.

Keywords

Cycloplegia; Dilation; Eye drops; Health care utilization

The human eye can absorb only 7 to 10 μl of fluid, yet the volume dispensed from commercially available eye dropper bottles is 30 to 50 μl.[1,2] This contributes to medical waste and problems with medication durability, in which patients run out of medication and are unable to obtain medication refills because of premature eye-drop bottle exhaustion.[3] Using small-volume eye drops could circumvent these issues. The efficacy of small-volume eye drops for dilation and cycloplegia has been supported by studies in infants and adults but not yet in pediatric patients.[4–7]

In addition to decreasing waste, larger eye-drop volumes may increase the likelihood of local and systemic adverse medication effects, especially because topical medications that reach the nasolacrimal duct and nasopharynx can be absorbed systemically through the mucosa, avoiding first-pass metabolism.[8,9] Major systemic side effects have been reported in children, including bradycardia, hypotension, and asthma attacks, after topical β-blocker use and anticholinergic symptoms and psychosis after topical cycloplegia.[10] Local side effects either resulting from the medication itself or medication preservatives also have been reported, including burning, infection, fluctuating visual acuity, hyperemia, conjunctival or eyelid edema, pruritus, and foreign body sensation.[11–14]

Instillation of a smaller-volume eye drop has numerous potential advantages, including prolonging the use of medication bottles, reducing waste, and minimizing systemic absorption and local toxicity. To date, no study has evaluated the efficacy of small-volume eye drops with the Nanodropper device in pediatric patients. The purpose of this study was

to evaluate the effectiveness of pediatric pupillary dilation and cycloplegia using a novel small-volume eye-drop adapter, the Nanodropper (Nanodropper, Inc), which administers 10.4 μl of eye drops. We hypothesized that small-volume eye drops will exhibit noninferior effects on pupillary dilation and cycloplegia compared with the standard of care (SOC).

Methods

This parallel-group randomized trial was approved by the University of California, San Francisco, Institutional Review Board. Research protocols adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all parents, and verbal assent from all participants was obtained. The trial was registered on ClinicalTrials.gov (identifier, NCT05274321). The intervention used was an eye-drop adaptor that attaches to conventional eye-drop bottles to elute small-volume eye drops. Use of this intervention was similar to the SOC because the same medications were used for pupillary dilation, except at a smaller volume.

Participants

Children 18 years of age or younger undergoing pupillary dilation as part of a routine eye examination at the University of California, San Francisco, at the Pediatric Ophthalmology Clinic between August 4, 2021, and November 19, 2021, were enrolled. Study activities and data collection also were conducted at this location. Exclusion criteria were inability to cooperate with study interventions (eye-drop administration, pupillometry, autorefraction); medication allergy to tropicamide, cyclopentolate, or phenylephrine; congenital or iatrogenic anterior segment abnormalities; anisocoria; or use of pupil-altering topical or systemic medications.

Pupillometry and Refraction

Pupil and refraction measurements were obtained directly before and 30 minutes after eye-drop administration. Handheld autorefraction was used to obtain spherical and cylindrical power and axis (Retinomax K plus 3; Lombart Instrument). Pupil measurements, including pupil constriction to a 180-μW flash, minimum and maximum pupil diameter, average constriction velocity, and latency of constriction, were obtained using a pupillometer (PLR-200; NeurOptics). Tonometry was performed immediately before and 30 minutes after dilation (IC100; Icare USA).

Randomization and Masking

Randomization was performed on a 1:1 ratio, stratified by participant (i.e., each participant was randomized to receive eye drops from a Nanodropper in either the right or left eye, and the other eye received SOC eye drops). A web-based random number generator was used to randomize either the right eye (odd number) or the left eye (even number) to receive eye drops with the Nanodropper. Three of the authors (C.B.H., B.W.K., and M.L.T.) generated the random allocation sequence, enrolled participants, and assigned participants to interventions. Participants and care providers were not informed which eye would receive the Nanodropper until after baseline measurements were completed. Outcome assessors were not masked to randomization allocation. Fifty-five participants (110 eyes)

were assigned randomly, 54 participants (108 eyes) received intended treatment (1 study dropout, 2 eyes), and 50 participants (100 eyes) were analyzed for the primary outcome after accounting for participants unable to cooperate with all measurements (4 patients, 8 eyes; Fig 1).

Pupillary Dilation

Pupillary dilation was performed with 1 drop of 1% cyclopentolate (Bausch & Lomb, Inc), followed by 1 drop of 1% tropicamide (Akorn, Inc), and finally 1 drop of 2.5% phenylephrine (Paragaron BioTeck, Inc). Eye-drop administration order was standardized as beginning with the right eye for each drop, regardless of which eye was randomized to receive eye drops via the Nanodropper. For eyes randomized to the small-volume eye dropper, the Nanodropper adaptor was secured on eye-drop bottles (Fig 2).

Outcomes

The 3 primary prespecified outcomes were (1) cycloplegia, defined as the change in spherical equivalent before and 30 minutes after dilation; (2) change in maximum pupillary diameter 30 minutes after dilation, measured by the pupillometer in dark lighting; and (3) change in pupillary constriction percentage from before and 30 minutes after dilation. All 3 coprimary outcomes were prespecified and, before analysis, were required to reach statistical significance to demonstrate noninferiority. Pupillary constriction percentage was calculated by the pupillometer in response to a 180-μW flash: (maximum – minimum) / maximum. Change in intraocular pressure before and after dilation was included as a secondary outcome.

Statistical Analysis

Sample size was determined based on a power calculation to reach significance for 1 outcome at $P = 0.05$. All data were entered and stored in Research Electronic Data Capture (Vanderbilt University) and were analyzed using Python, version 3.7 (Python Software Foundation). Change scores for each outcome were calculated by subtracting values after dilation from values before dilation for each eye; absolute between-eye differences then were calculated for each participant by subtracting the SOC change score from the Nanodropper change score. The confidence interval (CI) was set at 95%. Analysis of covariance was performed on each outcome after dilation with measurements before dilation, treatment arms were used as predictor variables, and participants were treated as a random effect variable. The noninferiority margin was determined by taking 10% of the SOC change score. Noninferiority was determined for each outcome if the noninferiority margin did not overlap with the regression coefficient's 95% CI. Wald P values were calculated by testing whether the regression coefficient met or exceeded the noninferiority margin. Given the 3 primary outcomes, the significance level was set to $P = 0.0167$ for each outcome. Eyes for each patient were analyzed separately.

Subgroups

Refractive error subgroups were classified by cycloplegic spherical equivalent (SE): myopia (SE, < 0 diopters [D]), emmetropia (SE, 0 D), or hyperopia (SE, > 0 D). Iris color subgroups

were classified into either dark (parent-reported brown or hazel irides) or light (parent-reported blue or green irides). Subgroups consisted of unpaired data because individuals differed in refractive error grouping between eyes.

Results

One hundred eyes of 50 participants were enrolled. Because each patient contributed 1 control and 1 intervention eye, 50 eyes were in the Nanodropper group, and 50 were in the SOC group. Mean ± standard deviation age was 9.12 ± 3.39 years, and 58% of patients (29 patients) were male. Most had dark irides (84% [42 eyes]). Baseline characteristics including SE were balanced between groups (Table 1).

Mean values from the measurements obtained before and after dilation are shown in Table 2. After dilation, the SE increased by 1.76 D (95% CI, 1.11–2.41 D) in the SOC group and 1.73 D (95% CI, 1.11–2.36 D) in the Nanodropper group. The maximum pupil diameter increased by 1.95 mm (95% CI, 1.77–2.13 mm) in the SOC group and 1.77 mm (95% CI, 1.58–1.96 mm) in the Nanodropper group after dilation. The constriction percentage reduced by 24.76 percentage points (95% CI, −27.53 to −22.00 percentage points) in the SOC group and 24.61 percentage points (95% CI, −26.72 to −22.49 percentage points) in the Nanodropper group after dilation. Study staff monitored participants for adverse effects including transient seizure, psychosis, subjective fever, and subjective tachycardia. No adverse effects were reported in either group.

Primary analyses are shown in Table 3, and the between-group differences are depicted with the prespecified noninferiority margins in Figure 3. The SE after dilation was 0.05 D more (95% CI, −0.28 to 0.37 D) in the Nanodropper arm than the SOC arm after controlling for baseline measurements, which did not meet criteria for noninferiority against a noninferiority margin of 0.18 D. The maximum pupil diameter after dilation was lower in the Nanodropper group than the SOC group after adjusting for baseline (mean, −0.01 mm; 95% CI, −0.20 to −0.03 mm), which did meet the noninferiority criteria judged against a noninferiority margin of −0.20 mm. The constriction percentage after dilation was 0.57 percentage points more (95% CI, −1.38 to 2.51 percentage points) in the Nanodropper group than the SOC group after adjusting for baseline, which did not meet the noninferiority criteria judged against a margin of 2.48%. Intraocular pressure after dilation, a secondary outcome, was lower in the Nanodropper group than the SOC group after adjusting for baseline (mean, −0.71 mmHg; 95% CI, −1.43 to −0.01 mmHg) and did not meet the noninferiority criteria, given a margin of −0.11 mmHg. When accounting for multiplicity, none of the outcomes met the $P = 0.0167$ threshold for statistical significance (Table 3). Subgroup analysis showed that the between-group differences were similar for each of the primary outcomes, regardless of refractive error or iris color (Table S1, available at www.aaojournal.org).

Discussion

Two of the most common uses of eye drops in the ophthalmology clinical setting are for mydriasis and cycloplegia. In this study, we found that using 10.4 μl of eye drops achieved

similar levels of pupillary dilation, cycloplegia, and pupillary constriction percentage compared with standard-volume eye drops in a cohort of children with a range of refractive errors. We found a noninferior effect of small-volume eye drops on the maximum pupil diameter, although SE, constriction percentage, and intraocular pressure did not meet strict noninferiority criteria. However, the small differences between SOC and Nanodropper treatment on SE after dilation, a measurement of the child's accommodation, were not statistically or clinically significant. The same was seen when comparing pupil constriction percentage and intraocular pressure between groups. We determined a clinically significant cutoff of the maximum pupil diameter to be 6.0 mm or less, a previously reported adequate diameter for eye examination.[15] All eyes in both groups of this study achieved > 6.0 mm of pupil dilation.

Numerous studies have explored the relationship between eye-drop volume and drug efficacy for adults and infants.[4–7] Dating back to 1997, Elibol et al[4] showed similar effects on pupillary diameter changes between small-volume and standard-volume drops in infants. Pasquale et al in 2018 showed significant intraocular pressure reduction for adults with glaucoma who used small-volume drops of latanoprost. Taken together, these studies demonstrate central findings that smaller eye drops cause fewer local eye symptoms and less severe systemic side effects than larger eye drops.[16] The present study is the first to support similar efficacy of eye drops administered with the Nanodropper device compared with standard-volume eye drops for pupillary dilation in pediatric patients and similar, but just shy of noninferior, effects on SE, pupil constriction percentage, and intraocular pressure after dilation (Fig 3).

The problem of eye dropper medication waste is compounded for those with difficulty instilling eye drops. One study showed that, for every 1 drop properly instilled by a patient, 7 drops are wasted during the instillation attempt.[1] Smaller-volume eye drops allow for greater administrative precision, which is particularly useful for pediatric patients who have difficulty with receiving eye drops.

Apart from efficacy, using smaller-volume eye drops has economic and health care system advantages. Recent work has highlighted the amount of medical waste generated from eye-drop use, particularly in settings with high degrees of regulation regarding multiuse bottles.[17] Similarly, survey data identified waste in the operating room (including dilating eye drops) as a major concern for ophthalmologists and other stakeholders.[18] On the patient level, many patients with glaucoma in particular face notoriously high costs of eye drops and frequently run into challenges at the end of each month when medications have been exhausted before an insurance authorization is allowed.[3,19] If equally effective to SOC, small-volume eye drops could result in cost savings to patients, health care providers, and the medical system.

This study has several limitations. We chose a non-inferiority margin of a loss of 10% of the treatment effect, which is more conservative than the 50% margin that has been recommended for some industry trials by the United States Food and Drug Administration.[20,21] Had a noninferiority margin of 50% been chosen, all 3 primary outcomes would meet criteria for noninferiority of the Nanodropper compared with SOC.

A strict noninferiority margin was chosen to ensure the quality of our conclusions, given that prior randomized controlled trials to establish a consistent noninferiority margin for this specific area of study have not been conducted. Study staff and participants were not masked to the intervention, although outcome measurements were obtained objectively using an autorefractor and pupillometer. Additionally, this cohort comprised predominantly children with dark irides, which is reflective of our patient demographic but could limit the generalizability of these results. Finally, although minimizing systemic side effects and local irritation are reasons to support the use of small-volume eye drops, we did not measure these effects in our study objectively.

Despite these limitations, these findings add to the knowledge that, as with adults and infants, small-volume eye drops are similar to SOC eye drops. Future studies could include an assessment of small-volume eye drops in patients with pupillary abnormalities or an assessment of the effect of multiple administrations of small-volume eye drops.

Conclusions

This study demonstrated similar efficacy of the Nanodropper compared with SOC on pupillary dilation and cycloplegia. We found noninferiority of the Nanodropper device with respect to pupil dilation but did not find noninferiority for cycloplegia. However, we determined that the small differences observed between groups on both dilation and cycloplegia were not clinically significant. Replacing standard eye drops with small-volume eye drops has the potential to decrease medical waste, to decrease local and systemic toxicity, and to extend the number of doses of diagnostic and therapeutic ocular medications for both physicians and patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Alejandra G. de Alba Campomanes, MD, MPH; Kristi Choy, OD; and Elise Harb, OD, PhD, for their assistance in referring patients to this study.

Supported in part by the National Eye Institute, National Institutes of Health, Bethesda, Maryland (grant nos.: EY002162 [Core Grant for Vision Research] and K12EY031372–03). The funding organization had no role in the design or conduct of this research. Nanodropper devices were provided by Nanodropper, Inc. who had no role in the design or conduct of this research.

Abbreviations and Acronyms:

CI	confidence interval
D	diopter
SE	spherical equivalent
SOC	standard of care

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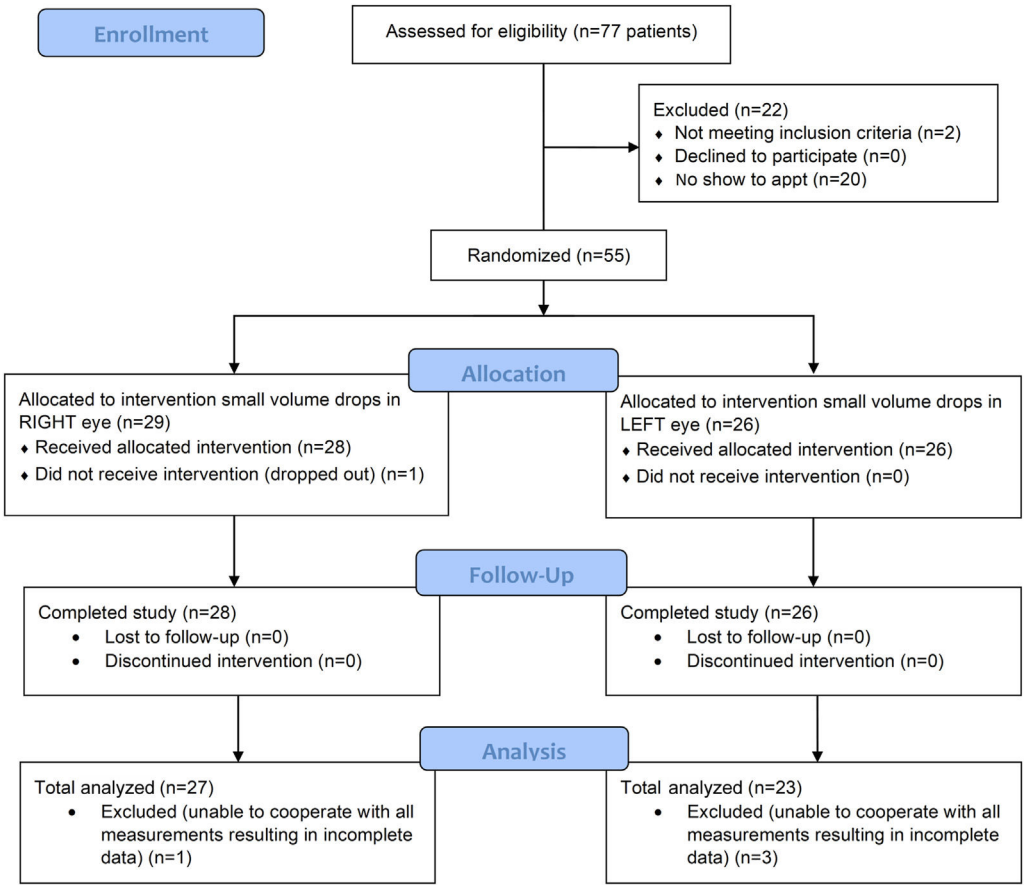

Figure 1.

Consolidated Standards of Reporting Trials diagram showing that, of the 77 patients assessed for eligibility, 55 patients were randomized to receive small-volume eye drops using the Nanodropper device in either the right or left eye. A total of 50 patients (100 eyes) were included in analysis, after excluding 5 patients who either did not receive the intervention (1 patient) or who were unable to cooperate with all study measurements and therefore did not have complete data (4 patients).

Figure 2.

Photograph showing that the Nanodropper adaptor (right bottle and right top; Nanodropper, Inc) comprises 3 parts: tip, base, and cap. The silicone tip tapers to a small-diameter opening to reduce drop volume and is secured to the existing bottle with the base, which screws onto the eye dropper over the original cap. The adaptor is attachable easily to most conventional eye-drop bottles by snapping the Nanodropper adaptor into place over the existing eye-drop bottle tip. A plastic cap is kept in place to protect the tip in between drop administrations.

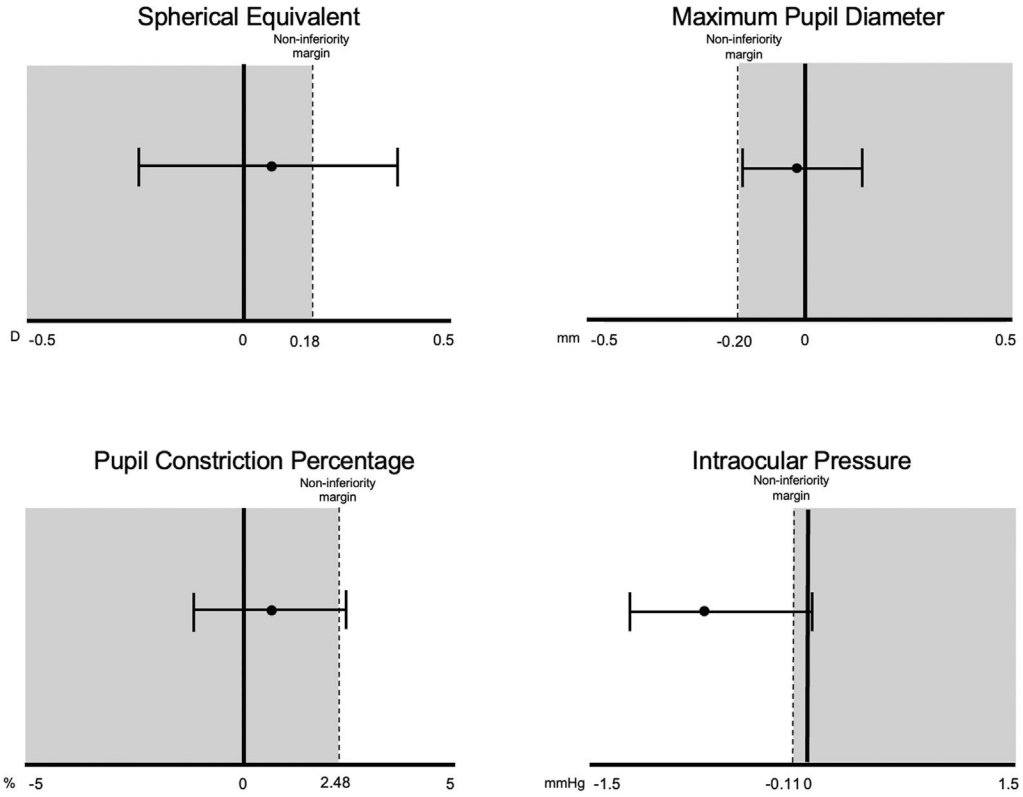

Figure 3.

Dot-and-whisker plots showing mean differences in after dilation measurements between the Nanodropper and standard of care (SOC) groups, adjusted for baseline. Dots and whiskers represent the mean difference and 95% confidence interval (CI) for each outcome. Positive values along the x-axis indicate higher measurements in the Nanodropper group; negative values indicate higher measurements in the SOC group. The areas of noninferiority are shaded grey; CIs would need to be completely within the shaded area to be considered noninferior. D = diopter.

Table 1.

Baseline Characteristics

Study Parameter	Nanodropper (n = 50 Eyes)	Standard of Care (n = 50 Eyes)
Noncycloplegic autorefraction Myopia *	42 (84)	42 (84)
Hyperopia †	8 (16)	8 (16)
SE, D	−2.28 ± 3.11	−2.62 ± 3.38
Maximum pupil diameter, mm	6.01 ± 0.73	5.95 ± 0.66
Constriction percentage, %	31.07 ± 5.37	30.44 ± 5.19
Tonometry, mmHg	18.13 ± 3.57	17.36 ± 3.90

D = diopter; SE = spherical equivalent. Data are presented as no. (%) or mean ± standard deviation unless otherwise indicated. Baseline metrics and demographics were similar across both groups for noncycloplegic autorefraction, SE, maximum pupil diameter, constriction percentage, and tonometry.

* Defined as SE of < 0 D.

† Defined as SE of ≥ 0 D.

Table 2.

Mean Nanodropper and Standard of Care Outcomes before and after Dilation witb Cbange Scores

Variable	Standard of Care			Nanodropper		
	Before Dilation	***After Dilation***	***Change Score***	***Before Dilation***	***After Dilation***	***Change Score***
Spherical equivalent, diopters	−2.62 (−3.59 to −1.65)	−0.86 (−1.75 to 0.03)	1.76 (1.11–2.41)	−2.28 (−3.17 to −1.39)	−0.55 (−1.43 to 0.34)	1.73 (1.11–2.36)
Maximum pupil diameter, mm	5.95 (5.76–6.14)	7.91 (7.72–8.10)	1.95 (1.77–2.13)	6.01 (5.80–6.22)	7.81 (7.61–8.01)	1.77 (1.58–1.96)
Constriction percentage	30.44 (28.95–31.93)	5.67 (3.21–8.14)	−24.76 (−27.53 to −22.00)	31.07 (29.53–32.61)	6.26 (4.35–8.17)	−24.61 (−26.72 to −22.49)
Intraocular pressure, mmHg	17.36 (16.24–18.48)	18.42 (17.31–19.53)	1.06 (−0.08 to 2.20)	18.13 (17.11–19.16)	17.96 (16.84–19.08)	−0.17 (−1.28 to 0.93)

Data are presented as mean (95% confidence interval).

Table 3.

Noninferiority Table

Variable	Regression Coefficient*	10% Noninferiority Margin (Based on Standard-of-Care Change Score)	Noninferiority P Value	Meets Criteria Based on Noninferiority Margin
Spherical equivalent, diopters	0.05 (−0.28 to 0.37)	0.18	0.22	No
Máximum pupil diameter, mm	−0.01 (−0.19 to −0.03)	−0.20	0.02	Yes
Constriction percentage	0.57 (−1.38 to 2.51)	2.48	0.03	No
Intraocular pressure, mmHg	−0.71 (−1.43 to −0.01)	−0.11	0.25	No

*Adjusted for baseline measurements and intereye correlation. Results are presented as regression coefficient (95% confidence interval).