Title: Randomized controlled non-inferiority trial evaluating the safety and efficacy of microdrops administered with the Nanodropper® in glaucoma patients

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Abbreviations and Acronyms:
IOP - intraocular pressure
SOC - standard of care.

Key Words: Glaucoma, ocular hypertension, eyedrops, microdrops, drug delivery, timolol maleate, IOP

Running head: Non-inferiority of Nanodropper for IOP Reduction

ABSTRACT

Objective or Purpose: Examine if 12.5 µL microdrops of 0.5% timolol maleate dispensed with the Nanodropper adaptor provide non-inferior intraocular pressure reduction compared to conventional, 28 µL drops in open-angle glaucoma and ocular hypertension patients.

Design: Prospective, non-inferiority, parallel, multicenter, single-masked RCT.

Subjects, Participants, and/or Controls: Treatment-naïve subjects that were recently diagnosed with OAG/OHT.

Methods, Intervention, or Testing: Subjects received one conventional drop or microdrop of 0.5% timolol maleate. The same treatment was administered to both eyes. We measured IOP, heart rate, and blood pressure at pre-drug baseline and 1, 2, 5, and 8 hours after timolol administration.

Main Outcome Measures: IOP was the primary outcome measure. Secondary outcomes were resting heart rate (HR), systolic blood pressure (sBP), and diastolic BP (dBP).

Results: Microdrops of timolol administered with Nanodropper are safer than and as efficacious as conventional drops.

Conclusions: Nanodropper-mediated microdrops of timolol provide comparable IOP reduction and reduce cardiovascular adverse effects compared to conventional drops though clinical

non-inferiority could not be established. Decreasing eyedrop volume and thereby extending bottle life with the Nanodropper may help glaucoma patients overcome several adherence barriers to therapy including medication cost and adverse events.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide.[1] Reducing intraocular pressure (IOP) has been shown to delay the onset and/or progression of this disease and is the only modifiable risk factor. IOP-lowering topical eyedrop medications are typically first-line therapies and are used throughout the course of this lifelong disease.[2] Consistent administration is important, as glaucoma patients who are less than 80% adherent are significantly more likely than adherent patients to have poor health outcomes (i.e., more severe visual field defects).[3,4] Unfortunately, reported rates of adherence to glaucoma medications range from 20-70%.[5,6] There are several known barriers to adherence including but not limited to forgetfulness, physical limitations, frequency of dosing and number of medications, inability to visualize the dropper tip, inability to identify the correct bottle, medication side effects, inadequate education regarding the use of eyedrops, trouble obtaining medications, and medication cost. Although these challenges are often discussed within the context of glaucoma management, they are not exclusive to IOP-lowering medications and can be more broadly applicable to all topical ophthalmics used to manage acute and chronic eye conditions alike, including post-operative eyedrops and over the counter eyedrops.

Many barriers to adherence stem from challenges with self-administering eyedrops. One study found that only 3% of subjects evaluated in a primary care setting exhibited correct eyedrop instillation technique,[7] and a review determined that for every drop that glaucoma patients successfully administer, seven drops are wasted.[8] Moreover, 25% of glaucoma patients report that they run out of their medication much earlier than expected, citing the following reasons:

more than one drop comes out of the bottle, the drops are too large or inconsistently sized, and not being able to see the bottle tip and/or hold the bottle steady.[9]

Several of the issues patients experience with self-administering eyedrops can be attributed to aspects of bottle design. Efforts to address these adherence barriers include the development and use of nose-pivoted drop delivery devices and other instillation aids that help with aiming and squeezing,[10,11] respectively, as well as providing patient education on proper eyedrop instillation techniques.[12] Although these solutions have been demonstrated to help patients administer eyedrops, they do not address an additional aspect of bottle design that can significantly impact patient adherence—the size of the drops. Importantly, the human eye can only absorb 7-10 µL of exogenous fluid,[13] yet most glaucoma medication bottles dispense drops that range from 30-60 µL.[14]

Importantly, the incidence and severity of both local and systemic side effects have been shown to be drop size dependent. When eyedrops are administered, a substantial fraction of the medication is drained by the nasolacrimal ducts at a volume-dependent rate and absorbed systemically through the nasal mucosa.[15] The medication avoids first-pass metabolism to deliver heightened pharmacologic effects on the rest of the body. [16–19] For example, IOP-lowering topical beta-blockers can cause cardiovascular depression including decreased heart rate (HR), decreased blood pressure (BP), and irregular pulse.[20,21] This can lead to the onset or exacerbation of cardiopulmonary pathologies that may require emergency care and hospitalization.[22]

Smaller eyedrops, or microdrops, have previously been posited as part of a solution to the aforementioned adherence barriers. A considerable body of clinical research supports that microdrops are as safe and efficacious as conventional drops.[23-25] Despite this longstanding knowledge, it wasn't until recently that a solution to oversized drops became commercially

available. The Nanodropper adaptor is an eyedrop bottle adaptor that creates microdrops by coupling to the existing (OEM) eyedrop bottle. The adaptor has been clinically validated: A study published in 2022 found that microdrops delivered with the Nanodropper provided non-inferior mydriasis relative to conventional drops in a pediatric population.[26]

Here, we sought to evaluate the use of Nanodropper with 0.5% topical timolol maleate. Although timolol's documented effects on the cardiovascular system limits its utility compared to safer topical alternatives, its IOP-lowering efficacy cements its status as a foundational treatment option for glaucoma.

The goal of the current non-inferiority randomized controlled trial was to determine if 12.5 µL microdrops of 0.5% timolol maleate administered with the Nanodropper adaptor improved timolol's safety profile by limiting systemic absorption while maintaining IOP-lowering efficacy.

MATERIALS & METHODS

Subjects, screening, and enrollment

We performed a randomized, parallel-group, single-masked, active-controlled, non-inferiority trial, which was approved by the Aravind Eye Hospital Ethics Committees in Madurai and Pondicherry, India. Research protocols adhered to the tenets of the Declaration of Helsinki, and informed consent was obtained from all subjects. The trial was registered on clinicaltrials.gov (NCT05181046) with the registry title "Evaluation of Nanodropper-mediated Microdrops vs. Standard Drops of 0.5% Timolol Maleate in Glaucoma Patients".

We recruited Aravind Eye Care System patients aged 18 years and older with a recent diagnosis of primary open angle glaucoma (OAG), pseudoexfoliation glaucoma, pigmentary glaucoma, ocular hypertension (OHT), or corticosteroid-induced OHT who were not taking any ophthalmic medications (treatment-naïve) and for whom 0.5% timolol maleate was not

contraindicated. Inclusion criteria consisted of corrected Snellen visual acuity of 6/60 or better in each eye and baseline IOP between 21-45 mm Hg as assessed via Goldmann applanation tonometry. Exclusion criteria were being pregnant or nursing, medical history of cardiovascular, pulmonary, cerebrovascular, or chronic renal disease, borderline or uncontrolled systemic arterial hypertension; within 6 months of study enrollment: history of ocular trauma, infection, or uveitis; within 30 days of study enrollment: use of systemic α-agonist or β-blocker, received general anesthesia. Enrolled subjects attended a pre-study evaluation where we collected baseline medical and ocular histories and performed a comprehensive dilated slit lamp examination including gonioscopy.

NanodropperAdaptor

The Nanodropper adaptor (Nanodropper.Inc., Rochester, MN) is an FDA-listed, volume-reducing adaptor for eyedrop bottles. The adaptor is comprised of three pre-assembled, sterilized parts: the tip, base, and cap (**Figure 1**). The medical-grade silicone tip tapers to a small diameter opening to reduce drop volume and is secured to the OEM bottle with the base, which screws onto the eyedrop bottle where the OEM cap would attach. The integrity of the OEM bottle tip is not violated. Nanodropper comes with its own snap-fit cap to protect the tip from potential contamination. A recent study determined that Nanodropper reduced the mean drop volume of nine different topical eye medications by over 62%, from 39.8 ± 2.1 μL to 15.1 ± 1.0 μL (mean ± SEM).[27] This corresponds to a 2.6x increase in the number of drops that can be dispensed per bottle with the adaptor.

Procedures

We randomly assigned study participants 1:1 to receive a single dose per eye of ~28 μL conventional drops or ~12.5 μL Nanodropper-mediated microdrops of 0.5% timolol maleate

(AUROTIM, Aurolab, Madurai, India). On test day, between 8 AM – 9 AM, before timolol was administered, we obtained baseline measurements including IOP, resting HR, and resting BP. Following baseline measurements, at time = 0, a trained technician administered timolol in each eye without nasolacrimal occlusion or forced eyelid closure. It wasn't possible to mask participants or the technician who administered drops to the treatment being delivered. Only the trained professionals that measured IOP, HR, and BP were masked to the treatment received by the participant. IOP, resting HR, and resting BP measurements were repeated at 1 hour, 2 hours, 5 hours, and 8 hours after timolol administration. All measurements were collected after subjects had been sitting down for a minimum of five minutes. A Goldmann applanation tonometer (Model: AT 900, Haag-Streit, Köniz, Switzerland) was used for all IOP measurements, and an electronic blood pressure monitor (Model: HEM-8712, Omron, Omrom Healthcare Co., Ltd., Kyoto, Japan) was used to collect resting HR and BP measurements.

Outcome measures

The primary outcome is IOP (mm Hg). Secondary outcomes include change in IOP from baseline, percent change in IOP from baseline, change in resting BP (systolic and diastolic, mm Hg) and HR (bpm) from baseline and peak change in resting BP and HR.

Sample size and statistical analyses

A sample size of 400 subjects (200/group) was required to assess whether timolol microdrops confer non-inferior IOP-lowering relative to conventional drops at each time point. This sample size was calculated via simulation assuming a common standard deviation of 3.5 mm Hg[28] (for both treatment groups and at all time points), a correlation of 0.6 between IOP measurements taken from the same patient at any two time points, a power of 95%, a 2-sided Type I error rate of 0.05, and a non-inferiority margin of 1.5 mm Hg at all time points.

All analyses were pre-specified and described in detail in the statistical analysis plan. IOP analyses used data from the eye with a higher baseline IOP. If both eyes had the same baseline IOP, analyses were conducted with data collected from the right eye. The primary non-inferiority analysis of IOP used two-sided 95% confidence intervals (CIs) for the difference in mean IOP under timolol microdrops compared to conventional drops at 1, 2, 5, and 8 hours after timolol administration. If the upper limit of the two-sided 95% CI for the difference (microdrops - conventional drops) was within the non-inferiority margin of 1.5 mm Hg at all four time points, then microdrops will be considered clinically non-inferior to conventional drops. The two-sided 95% CIs for the mean differences were generated using a weighted least squares linear model for IOP as a function of treatment group (indicator for microdrops vs. conventional drops), time (three indicators for 2, 5, and 8 hours) and the interaction between treatment group and time, assuming an unstructured covariance model for the repeated IOP measures within the patients.[29] The planned non-inferiority analysis was conducted on patients with IOP measured at all 4 follow-up time points, i.e., the per-protocol sample; however, all randomized patients completed the 8-hour follow-up such that the primary analytic sample is the intention-to-treat (ITT) sample.

Secondary analyses of IOP compared the mean change and mean percent change in IOP from baseline across treatment groups at each time point. The model for change from baseline was constructed using a weighted least squares linear model for IOP as a function of treatment, time, and the interaction of treatment and time adjusting for baseline IOP, allowing for an unstructured within patient covariance model.[30,31] Comparisons of the mean percent change in IOP from baseline were fit using the same weighted least squares linear model specified for the primary analysis of IOP.

Analysis of the secondary safety variables, resting HR and BP, compared the mean change from baseline for these variables between treatments at each timepoint using the same

analyses described above for IOP changes from baseline. In addition, the mean peak change from baseline across the treatment groups was compared at each time point, where the peak change may occur at different timepoints across patients and treatment groups. Specifically, the smallest resting HR and BP post-baseline was regressed on treatment adjusting for the baseline resting HR or BP using linear regression models. All analyses of the safety variables followed the a priori planned ITT principle. With the exception of the test for non-inferiority, we considered p values < 0.05 to be statistically significant.

RESULTS

Subject demographics and baseline characteristics

We identified 473 eligible subjects for this study. A total of 49 eligible subjects declined to participate. We therefore enrolled and randomized a total of 424 subjects with diagnosed glaucoma (POAG, pseudoexfoliation glaucoma, pigmentary glaucoma) or OHT in this study. Two hundred and ten subjects received conventional drops and 214 subjects received microdrops of 0.5% timolol maleate delivered with the Nanodropper. We included 419 subjects in the analysis (207 conventional drops subjects and 212 microdrops subjects) after excluding subjects whose baseline IOPs were less than 21 mm Hg (n = 3) and subjects for which data was missing due to misplacing the case report forms (n = 2) (**Figure 2**). Subject demographics and baseline characteristics can be found in **Table 1**.

IOP

Timolol's IOP-lowering efficacy was volume-independent, as both conventional drops and microdrops of timolol significantly decreased IOP at all timepoints relative to pre-drug baseline (**Figure 3**, **Table 2**). The largest mean IOP reduction relative to baseline occurred at hour 5 in both groups. Here, delivery of conventional drops of timolol decreased IOP by 8.53 mm Hg (95% CI: -9.15 to -7.90 mm Hg) relative to baseline, from 27.24 ± 4.61 mm Hg to 18.71 ± 4.79 mm Hg (**Table 2**; mean ± SD), and timolol microdrops reduced IOP by 7.78 mm Hg (95% CI: -

8.40 to -7.17 mm Hg), from 27.21 ± 4.37 mm Hg to 19.42 ± 4.24 mm Hg (mean ± SD; **Table 2**). The mean IOP decreases from baseline at hour 5 correspond to mean percentage decreases of 30.91% (95% CI: -32.95 to -28.88%) and 27.97% (95% CI: -29.89 to -26.05%) in the conventional drops and microdrops groups, respectively (**Table 2**). Hour 5 is also when the largest between-group difference in mean IOP observed in this study of 0.71 mm Hg (95% CI: -0.15 to 1.58 mm Hg) occurred (**Table 2**).

To meet pre-specified criteria for non-inferiority, IOP under timolol microdrops needed to be non-inferior to IOP under conventional drops at all four timepoints. Our results met non-inferiority criteria at hours 1, 2, and 8 but not at hour 5, where the upper limit of the 95% CI for the difference in mean IOP comparing timolol microdrops to conventional drops exceeded our non-inferiority margin of 1.5 mm Hg by 0.08 mm Hg (**Table 2**). Importantly, between-group comparisons of mean IOP and mean IOP decrease from baseline did not reach statistical significance at any timepoint (**Table 2**).

Cardiovascular effects

Conventional drops and microdrops of timolol significantly decreased sBP compared to baseline at hours 1, 2, and 5 but not at hour 8 (**Table 3**). The percentage decrease in sBP from baseline was significant in both groups at hours 1 and 2 but not at hours 5 and 8 (**Supplemental Figure 1A, Table 3**). Compared to baseline sBPs in the conventional drops and microdrops groups of 137.38 ± 19.95 mm Hg and 139.41 ± 20.76 mm Hg (mean ± SD), respectively, the largest sBP decreases (i.e., lowest sBPs) observed in this study were 126.93 ± 18.58 mm Hg in the conventional drops group and 128.27 ± 18.13 mm Hg in the microdrops group (mean ± SD; **Table 3**). There were not significant between-group differences in sBP decrease or percentage decrease at any timepoint (**Table 3**).

Conventional drops and microdrops of timolol significantly decreased dBP compared to baseline at hour 2 but not at hours 1, 5, and 8 (**Table 4**). The percentage decrease in dBP from baseline was significant in the microdrops group at hours 2 and 5 but not at hours 1 and 8 (**Supplemental Figure 1B, Table 4**). Conventional drops of timolol didn't significantly affect the percent decrease in dBP from baseline at any timepoint (**Table 4**). Compared to baseline dBPs in the conventional drops and microdrops groups of 81.73 ± 10.83 mm Hg and 84.12 ± 11.14 mm Hg (mean ± SD), respectively, the largest dBP decreases (i.e., lowest dBPs) observed in this study were 75.19 ± 10.82 mm Hg in the conventional drops group and 76.45 ± 10.79 mm Hg in the microdrops group (mean ± SD; **Table 4**). There were not significant between-group differences in dBP decrease or percentage decrease at any post-baseline timepoint (**Table 4**).

Both conventional drops and microdrops of timolol significantly decreased HR relative to pre-drug baseline at all timepoints (**Figure 4**, **Table 5**). The HR percentage decrease from baseline was significant in both groups at all timepoints barring hour 1 in the microdrops group (**Table 5**). The largest within-group resting HR decrease from baseline occurred at hour 2 (**Table 5**). Here, timolol conventional drops and microdrops decreased resting HR relative to baseline by 6.70 bpm (95% CI: -8.01 to -5.39 bpm) and 3.68 bpm (95% CI: -5.23 to -2.13 bpm), respectively (**Table 5**). These decreases correspond to 7.36% (95% CI: -8.94 to -5.78%) and 3.37% (95% CI: -5.36 to -1.38%) decreases from baseline at hour 2 in the conventional drops and microdrops groups, respectively (**Table 5**). Compared to baseline HRs in the conventional drops and microdrops groups of 80.47 ± 13.77 bpm and 78.97 ± 14.17 bpm (mean ± SD), respectively, the largest HR decreases (i.e., lowest HRs) observed in this study were 69.92 ± 10.51 bpm in the conventional drops group and 70.37 ± 11.56 bpm in the microdrops group (mean ± SD; **Table 5**).

Interestingly, the between-group differences in HR decrease and percentage decrease from baseline were significant at all timepoints, revealing that subjects that received timolol

microdrops experienced significantly less of a decrease and percentage decrease in resting HR from baseline compared to subjects treated with conventional drops (**Table 5**). The largest between-group difference in HR decrease occurred at hour 2, where the conventional drops group's resting HR decrease from baseline was 3.02 bpm (95% CI: 1.00 to 5.04 bpm) greater than the microdrops group, which corresponds to a 3.99% (95% CI: 1.46 to 6.52%) greater HR reduction in the conventional drops group compared to the microdrops group (**Table 5**).

DISCUSSION

We conducted this study to assess the safety and efficacy of timolol maleate 0.5% microdrops dispensed with the Nanodropper adaptor. This is the first RCT to evaluate use of the volume-reducing Nanodropper adaptor with an IOP-lowering medication in a POAG/OHT patient population. We found that timolol microdrops and conventional drops did not significantly differ in their IOP-lowering efficacy, and timolol microdrops had a more favorable side effect profile as reflected by the attenuated HR reduction observed in subjects that received microdrops compared to conventional drops. Timolol microdrops met IOP non-inferiority criteria at 1, 2, and 8 hours after timolol administration. Despite not meeting NI criteria at hour 5, the between-group IOP difference at this timepoint was only 0.71 mm Hg. This was the largest between-group IOP difference observed in our study.

The IOP reduction we observed following administration of a single dose of 0.5% timolol compares favorably to similarly structured single-dose studies of 0.5% timolol conducted in healthy volunteers and OAG/OHT patients. Compared to pre-drug baseline, our study and other studies found that 0.5% timolol decreased IOP by 20.22 ± 14.17% (mean ± SD) and 17-31% at hour 1,[32–35] 28.56 ± 14.22% and 20-31% at hour 2,[32–34,36] 29.43 ± 14.58% and 28% at hour 5,[34]and 28.43 ± 14.20% and 35% at hour 8,[36]respectively.

We found variable treatment-related effects of timolol on resting sBP or dBP. Both treatments produced significant and transient decreases (i.e., didn't persist for the duration of the study) in resting BP compared to pre-drug baseline.

However, timolol microdrops caused significantly less of a reduction in resting HR rom baseline compared to conventional drops at all timepoints, suggesting systemic absorption of timolol was minimized in subjects that received microdrops compared to conventional drops. Previous single-dose, single-day 0.5% timolol studies in healthy volunteers and OAG/OHT patients found that whereas timolol significantly decreased HR, it had variable effects on BP compared to pre-drug baseline.[35,37,38] Montoro et al. and Korte et al. found that timolol didn't affect BP.[35,37] In contrast, Nordlund et al. observed a significant decrease in BP at two but not four hours after timolol administration.[38] Exploring volume-dependent effects of timolol on systemic adverse events, Montoro et al. showed that 50 µL and 30 µL of timolol significantly decreased resting HR relative to pre-drug baseline by 13.3% and 6.5%, respectively, suggesting that subjects that received smaller drops experienced comparatively less systemic absorption of the medication.[35]Overall, our results align with others in that we observed a volume-dependent, timolol-induced decrease in resting HR but not BP.

This study adds to the growing body of peer-reviewed literature supporting that microvolume delivery of topical ophthalmics can provide clinically meaningful therapeutic effects while limiting medication adverse effects and exposure to preservatives. Numerous studies in human subjects dating back to 1980 demonstrate that microdrops are as efficacious as conventional drops and can have more favorable local and systemic side effect profiles.[23-26,35,39-55]

We acknowledge several limitations of our study. The size of the conventional drops we used, 28 µL, is on the lower end of the 30-60 µL drop volume range for commercially available

glaucoma medications. Moreover, the 12.5 µL microdrops we administered exceeded the upper limit of the eye's functional reserve tear volume (i.e., absorption capacity for topical medications) of 10 µL,[56] possibly resulting in enhanced systemic absorption relative to what would have occurred using smaller microdrops. If we had utilized larger conventional drops and smaller microdrops, it is conceivable that the effect sizes for the endpoints we assessed would have been greater. We also didn't study the effect of timolol microdrops on other cardiopulmonary variables (e.g., modified Bruce Protocol and spirometry).

Despite these limitations, the results of our study provide compelling evidence supporting the Nanodropper as a clinical tool to limit systemic absorption and improve tolerability of topical ophthalmic medications. The microvolume delivery adaptor may have the added benefit of minimizing medication waste and resultant early bottle exhaustion. Future directions include an outpatient glaucoma study that evaluates long-term usability of the Nanodropper and the safety and efficacy of IOP-lowering microdrops compared to conventional drops. This study will allow for side effects, bottle exhaustion, medication cost, and adherence to be assessed and ultimately quantified.

The results of the current study were quite encouraging. Eyedrop size is an issue that has not been commercially addressed in the past. There are many ophthalmic conditions that require treatment and/or management with eyedrops, and we believe that the Nanodropper might offer potential solutions in the form of less waste and better safety profiles in various other ophthalmic subspecialties.

CONCLUSION

We found that delivering 12.5 µL 0.5% timolol maleate microdrops with the Nanodropper adaptor provided comparable IOP-lowering efficacy and potentially greater safety relative to the administration of conventional drops, the current standard of care. Overall, the results of this

study present the Nanodropper as a viable solution to oversized drop-induced nonadherence, and as a tool to optimize topical management of ophthalmic conditions.

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Legends :

Table 1 : Demographic and baseline clinical details of the study participants

Table 2: Mean IOP at baseline and post-administration of 0.5% timolol maleate conventional drops or microdrops

Table 3: Mean resting systolic BP at baseline and post-administration of 0.5% timolol Maleate conventional drops or microdrops

Table 4: Mean resting diastolic BP at baseline and post-administration of 0.5% timolol maleate conventional drops or microdrops

Table 5: Mean resting HR at baseline and post-administration of 0.5% timolol maleate conventional drops or microdrops

Figure 1: Image of Nanodropper instilled on a bottle

Figure 2: CONSORT flow diagram describing showing participant flow through each stage of the randomized controlled trial.

Figure 3. Conventional drops and microdrops of timolol maleate 0.5% reduce IOP in OAG/OHT patients relative to pre-drug baseline.

Figure 4. Conventional drops and microdrops of timolol maleate 0.5% reduce resting HR in OAG/OHT patients relative to pre-drug baseline

Supplemental Figure 1. Conventional drops and microdrops of timolol maleate 0.5% transiently reduce resting sBP and dBP in OAG/OHT patients relative to pre-drug baseline

Table 1. Study participants' demographic and baseline information[a]			
	Conventional drops (n = 207)	**Microdrops (n = 212)**	**All (n = 419)**
Age	57.46 ± 11.08	57.19 ± 11.06	57.32 ± 11.07
Sex, n (%)			
Female	74 (35.75)	79 (37.26)	153 (36.52)
Male	133 (64.25)	133 (62.74)	266 (63.48)
IOP	27.24 ± 4.61	27.21 ± 4.37	27.22 ± 4.48
HR	80.47 ± 13.77	78.97 ± 14.17	79.71 ± 13.97
Systolic BP	137.38 ± 19.95	139.41 ± 20.76	138.4 ± 20.36
Diastolic BP	81.73 ± 10.83	84.12 ± 11.14	82.94 ± 11.04
Systemic illness, n (%)			
Yes	109 (52.66)	93 (43.87)	202 (48.21)
No	98 (47.34)	119 (56.13)	217 (51.79)
Diagnosis, n (%)			
POAG	84 (40.58)	84 (39.62)	168 (40.1)
OHT	102 (49.28)	109 (51.42)	211 (50.36)
PXFG	17 (8.21)	19 (8.96)	36 (8.59)
Secondary glaucoma	2 (0.97)	-	2 (0.48)
Pigmentary glaucoma	1 (0.48)	-	1 (0.24)
Angle recession glaucoma	1 (0.48)	-	1 (0.24)

[a]Values are expressed as mean ± SD unless otherwise indicated.

Table 2. Mean IOP at baseline and post-administration of 0.5% timolol maleate conventional drops or microdrops				
	Conventional drops	Microdrops	Microdrops – Conventional drops	
	Mean ± SD or Mean (95% CI)	Mean ± SD or Mean (95% CI)	Mean difference (95% CI)	Met non-inferiority criteria
Baseline IOP, mm Hg	27.24 ± 4.61	27.21 ± 4.37	-0.03 (-0.89 to 0.83)	-
1 hour				
IOP, mm Hg	21.56 ± 5.39	21.76 ± 4.78	0.20 (-0.77 to 1.17)	Yes
IOP change from baseline, mm Hg	-5.68 (-6.24 to -5.11)*	-5.45 (-6.01 to -4.89)*	-0.23 (-0.56 to 1.03)	
Percentage change from baseline, %	-20.77 (-22.75 to -18.79)*	-19.68 (-21.57 to -17.80)*	1.09 (-1.62 to 3.80)	
2 hours				
IOP, mm Hg	19.14 ± 5.01	19.58 ± 4.50	0.43 (-0.48 to 1.34)	Yes
IOP change from baseline, mm Hg	-8.09 (-8.69 to -7.49)*	-7.63 (-8.22 to -7.04)*	-0.46 (-0.38 to 1.30)	
Percentage change from baseline, %	-29.52 (-31.51 to -27.53)*	-27.63 (-29.51 to -25.75)*	1.89 (-0.83 to 4.60)	
5 hours				
IOP, mm Hg	18.71 ± 4.79	19.42 ± 4.24	0.71 (-0.15 to 1.58)	No
IOP change from baseline, mm Hg	-8.53 (-9.15 to -7.90)*	-7.78 (-8.40 to -7.17)*	-0.75 (-0.13 to 1.61)	
Percentage change from baseline, %	-30.91 (-32.95 to -28.88)*	-27.97 (-29.89 to -26.05)*	2.94 (0.17 to 5.72)*	
8 hours				
IOP, mm Hg	19.17 ± 4.81	19.44 ± 3.83	0.27 (-0.56 to 1.10)	Yes
IOP change from baseline, mm Hg	-8.06 (-8.70 to -7.42)*	-7.76 (-8.36 to -7.16)*	-0.30 (-0.57 to 1.17)	
Percentage change from baseline, %	-29.11 (-31.15 to -27.07)*	-27.76 (-29.59 to -25.93)*	1.35 (-1.37 to 4.06)	

*$p<0.05$

Table 3. Mean resting systolic BP at baseline and post-administration of 0.5% timolol maleate conventional drops or microdrops			
Timepoint	Conventional drops	Microdrops	Microdrops – Conventional drops
	Mean ± SD or Mean (95% CI)	Mean ± SD or Mean (95% CI)	Mean difference (95% CI)
Baseline sBP, mm Hg	137.38 ± 19.95	139.41 ± 20.76	2.03 (-5.92 to 1.86)
1 hour			
sBP, mm Hg	134.72 ± 20.09	136.31 ± 19.81	1.58 (-5.39 to 2.23)
sBP change from baseline, mm Hg	-2.65 (-4.43 to -0.88)*	-3.10 (-4.93 to -1.27)*	-0.45 (-2.97 to 2.08)
Percentage change from baseline, %	-1.55 (-2.84 to -0.26)*	-1.74 (-3.00 to -0.47)*	-0.19 (-1.98 to 1.61)
2 hours			
sBP, mm Hg	132.54 ± 19.84	135.15 ± 19.73	2.62 (-6.40 to 1.17)
sBP change from baseline, mm Hg	-4.84 (-6.67 to -3.01)*	-4.25(-6.20 to -2.31)*	0.59 (-2.07 to 3.24)
Percentage change from baseline, %	-3.14 (-4.45 to -1.83)*	-2.49 (-3.85 to -1.13)*	0.65 (-1.22 to 2.52)
5 hours			
sBP, mm Hg	134.94 ± 21.07	136.82 ± 19.49	1.88 (-5.76 to 1.99)
sBP change from baseline, mm Hg	-2.44 (-4.47 to -0.41)*	-2.58 (-4.46 to -0.71)*	-0.15 (-2.88 to 2.59)
Percentage change from baseline, %	-1.37 (-2.84 to 0.10)	-1.28 (-2.64 to 0.08)	0.09 (-1.90 to 2.08)
8 hours			
sBP, mm Hg	137.11 ± 20.42	140.16 ± 20.60	3.05 (-6.97 to 0.87)
sBP change from baseline, mm Hg	-0.27 (-2.23 to 1.69)	0.75 (-1.26 to 2.76)	1.02 (-1.77 to 3.81)
Percentage change from baseline, %	0.26 (-1.18 to 1.70)	1.12 (-0.33 to 2.58)	0.86 (-1.17 to 2.89)
sBP smallest post-baseline value (peak change), mm Hg	126.93 ± 18.58	128.27 ± 18.13	-0.08 (-2.31 to 2.15)

*$p<0.05$

Table 4. Mean resting diastolic BP at baseline and post-administration of 0.5% timolol maleate conventional drops or microdrops			
Timepoint	Conventional drops	Microdrops	Microdrops – Conventional drops
	Mean ± SD or Mean (95% CI)	Mean ± SD or Mean (95% CI)	Mean difference (95% CI)
Baseline dBP, mm Hg	81.73 ± 10.83	84.12 ± 11.14	2.39 (0.27 to 4.49)*
1 hour			
dBP, mm Hg	81.79 ± 11.24	83.50 ± 12.06	1.72 (-3.95 to 0.51)
dBP change from baseline, mm Hg	0.05 (-1.11 to 1.22)	-0.62 (-1.92 to 0.68)	-0.67 (-2.40 to 1.06)
Percentage change from baseline, %	0.59 (-0.95 to 2.13)	-0.19 (-1.87 to 1.49)	-0.78 (-3.05 to 1.48)
2 hours			
dBP, mm Hg	80.26 ± 11.67	81.76 ± 11.38	1.50 (-3.70 to 0.70)
dBP change from baseline, mm Hg	-1.47 (-2.81 to -0.14)*	-2.36 (-3.85 to -0.88)*	-0.89 (-2.87 to 1.09)
Percentage change from baseline, %	-1.20 (-2.90 to 0.50)	-2.02 (-3.80 to -0.24)*	-0.83 (-3.27 to 1.61)
5 hours			
dBP, mm Hg	80.90 ± 11.78	82.70 ± 11.19	1.80 (95% CI)
dBP change from baseline, mm Hg	-0.84 (-2.28 to 0.61)	-1.42 (-2.78 to -0.06)*	-0.58 (-2.55 to 1.38)
Percentage change from baseline, %	-0.33 (-2.17 to 1.52)	-0.99 (-2.67 to 0.68)	-0.66 (-3.13 to 1.81)
8 hours			
dBP, mm Hg	81.59 ± 11.43	83.06 ± 11.44	1.46 (-3.65 to 0.72)
dBP change from baseline, mm Hg	-0.14 (-1.66 to 1.38)	-1.07 (-2.47 to 0.34)	-0.93 (-2.98 to 1.13)
Percentage change from baseline, %	0.69 (-1.26 to 2.63)	-0.54 (-2.29 to 1.21)	-1.23 (-3.83 to 1.36)
dBP smallest post-baseline value (peak change), mm Hg	75.19 ± 10.82	76.45 ± 10.79	-0.12 (-1.81 to 1.57)

*$p<0.05$

Table 5. Mean resting HR at baseline and post-administration of 0.5% timolol maleate conventional drops or microdrops			
Timepoint	Conventional drops	Microdrops	Microdrops – Conventional drops
	Mean ± SD or Mean (95% CI)	Mean ± SD or Mean (95% CI)	Mean difference (95% CI)
Baseline HR, bpm	80.47 ± 13.77	78.97 ± 14.17	-1.50 (-1.17 to 4.17)
1 hour			
HR, bpm	75.95 ± 11.95	76.82 ± 13.40	0.87 (-3.30 to 1.55)
HR change from baseline, bpm	-4.53 (-5.74 to -3.31)*	-2.15 (-3.59 to -0.71)*	2.38 (0.50 to 4.25)*
Percentage change from baseline, %	-4.83 (-6.29 to -3.37)*	-1.64 (-3.53 to 0.26)	3.19 (0.81 to 5.57)*
2 hours			
HR, bpm	73.77 ± 11.22	75.29 ± 12.79	1.52 (-3.82 to 0.78)
HR change from baseline, bpm	-6.70 (-8.01 to -5.39)*	-3.68 (-5.23 to -2.13)*	3.02 (1.00 to 5.04)*
Percentage change from baseline, %	-7.36 (-8.94 to -5.78)*	-3.37 (-5.36 to -1.38)*	3.99 (1.46 to 6.52)*
5 hours			
HR, bpm	75.25 ± 10.9	76.02 ± 12.85	0.77 (-3.05 to 1.51)
HR change from baseline, bpm	-5.22 (-6.62 to -3.83)*	-2.95 (-4.48 to -1.42)*	2.27 (0.22 to 4.33)*
Percentage change from baseline, %	-5.31 (-7.04 to -3.58)*	-2.44 (-4.42 to -0.46)*	2.87 (0.26 to 5.49)*
8 hours			
HR, bpm	74.81 ± 11.51	75.42 ± 11.89	0.61 (-2.84 to 1.63)
HR change from baseline, bpm	-5.67 (-7.05 to -4.28)*	-3.56 (-5.12 to -1.99)*	2.11 (0.04 to 4.19)*
Percentage change from baseline, %	-6.02 (-7.69 to -4.35)*	-3.01 (-5.05 to -0.97)*	3.00 (0.38 to 5.63)*
HR smallest post-baseline value (peak change), bpm	69.92 ± 10.51	70.37 ± 11.56	1.33 (-0.09 to 2.75)

*$p<0.05$

Figure 1. A Nanodropper adaptor installed on an OEM bottle. Since the Nanodropper replaces the OEM bottle's colored cap, colored labels are used by patients to identify their eyedrops based on the color-coding guidelines for topical ophthalmic medications established by the American Academy of Ophthalmology. The yellow labels pictured here are used for beta-blocker medications. The circular sticker with sun and moon icons serves as a dosing reminder for patients. This sticker depicts an example of BID

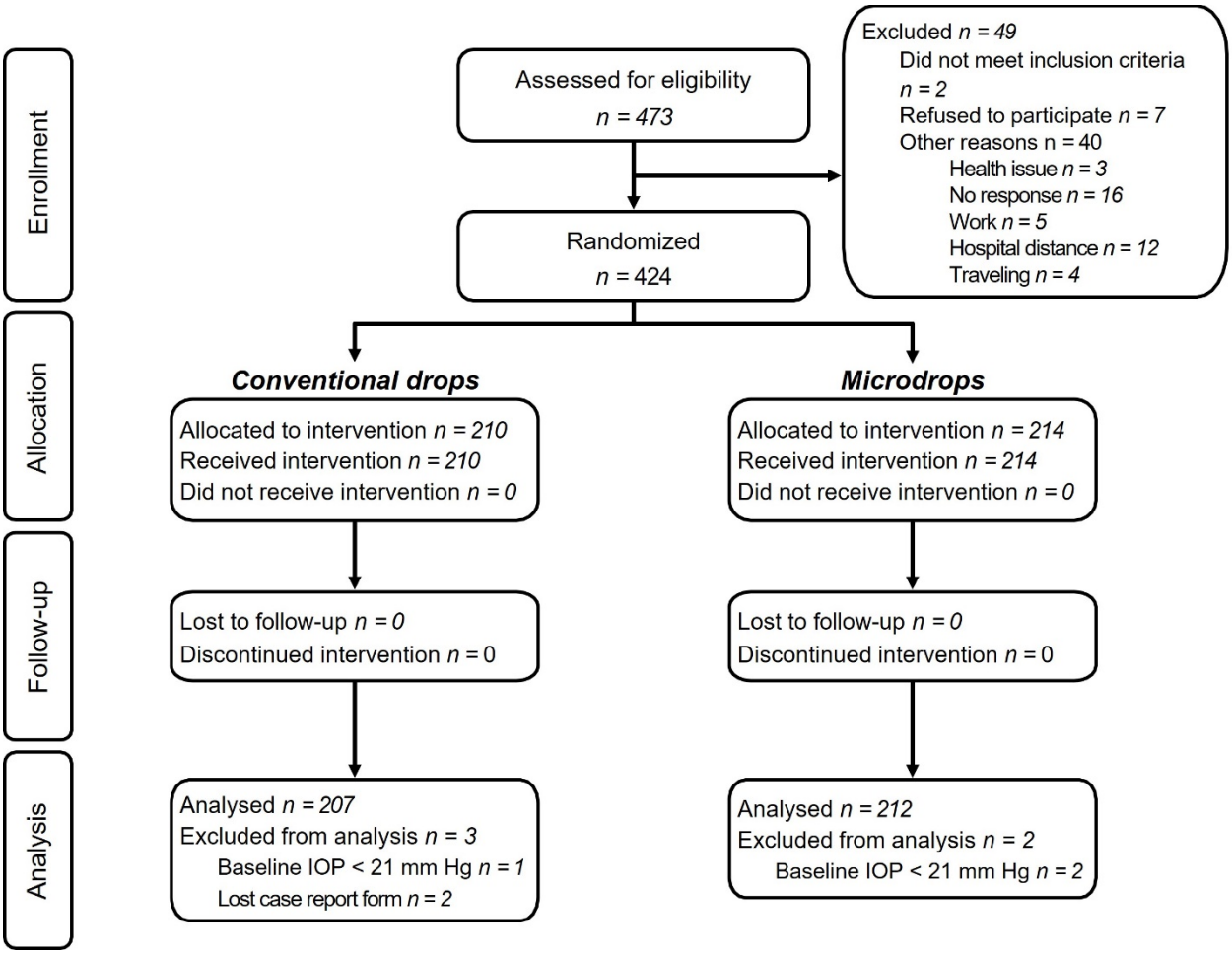


Figure 2. CONSORT flow diagram describing showing participant flow through each stage of the randomized controlled trial.

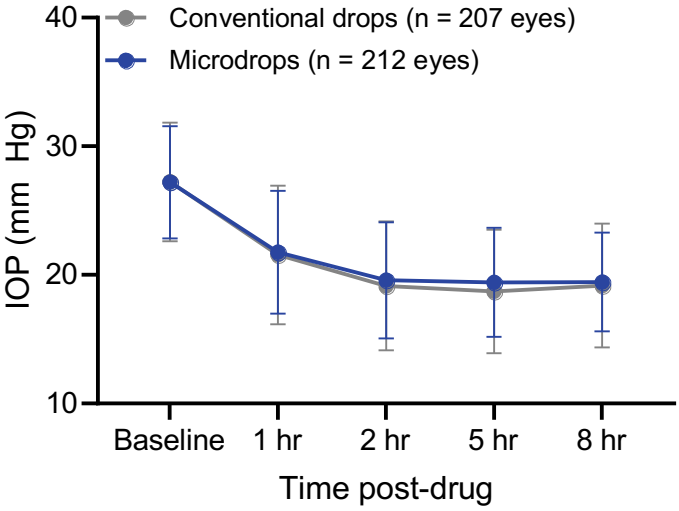


Figure 3. Conventional drops and microdrops of timolol maleate 0.5% reduce IOP in OAG/OHT patients relative to pre-drug baseline. Data graphed are mean ± SD.

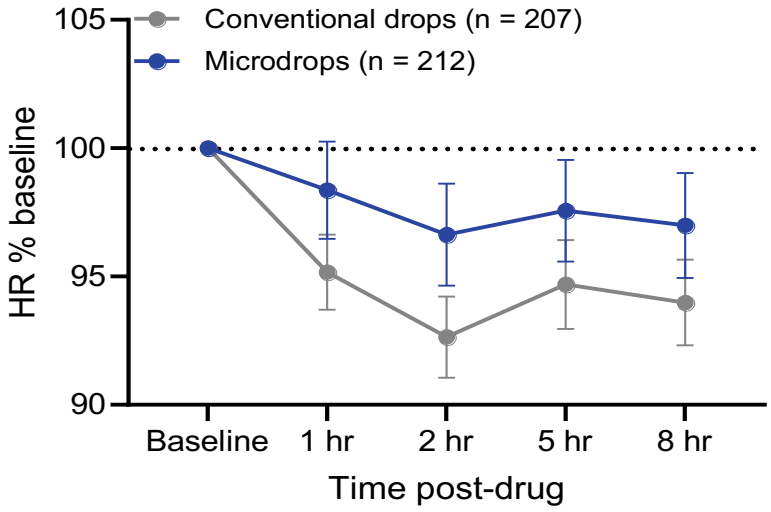
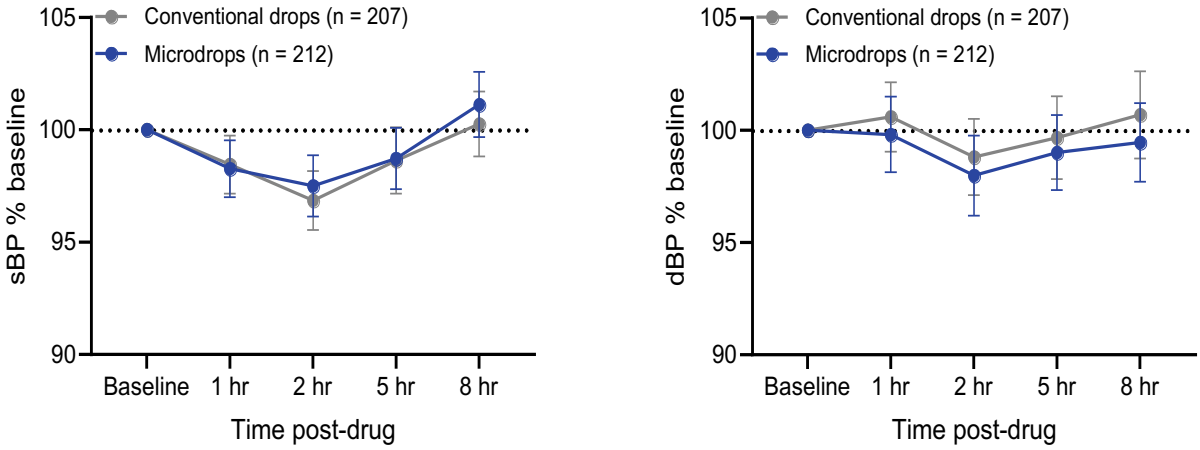


Figure 4. Conventional drops and microdrops of timolol maleate 0.5% reduce resting HR in OAG/OHT patients relative to pre-drug baseline. Data graphed are mean ± 95% CI



Supplemental Figure 1. Conventional drops and microdrops of timolol maleate 0.5% transiently reduce resting sBP and dBP in OAG/OHT patients relative to pre-drug baselineS. (A) sBP data represented as percent change from baseline, **(B)** dBP data represented as percent change from baseline. Data graphed are mean ± 95% CI