Efficacy and Safety of Pilocarpine Eye Drops Combinations for Treating Presbyopia in a Thai Population: A Randomized Crossover Trial

Thammanoon Surachatkumtonekul, M.D.[1,*], Pinpilai Jutasompakorn, M.D.[2], Anchalika Klinniyom, M. Pharm.[3], Wasawat Sermsripong, M.D.[1], Kiatthida Hokierti, M.D.[1], Prapasson Sangsre, M.Sc.[1], Ketchanya Rungsiri, BPH[1]

[1]Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [2]Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, [3]Pharmacy Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

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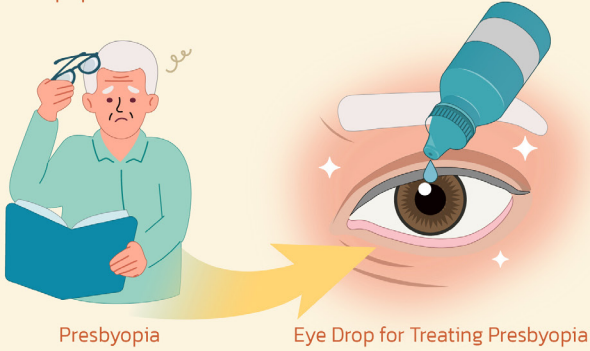
Objectives

This study aimed to assess the **effectiveness** and **side effects** of various concentrations of pilocarpine eye drops (1.5%, 1.25%, and 1%), with and without 0.1% brimonidine, in treating presbyopia in a Thai population.



Methods

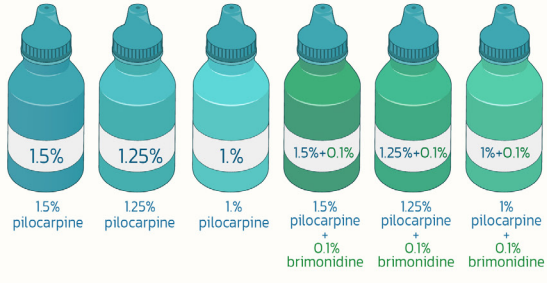
Prospective

Randomized

Double-blinded

Crossover

The participants ranged from 40 to 60 with presbyopia
Participants were randomly assigned to **6 groups** concentrations and type of eyedrops to receive :



Results

N=10 **30%** male, median age **46.5** years old with presbyopia, Refractive errors +/- 0.5D

1.25% pilocarpine | 1.25% pilocarpine + 0.1% brimonidine

showed significant **improvement in near visual acuity** at all time points (statistically significant with Bonferroni correction)

ADVERSE EFFECTS

More common with **1.5% pilocarpine + 0.1% brimonidine**, including **red eye**

Hours after application	Pre	2	4	6
1.25% pilocarpine	0.18 (0.18,0.3)	0.1 (0,0.18)*	0.1 (0,0.18)*	0.09 (0,0.18)*
1.25% pilocarpine + 0.1% brimonidine	0.18 (0.1,0.18)	0 (0,0.18)*	0 (0,0.18)*	0.05 (0,0.18)

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*Corresponding author: Thammanoon Surachatkumtonekul
E-mail: si95thim@gmail.com
Received 25 April 2024 Revised 8 July 2024 Accepted 8 July 2027
ORCID ID:http://orcid.org/0000-0002-0037-6863
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ABSTRACT

Objective: This study aimed to assess and compare the effectiveness and side effects of various concentrations of pilocarpine eye drops (1.5%, 1.25%, and 1%), with and without 0.1% brimonidine, in treating presbyopia, specifically in a Thai population.

Materials and Methods: A prospective, randomized, double-blinded, and crossover trial was conducted at Siriraj Hospital from August 2022 to April 2023. The study included emmetropic individuals aged 40 to 60 with presbyopia (near visual acuity not exceeding J1+) and refractive errors within +/- 0.5D. Ten subjects were randomly assigned to six groups for the different concentrations and type of eye drops using a computer-generated systematic randomization to receive 1.5%, 1.25%, and 1% pilocarpine with and without 0.1% brimonidine. And visual outcomes including visual acuity at distance and near were measured at 2, 4, and 6 hours post-application, with adverse effects monitored. Primary outcome was visual acuity at near after applied topical eye drops.

Results: Among the 10 participants (30% male, median age 46.5 years old), 1.25% pilocarpine and combined 1.25% pilocarpine + 0.1% brimonidine significantly improved near visual acuity at all time points (statistically significant with Bonferroni correction). Adverse effects, such as dry eye and irritation, were more common with 1.5% pilocarpine + 0.1% brimonidine.

Conclusion: In this preliminary study, 1.25% pilocarpine and 1.25% pilocarpine + 0.1% brimonidine showed promise in effectively treating presbyopia in the Thai study population, with acceptable side effect rates. Further research with larger sample sizes is needed to confirm these findings and provide more robust insights into presbyopia management in the Asian demographic.

Keywords: Presbyopia; pilocarpine; brimonidine; refractive errors (Siriraj Med J 2024; 76: 722-730)

INTRODUCTION

Presbyopia, a condition where the eye loses its ability to focus on near objects as people age, typically begins around the age of 40 years old, and is attributed to the crystalline lens becoming harder and losing its capacity to adjust power.[1-3] In 2015, an estimated 1.8 billion people worldwide experienced presbyopia, a number that may have potentially increased to 2.1 billion by 2020.[4,5] Notably, presbyopic individuals often report a lower quality of life, and uncorrected presbyopia is linked to productivity loss.[6-8]

Various treatment options exist for presbyopia, ranging from single reading glasses and bifocal or progressive glasses to monovision and multifocal contact lenses, refractive surgery, corneal inlays, and even 1.25% pilocarpine eye drops.[9,10]

Pilocarpine, which was discovered in 1874, has been employed in glaucoma treatment for well over a century now.[11,12] Its mechanism involves contracting the pupil and ciliary muscle, leading to pupil miosis and enhanced accommodation.[13,14] The resultant pupil miosis induces a pinhole effect, increasing the eye's depth of focus.[15] Brimonidine, an alpha-2 agonist affecting both the central and peripheral nervous systems, binds to the alpha-2 receptor and inhibits norepinephrine release. This action prevents pupil dilatation, resulting in a more miotic pupil in low light conditions.[16,17]

Despite various presbyopia treatments, the effectiveness of pilocarpine topical drugs in the darker iris pupil of the Asian population, potentially yielding distinct drug responses compared to Western populations should be kept in mind. Lyons JS et al. mentioned that pilocarpine has a potential to binds melanin in the iris and ciliary body, So we assumed that iris color may influence its desired response.[18]

Thus, this study aimed to evaluate the effectiveness and side effects of different concentrations of pilocarpine eye drops (1.5%, 1.25%, and 1%), both with and without 0.1% brimonidine, in treating a presbyopic Thai population.

MATERIALS AND METHODS

This study was performed according to the Consolidated Standards of Reporting Trials (CONSORT) guideline. The study protocol was reviewed and approved by the Siriraj Institutional Review Board. (SIRB), Siriraj Hospital, Mahidol University, Bangkok, Thailand. The IRB number was SI 611/2022. The registered number of the Thai clinical trials Registry was TCTR20220930004.

Prior to enrollment, all participants provided written informed consent. The sample size was determined using nQuery Advisor. Referring to a previous study[3], the mean near vision before treatment was J 8.6 with a standard deviation (SD) of 1.5, while at 2 hours post-treatment it was J 3.6 (SD=1), and the mean change was

5.9 (SD=0.8), with clinical significance set at 0.05 (type 1 error = 0.05, 2-sided) and power at 95%. Considering a 20% dropout rate, the total sample size for this study was established as 10 cases.

In defining the inclusion criteria, participants aged 40–60 years old with a distance visual acuity of 6/6 in both eyes were considered. All the participants demonstrated +/- 0.5 diopter (D) and astigmatism within 0.5 D as assessed by an autorefractor. To be classified as having presbyopia, participants were required to be unable to achieve J1+ with Rosenbaum near card visual acuity at 14 inches in each eye. The exclusion criteria were participants with myopia, hyperopia, or astigmatism exceeding 0.5 D. Individuals with other ophthalmic diseases impacting their vision, such as leukoma, cataract, glaucoma, and macular degeneration, were also excluded. Additionally, participants who had previously received drugs that could affect eye accommodation, such as psychotic drugs or anticholinergic drugs, were deemed ineligible for participation.

The withdrawal or termination criteria included participants experiencing serious side effects from the eye drops, such as severe conjunctivitis, keratitis, blurred vision, eye pain, or headache. Participants expressing an unwillingness to continue in the study were also subject to withdrawal.

Pilocarpine eye drops at concentrations of 1%, 1.25%, and 1.5% were prepared by diluting 2% pilocarpine eye drops with a balanced salt solution from the pharmacy unit at Siriraj Hospital. The 0.1% brimonidine eye drops used in the study were from AbbVie Inc. (USA). All the participants had a complete eye examination and their non-dominant eye was detected by the same ophthalmologist (TS). All the participants had tested visual acuity at distance and near which was performed by the same investigator, autorefraction, IOL Master 700 measure lens thickness and also pupil size, pre-instill the eye drop, and post-instill the eye drop at 2, 4 and 6 hours.

A crossover design was applied to our study because it provides an effective counterfactual comparison and helps eliminate baseline characteristic differences. This method is well-suited for research on presbyopia and the interventions using pilocarpine and brimonidine eye drops. Presbyopia, which is blurred near-sighted vision, is not curable with standard treatments. Both eyedrop medications have a rapid effect on accommodation. For these reasons, the crossover design was appropriate for this research.

Six different concentrations of the drug were utilized: 1% pilocarpine, 1.25% pilocarpine, 1.5% pilocarpine, 1% pilocarpine combined with 0.1% brimonidine, 1.25% pilocarpine combined with 0.1% brimonidine, and 1.5% pilocarpine combined with 0.1% brimonidine (separated bottle between pilocarpine and brimonidine). The initial concentration administered to each subject was randomized using the computer-generated systematic random sampling method, followed by the subsequent concentrations in the aforementioned order. Each bottle was administered 5 minutes apart. All participants would receive each eye drops (1%, 1.25%, 1.5% pilocarpine eye drops or combined with 0.1% brimonidine eye drop) in the same room and same luminance and had tested visual acuity at distance and near, autorefraction, pupil size, and lens thickness pre-instill the eye drop, and post-instill the eye drop at 2, 4 and 6 hours by each eye drops for 1 week apart.

The range of the duration of pilocarpine in USFDA was 3-12 hour and only one drop of each eye drops was then stopped to allow a 1-week wash-out period. After drug washout, randomly assigned to another group until the process was completed. Thus, the carryover effect was not established in this study.

Statistical analysis

Descriptive statistics were used to summarize the patients' demographic data and clinical characteristics, presented as frequencies and percentages for the categorical data. For the continuous data, the mean and standard deviation (SD) or median and interquartile range (IQR) were reported based on the data distribution. Visual acuity data were transformed into logarithm of the minimum angle of resolution (LogMAR) units when the participants could correctly read more than half of each line.

To compare the baseline characteristics with outcomes at 2, 4, and 6 hours after topical drug application within the same participant, statistical analyses was conducted. For non-normally distributed data, we applied the Wilcoxon signed-rank test; for normally distributed data, we used the paired t-test. The Bonferroni correction was incorporated to address multiple testing and adjust the p-value for statistical significance. All the analyses were performed using STATA version 16 (StataCorp, Lakeway, TX, USA).

RESULTS

In this study, we enrolled 10 emmetropic individuals, defined as having refractive errors within the range of +/- 0.5 D, with ages ranging from 41.8 to 50.5 years old (median 46.5), and all diagnosed with presbyopia (near visual acuity not reaching J1+). Comprehensive demographic data are provided in Table 1. Table 2

specifically outlines the participants' distance visual acuity, presented in LogMAR.

All ten subjects were randomly assigned to ten different sequences, as shown in Fig 1. Every subject completed the intended randomization protocol. All subjects were analyzed using intention-to-treat analysis, and no subject deviated from or dropped out of the protocol.

The comprehensive findings, covering visual acuity at near, pupil size, anterior chamber depth, lens thickness at pre-instillation and post-instillation points (2, 4, and 6 hours), and side effects were systematically documented, as shown in Tables 3-7.

Analyzing the data, we observed that visual acuity at distance (VAD) remained unchanged after instilling the eye drops across all groups involving the different treatments and combinations (Table 2). However, visual acuity at near (VAN) showed improvement in all groups after the instillation of eye drops, with clinical significance achieved at 2, 4, and 6 hours observed specifically in the 1.25% pilocarpine group and the 1.25% pilocarpine combined with 0.1% brimonidine group (Fig 2, Table 3). Notably, the VAN between the 1.25% pilocarpine and 1.25% pilocarpine combined with 0.1% brimonidine groups at all time points did not differ significantly.

Significant pupil constriction was found in all groups after the instillation of eye drops at all measured time points (Fig 3, Table 4). The anterior chamber depths were notably shallowed in all eye drops groups after instillation, with the exception of the 1% pilocarpine group (Fig 4, Table 5). Moreover, the lens thickness exhibited a significant increase in all combined groups (pilocarpine + brimonidine) (Fig 5, Table 6).

Adverse drug reactions, specifically eye discomfort, red eye, and blurred vision, were consistently observed in all eye drop groups, as evidenced in Table 7.

DISCUSSION

This investigation revealed that all concentrations of pilocarpine eye drops and the combination of pilocarpine and 0.1% brimonidine eye drops led to an improvement in near visual acuity. However, noteworthy clinical significance in the enhancement of near visual acuity at 2, 4, and 6 hours post-application was observed exclusively in the 1.25% pilocarpine eye drops and the combined 1.25% pilocarpine + 0.1% brimonidine eye drops groups.

Interestingly, the application of these eye drops did not disrupt the distance visual acuities in any of the groups. Pupil constriction was a consistent outcome in all groups, indicating a potential pinhole effect contributing to an increased depth of focus. While this pinhole effect can result in a clearer image by allowing only central light rays to reach the retina[19], it comes at the cost of reduced brightness, visual field, and optimal visual acuity.[20,21]

The shallowing of the anterior chamber depths was consistently observed in all eye drops groups, with the exception of the 1% pilocarpine eye drops group. This suggests that the iris-lens diaphragm moved forward more prominently with pilocarpine concentrations exceeding 1%, potentially inducing myopia. Pilocarpine's

TABLE 1. Patients' demographic data

Total n = 10 (%)	n (%)
Sex	
Male	3 (30%)
Female	7 (70%)
Underlying medical conditions	
HT	2 (20%)
DLP	2 (20%)
DM	2 (20%)
Ophthalmic diseases	
Dry eye disease	1 (10%)
Allergic conjunctivitis	1 (10%)
Age (median (IQR))	46.5 (41.8–50.5)
Non-dominant eye	
Right	5 (50%)
Left	5 (50%)

Abbreviations: HT = hypertension, DLP = dyslipidemia, DM = Diabetes mellitus, IQR = interquartile range

TABLE 2. VA at distance (LogMAR) after topical application: Median (Range)

Hours after application	Pre	2	4	6
1% pilocarpine	0 (0,04)	0 (0,0.44)	0 (0,0.2)	0 (0,0.06)
1.25% pilocarpine	0 (0,0.14)	0 (0,0.28)	0 (0,0.06)	0 (0,0.12)
1.5% pilocarpine	0 (0,0)	0 (0,0.24)	0 (0,0.34)	0 (0,0.34)
1% pilocarpine +	0 (0,0.18)	0 (0.12)	0 (0,0.42)	0 (0,0.22)
1.25% pilocarpine + 0.1% brimonidine	0 (0,0.22)	0 (0,0.74)	0 (0,0.36)	0 (0,0.42)
1.5% pilocarpine + 0.1% brimonidine	0 (0,0.06)	0 (0,0.76)	0 (0,0.84)	0 (0,0.48)

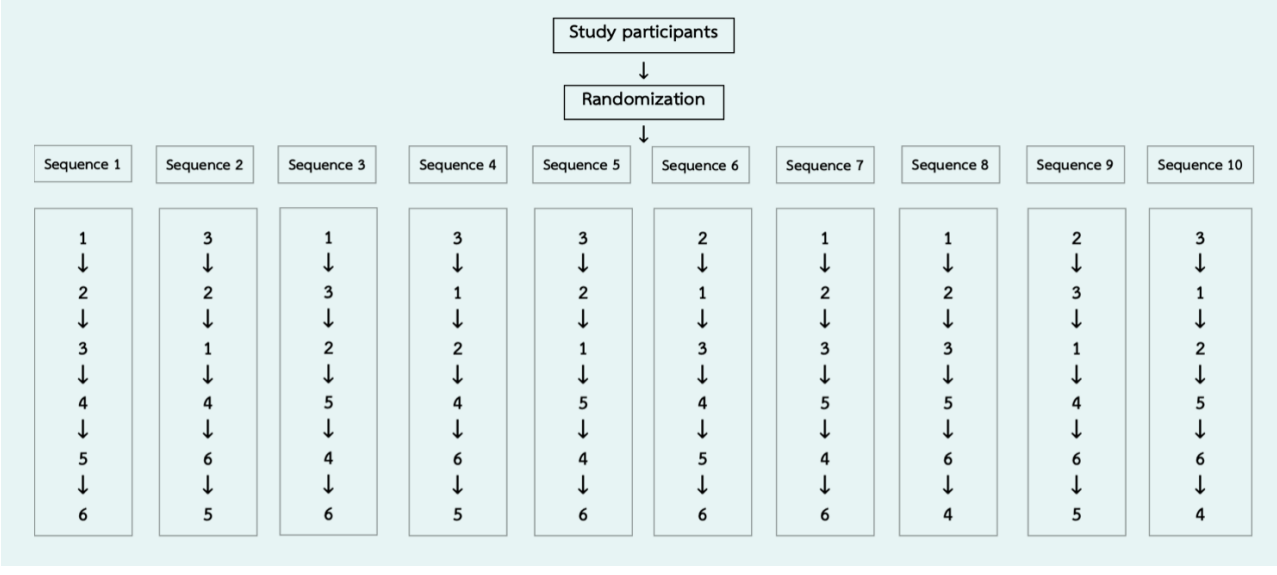

Fig 1. Flowchart, randomized controlled crossover design.
1 =1 % pilocarpine, 2 = 1.25% pilocarpine, 3 = 1.5% pilocarpine, 4 = 1% pilocarpine + 0.1% brimonidine, 5 = 1.25% pilocarpine + 0.1% brimonidine, 6 = 1.5% pilocarpine + 0.1% brimonidine

TABLE 3. VA at near (LogMAR) after topical application: Median (IQR)

Hours after application	Pre	2	4	6
1% pilocarpine	0.18 (0.1,0.18)	0.05 (0,0.18)	0.1 (0,0.18)	0 (0,0.18)
1.25% pilocarpine	0.18 (0.18,0.3)	0.1 (0,0.18)*	0.05 (0,0.18)*	0.09 (0,0.18)*
1.5% pilocarpine	0.14 (0.1,0.3)	0 (0,0.18)*	0.05 (0,0.3)	0.05 (0,0.18)
1% pilocarpine + 0.1% brimonidine	0.14 (0.1,0.18)	0.05 (0,0.18)	0.05 (0,0.18)	0.09 (0,0.18)
1.25% pilocarpine + 0.1% brimonidine	0.18 (0.1,0.18)	0 (0,0.18)*	0 (0,0.18)*	0.05 (0,0.18)*
1.5% pilocarpine + 0.1% brimonidine	0.1 (0,0.18)	0.05 (0,0.1)	0.05 (0,0.18)	0.05 (0,0.18)

Abbreviations: IQR = Interquartile range, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction.

TABLE 4. Pupil size after topical application: Mean (SD)

Hours after application	Pre	2	4	6
1% pilocarpine	4.4 (0.93)	2.72 (0.67)*	2.96 (0.81)*	3.28 (0.87)*
1.25% pilocarpine	4.32 (0.71)	2.67 (0.73)*	2.98 (0.9)*	3.03 (0.74)*
1.5% pilocarpine	4.25 (0.77)	2.3 (0.49)*	2.47 (0.59)*	2.79 (0.53)*
1% pilocarpine + 0.1% brimonidine	4.37 (0.81)	2.21 (0.50)*	2.35 (0.61)*	2.52 (0.58)*
1.25% pilocarpine + 0.1% brimonidine	4.18 (0.88)	2.13 (0.55)*	2.28 (0.76)*	2.49 (0.71)*
1.5% pilocarpine + 0.1% brimonidine	4.24 (0.85)	2.07 (0.37)*	2.18 (0.40)*	2.34 (0.54)*

Abbreviations: SD = standard deviation, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction

TABLE 5. Anterior chamber depth after topical application: Mean (SD)

Hours after application	Pre	2	4	6
1% pilocarpine	3.14 (0.29)	3.13 (0.27)	3.12 (0.28)	3.10 (0.31)
1.25% pilocarpine	3.14 (0.29)	3.11 (0.28)*	3.10 (0.28)*	3.11 (0.29)*
1.5% pilocarpine	3.14 (0.28)	3.11 (0.28)*	3.10 (0.27)*	3.10 (0.29)*
1% pilocarpine + 0.1% brimonidine	3.14 (0.28)	3.08 (0.27)*	3.08 (0.27)*	3.10 (0.27)*
1.25% pilocarpine + 0.1% brimonidine	3.14 (0.27)	3.07 (0.27)*	3.07 (0.26)*	3.10 (0.28)*
1.5% pilocarpine + 0.1% brimonidine	3.14 (0.28)	3.05 (0.26)*	3.05 (0.26)*	3.08 (0.25)*

Abbreviations: SD = standard deviation, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction

TABLE 6. Lens thickness after topical application: Mean (SD)

Hours after application	Pre	2	4	6
1% pilocarpine	4.33 (0.34)	4.33 (0.34)	4.34 (0.34)	4.30 (0.34)
1.25% pilocarpine	4.34 (0.34)	4.34 (0.35)	4.34 (0.35)	4.34 (0.34)
1.5% pilocarpine	4.33 (0.34)	4.34 (0.34)	4.34 (0.34)	4.34 (0.35)*
1% pilocarpine + 0.1% brimonidine	4.33 (0.33)	4.36 (0.34)	4.36 (0.34)*	4.35 (0.34)
1.25% pilocarpine + 0.1% brimonidine	4.33 (0.34)	4.36 (0.34)*	4.36 (0.35)*	4.35 (0.35)
1.5% pilocarpine + 0.1% brimonidine	4.32 (0.34)	4.36 (0.35)*	4.37 (0.34)*	4.35 (0.34)*

Abbreviations: SD = standard deviation, * = statistically significant with the Wilcoxon signed-rank test and Bonferroni correction

TABLE 7. Side effects (Percentage)

Hours after application	2	4	6
1% pilocarpine	Eye discomfort (10%), Red eye (10%)	Eye discomfort (10%), Red eye (10%)	Eye discomfort (10%)
1.25% pilocarpine	Eye discomfort (20%)	Blurred (10%), Eye discomfort (20%)	Blurred (10%), Eye discomfort (20%)
1.5% pilocarpine	Blurred (20%), Eye discomfort (10%), Red eye (30%),	Blurred (20%), Eye discomfort (10%)	Blurred (20%), Eye discomfort (10%)
1% pilocarpine + 0.1% brimonidine	Blurred (20%)	Blurred (10%), Eye discomfort (20%)	Blurred (10%), Eye discomfort (30%)
1.25% pilocarpine + 0.1% brimonidine	Eye discomfort (30%), Blurred (20%)	Blurred (10%), Eye discomfort (30%),	Blurred (10%), Eye discomfort (10%)
1.5% pilocarpine + 0.1% brimonidine	Blurred (30%), Eye discomfort (30%)	Blurred (30%), Eye discomfort (20%)	Blurred (10%), Eye discomfort (50%)

physiological effects, including ciliary muscle contraction, pupil miosis, and lens forward movement, have been reported to contribute to this phenomenon.[22]

Apart from previously mentioned, Pilocarpine produces a variety of ocular and systemic adverse reactions. Ocular side effects include miosis, accommodative spasm, frontal headaches, twitching lids, conjunctival injection, cataractous changes, allergic reactions, increased permeability of the blood-aqueous barrier. Iritis and risk of retinal detachment also have been mentioned by USFDA[23] but very rare effects.

During the study, no severe adverse events were observed throughout the study The most frequently observed adverse events included discomfort, red eye, and blurred vision. These reactions were generally mild and of short duration.

Despite adverse drug reactions, such as eye discomfort, red eye, and blurred vision, being reported across all eye drops groups, these effects were not severe enough to pose a threat to vision or warrant the termination of the study or any participant's participation.

Although 1.25% pilocarpine eye drops have been approved by the US FDA for presbyopia treatment since 2021[24,25], they are currently unavailable in Thailand. This challenge fueled our team's curiosity, leading us to explore how to prepare and determine the most effective concentration of pilocarpine or combination of pilocarpine and 0.1% brimonidine eye drops for improving near vision in the Thai population. Our study demonstrated that both 1.25% pilocarpine eye drops and the combined 1.25% pilocarpine + 0.1% brimonidine eye drops significantly improved near visual acuity at 2, 4, and 6 hours post-application. Notably, these two concentrations did not exhibit a clinically significant difference in near vision at each time point. As a result, we recommend the preparation and use of 1.25% pilocarpine eye drops for presbyopia treatment

However, Evaluation of the efficacy of these agents is limited by heterogeneity in outcomes definition and the small number of comparative studies. Other limitations include the potential bias introduced by remembering the number on the Snellen chart in each sequence concentrations. We suggest a sample size that is larger will be better representative of the population and will hence provide more accurate results.

CONCLUSION

In summary, 1.25% pilocarpine eye drops and the combination of 1.25% pilocarpine + 0.1% brimonidine eye drops exhibited clinically significant improvements in near visual acuity at 2, 4, and 6 hours post-application without causing serious side effects. To deepen our comprehension, the process of diluting pilocarpine eye drops may require additional investigation regarding the stability and sterility of the dilution, particularly for their potential utilization in clinical practice.

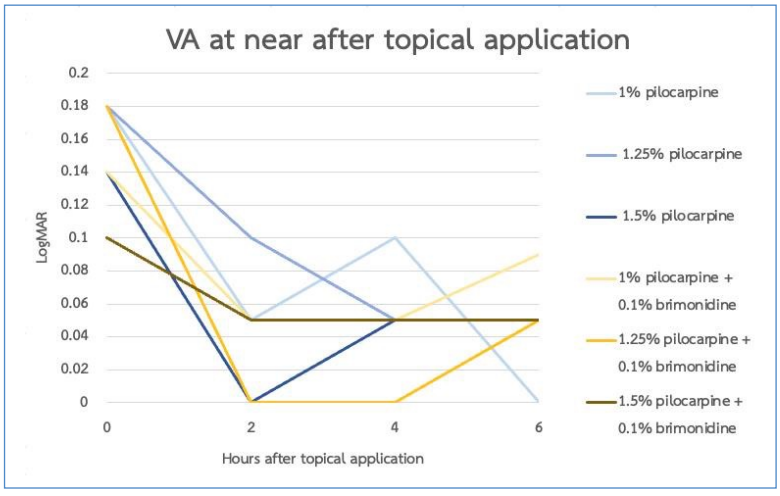

Fig 2. VA at near (LogMAR) after topical application.

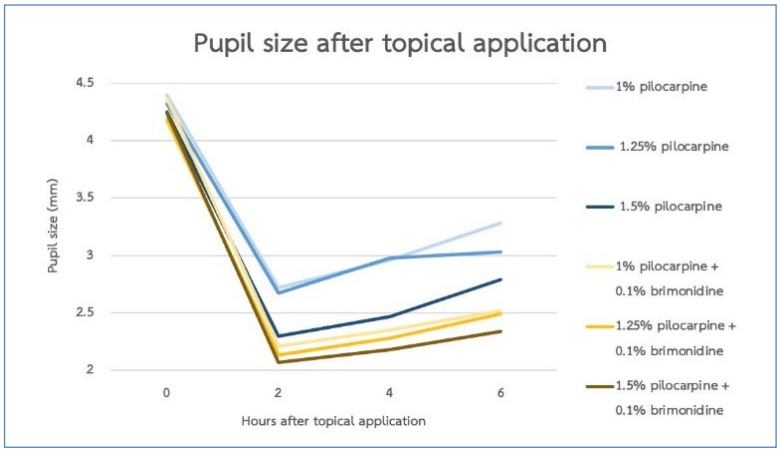

Fig 3. Pupil size after topical application.

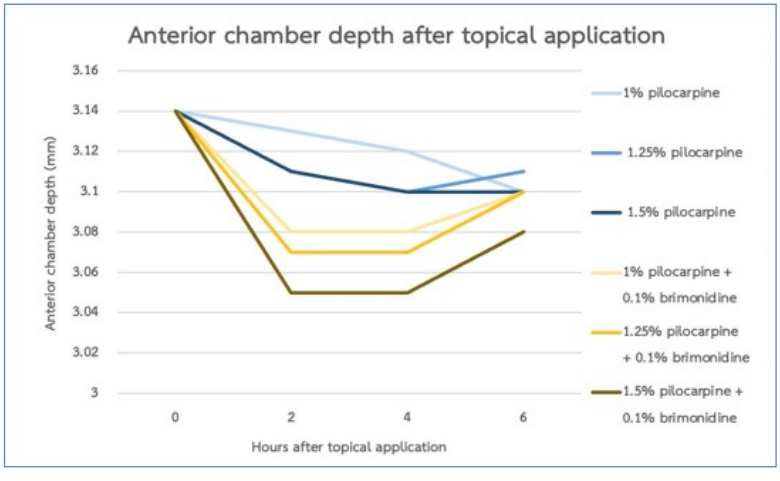

Fig 4. Anterior chamber depth after topical application.

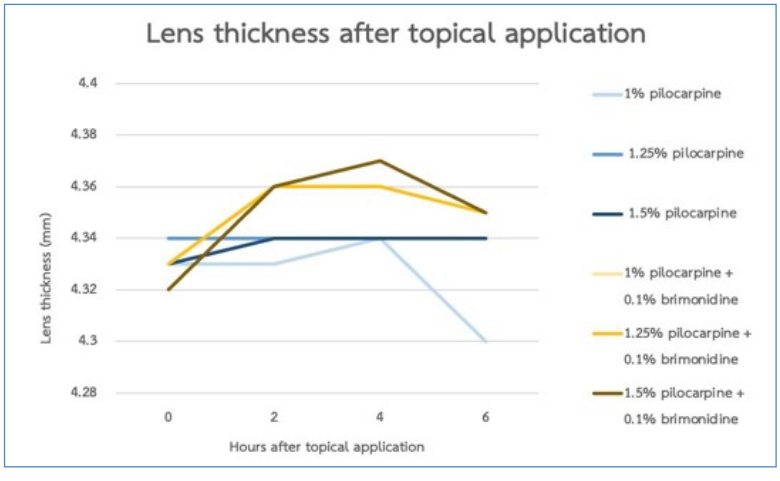

Fig 5. Lens thickness after topical application.

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to the publication of this research.

Author Contributions

TS: general research process, framework of the study, supervision, procedure, data analysis, writing-original draft preparation, review and editing; WS: framework of the study, methodology, data analysis, review and editing; KH: framework of the study, validation, resources, methodology, data collection; PJ: provided access to crucial research components (equipment, drug), resources; AK: provided access to crucial research components (equipment, drug), resources; PS: data collection, investigation, project administration; KR: data collection, investigation, project administration. All authors read and approved the final manuscript.

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