RESEARCH ARTICLE

pISSN: 0126-074X | eISSN: 2338-6223
https://doi.org/10.15395/mkb.v56.3311
Majalah Kedokteran Bandung. 2024;56(3):214–220

Majalah Kedokteran Bandung (MKB)

Received: April 5, 2023
Accepted: February 2, 2024
Available online: September 30, 2024

Comparison of Different Cycloplegic Refraction Regimens for Children

Irawati Irfani, Fany Gunawan, Karmelita Satari, Maya Sari, Primawita Oktarima, Sesy Caesarya, Feti Karfiati

Department of Ophthalmology, Faculty of Medicine Universitas Padjadjaran
Cicendo National Eye Hospital, Bandung, Indonesia

Abstract

In the process of a pediatric eye exam, cycloplegic refraction is a crucial step. Since no single cycloplegic drug is ideal, a combination regimen is employed. This study compares the ocular (refractive power and pupil diameter) and systemic (blood pressure and heart rate) effects of administering a combination of 1% cyclopentolate and 2.5% phenylephrine, with or without 1% tropicamide, to children with refractive errors. This study aimed to discover a more feasible regimen for children. This was a single-blind study, a randomized clinical trial conducted from November–December 2020 in children with mild to moderate refractive errors. Group A received 1% cyclopentolate, 2.5% phenylephrine, and 1% tropicamide (SFT), whereas group B received 1% cyclopentolate and 2.5% phenylephrine (SF). The outcomes were measured using an auto refractometer and IOL Master® 700. Before and 60 minutes after medication was administered, blood pressure and heart rate were measured. There were 54 participants (108 eyes) with an average age of 12.85±2.84 years. Although the SFT group's refractive power and pupil width were greater than those of the SF group, the differences were not statistically significant (p=0.271 and p=0.088). Heart rate (p=0.521) and blood pressure (systolic p=0.201; diastolic p=0.950) did not significantly differ between the two groups. Despite mydriasis manifested more rapidly in the SFT group, there was no discernible difference in the cycloplegic effects between those groups. SF might be a more feasible regimen for cycloplegic refraction in children with refractive errors.

Keywords: Cyclopentolate, cycloplegic, mydriasis, phenylephrine, tropicamide

Introduction

The second most common factor contributing to vision impairment and blindness worldwide is uncorrected refractive errors (URE). Up to 19 million children worldwide suffer from visual impairments, 12 million of which are brought on by URE. In Bandung's suburbs, children between the ages of 11 and 15 are more likely to have refractive errors (15.9%), with 12.1% of those cases remaining uncorrected.[1–4]

It's essential to address refractive errors in children since they can lead to blindness, amblyopia, as well as other visual impairments.[1,4] The high accommodation tone in children makes a cycloplegic examination a crucial part of a pediatric eye exam. The best cycloplegic medication should have minimal local or systemic side effects, a rapid onset of action, quick recovery, and adequate cycloplegia. The most common cycloplegic medications are cyclopentolate and tropicamide.[5–10] There are no recommendations on the best regimen for children, however many clinicians have moved to combination regimens and added sympathomimetic drugs, including phenylephrine, to enhance their mydriasis effect. When paired with tropicamide, cyclopentolate can enhance the cycloplegic effects, especially in eyes with dark irises. However, other investigations showed that tropicamide had a less potent effect on the same muscarinic receptors as cyclopentolate and did not change the latter's effect when it was withdrawn. While this is going on, using combinations of eye drugs can raise the chance of side effects, costs, and discomfort from stinging during instillation. The composition of the regimen, instillation patterns, and drug concentrations that are deemed best for children are not standardized.[5,8,10-12.]

The best treatment plans for children should minimize systemic and ocular side effects, reduce waiting times for examinations, lower

Corresponding Author:
Irawati Irfani
Department of Ophthalmology, Faculty of Medicine
Universitas Padjadjaran
Cicendo National Eye Hospital, Bandung, Indonesia
Email: irawati.irfani@unpad.ac.id

unnecessary operational costs, and alleviate discomfort for young patients. To address these concerns, we conducted a study to identify the most comfortable approach for pediatric patients. Specifically, if two drugs can achieve the same outcomes as three, we can decrease the number of drops administered, thereby enhancing comfort for children, reducing drug costs, and shortening clinic wait times. This study aims to compare the effects of 1% cyclopentolate and 2.5% phenylephrine, both with and without 1% tropicamide, on ocular parameters (changes in refractive power and pupil diameter) and systemic parameters (changes in blood pressure and heart rate) during cycloplegic refraction in children.

Methods

This single-blind, randomized clinical trial was conducted at the pediatric ophthalmology division of Cicendo National Eye Hospital in Bandung, Indonesia, from November to December 2020. The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran, under ethics number 985/UN6.KEP/EC/2020.

The trial included children aged 6 to 18 years who had mild to moderate refractive errors (myopia <6.00 D, hyperopia <3.00 D, and astigmatism <3.00 D) prior to the administration of cycloplegic agents. Exclusion criteria were as follows: history of eye surgery; pupillary abnormalities or other neurological disorders; history of cardiovascular disease; use of systemic or ocular medications affecting pupil function and/or accommodation; high anisometropia; visual disturbances unrelated to refractive errors (e.g., corneal opacities, uveitis, glaucoma, cataracts, posterior segment disorders, optic nerve disorders); strabismus; amblyopia; light-colored irises (e.g., green or blue); albinism; allergy to any component of the study drugs; and uncooperative behavior during drug administration. Additionally, children who failed to complete auto-refractometer and pupil diameter measurements or experienced adverse drug reactions were excluded from the study.

Block randomization was used to divide the sample into two groups. Group B received only 1% cyclopentolate and 2.5% phenylephrine (SF), while Group A received a combination of 1% cyclopentolate, 2.5% phenylephrine, and 1% tropicamide (SFT). Both eyes' visual acuity and autorefractometry were measured without the use of cycloplegics. The patient was then subject to an ophthalmological examination, which included assessing the patient's intraocular pressure, pupillary reflex, anterior segment, and funduscopy, as well as the position and movement of the patient's eyes. The study comprised patients who matched the inclusion criteria and did not meet the exclusion criteria.

The following dosage instructions were followed: (1) The SFT regimen consists of one drop each of 1% cyclopentolate, 2.5% phenylephrine, and 1% tropicamide; (2) The SF regimen consists of one drop each of 1% cyclopentolate and 2.5% phenylephrine. Each drop is administered in 5-minute intervals. One drop of 0.5% tetracaine is given 5 minutes before the first drop of the regimen. The lacrimal punctum is closed after each drop of the drug by applying pressure to the medial canthus for 10 seconds. IOL Master® 700 and an autorefractometer were used to measure the refractive power and pupil diameter prior to, 20, 30, 45, and 60 minutes following the administration of the medication. Each examination used the same intensity of room illumination. Before and 60 minutes after the administration of the medication, blood pressure and heart rate were measured.

The difference between refractive power before and after drug administration was the change in refractive power. For myopia and hyperopia, spherical power was applied in the calculation; for astigmatism, spherical equivalent (SE) was used. The difference between the pupil's size before and after the drug's delivery was the change in pupil diameter. The time started with the first drop of the regimen when the refractive power is achieved and maintained within 0.25 D of the previous refractive power is known as the cycloplegic peak time. The time measured from the first drop of the regimen with a pupil diameter greater than or equal to 7.0 mm is the mydriasis peak time. Peak periods of mydriasis and cycloplegia were recorded at 20, 30, 45, and 60 minutes.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) formed up the blood pressure. Before and after the administration of medications, the value of the difference between SBP, DBP, and heart rate (HR) was measured. It expressed itself as a change in systolic blood pressure (ΔSBP), a change in diastolic blood pressure (ΔDBP), and a change in heart rate (ΔHR).

Data analysis was conducted using IBM SPSS

Statistics for Windows 26.0 and Microsoft® Excel 2010. Descriptive statistics were presented in tables and figures. To evaluate changes in refractive power and pupil diameter between the two groups, both the unpaired t-test and the Mann-Whitney test were employed. The peak times for cycloplegia and mydriasis were compared between the groups using the Chi-square test and the Kolmogorov-Smirnov test. Differences in diastolic blood pressure and heart rate between the groups were analyzed using the Mann-Whitney test, while systolic blood pressure was assessed with the unpaired t-test. A p-value of <0.05 was considered statistically significant.

Results

Table 1 shows the characteristics of the subjects in each group. There were 54 patients in total (108 eyes), with a median age of 13 years (mean 12.85±2.84 years). Forty girls (74.1%) and 14 boys (25.9%) composed the subjects. Astigmatism myopia compound (51.9%) and simple myopia (35.2%) were the most common refractive errors. All subjects had an average refractive power of -2.77±2.092 D with a pupil diameter of 5.61±0.70 mm.

Table 2 presents the changes in refractive power and pupil size following drug administration. At 20-, 30-, 45-, and 60-minutes post-administration, both parameters showed increasing trends in each group, indicating a reduction in accommodation and progressive pupil dilation. Throughout these time points, the mean values of refractive power and pupil diameter were higher in the SFT group compared to the SF group. However, there were no significant differences between the two groups regarding changes in refractive power. Pupil diameter did not show significant

Table 1 Comparison of the Subject Characteristics Between SFT and SF

	SFT (n=54)	SF (n=54)	p-value
Sex			0.667[a]
Boys	14 (25.9%)	16 (29.6%)	
Girls	40 (74.1%)	38 (70.4%)	
Age (years)			0.921[b]
Mean ± SD	12.85 ± 2.929	12.85 ± 2.771	
Age category			1.000[a]
6–12 years	20 (37.0%)	20 (37.0%)	
13–18 years	34 (63.0%)	34 (63.0%)	
Refractive state			1.000[c]
Simple myopia	19 (35.2%)	16 (29.6%)	
Simple Hypermetropia	0 (0.00%)	2 (3.7%)	
Astigmatism Myopia Simple	2 (3.7%)	6 (11.1%)	
Astigmatism Myopia Compound	28 (51.9%)	27 (50.0%)	
Astigmatism Hypermetrop Simple	3 (5.6%)	0 (0.00%)	
Astigmatism Hypermetrop Compound	1 (1.9%)	0 (0.00%)	
Astigmatism Mixtus	1 (1.9%)	3 (5.6%)	
Refractive power(D)			0.220[b]
Mean±SD	-2.98 ± 2.024	-2.56 ± 2.156	
Pupil diameter (mm)			0.946[d]
Mean±SD	5.61 ± 0.673	5.60 ± 0.733	

Notes: SFT: combination of 1% cyclopentolate, 2.5% phenylephrine, and 1% tropicamide; SF: combination of 1% cyclopentolate and 2.5% phenylephrine; [a]Chi-square test; [b]Mann-Whitney test; [c]Kolmogorov-Smirnov test; [d]Unpaired t test

Table 2. Comparison of the Differences Between SFT and SF's Refractive Power, Pupil Diameter, Cycloplegic and Mydriasis Peak Time, Blood Pressure and Heart Rate Variation

		SFT (n=54)	SF (n=54)	p-value
ΔRefractive power (D) (Mean ± SD)				
20 minutes		+0.36 ± 0.499	+0.25 ± 0.375	0.357[a]
30 minutes		+0.43 ± 0.542	+0.27 ± 0.401	0.104[a]
45 minutes		+0.46 ± 0.542	+0.36 ± 0.428	0.382[a]
60 minutes		+0.50 ± 0.551	+0.37 ± 0.428	0.271[a]
ΔPupil diameter (mm) (Mean ± SD)				
20 minutes		1.26 ± 0.721	1.01 ± 0.615	0.089[a]
30 minutes		2.36 ± 0.805	1.64 ± 0.709	0.0001*[d]
45 minutes		2.85 ± 0.841	2.38 ± 0.761	0.003*[b]
60 minutes		3.04 ± 0.878	2.77 ± 0.734	0.088[b]
Cycloplegic peak time				1.000[c]
Unable to identified[a']		29 (53.7%)	32 (59.3%)	
20 minutes		19 (35.2%)	14 (25.9%)	
30 minutes		2 (3.7%)	3 (5.6%)	
45 minutes		2 (3.7%)	5 (9.3%)	
60 minutes		2 (3.7%)	0 (0.0%)	
Mydriasis peak time				0.031[c*]
20 minutes		27 (50.0%)	18 (33.3%)	
30 minutes		25 (46.3%)	19 (35.2%)	
45 minutes		2 (3.7%)	15 (27.8%)	
60 minutes		0 (0.0%)	2 (3.7%)	
ΔSBP (mmHg)[a]	Mean ± SD Range	2.37 ± 7.256 -12 – 18	0.30 ± 4.886 -10 – 10	0.201[b]
ΔDBP (mmHg)[a]	Mean ± SD Range	1.47 ± 6.361 -10 – 14	1.57 ± 5.987 -9 – 14	0.950[b]
ΔHR (times/minute)[a]	Mean ± SD Range	1.00 ± 4.386 -10 – 11	1.40 ± 4.407 -7 – 8	0.521[a]

Notes: SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate [a]Mann-Whitney test; [b]Unpaired t test; a':The difference in SE between before and 60 minutes after instillation was only ±0.25 D so that cycloplegic peak time could not be identified; [c]Kolmogorov-Smirnov test; Δ[a]: The value of the difference in measurement between before and after drug administration; *p value <0.05 is considered to have a statistically significant difference

differences between the groups at 20 and 60 minutes (p ≥ 0.05), although significant variation was observed at 30 and 45 minutes (< 0.05).

Due to the minimal difference in spherical equivalent (SE) refractive power (±0.25D), the cycloplegic peak time could not be determined for 32 subjects (59.3%) in the SF group and 29 subjects (53.7%) in the SFT group. The cycloplegic peak time did not show a statistically significant difference between the SFT and SF groups (p=0.031). Table 2 presents the peak times for cycloplegia and mydriasis in both groups. Peak times were reported as cumulative percentages, and data that could not be classified were excluded from the analysis. At 45 minutes, 92% of the SFT group and 100% of the SF group had reached their cycloplegic peak. In contrast, by the same time point, only 69% of the SF group had reached the mydriasis peak, while a total of 96% of the SFT group had achieved this

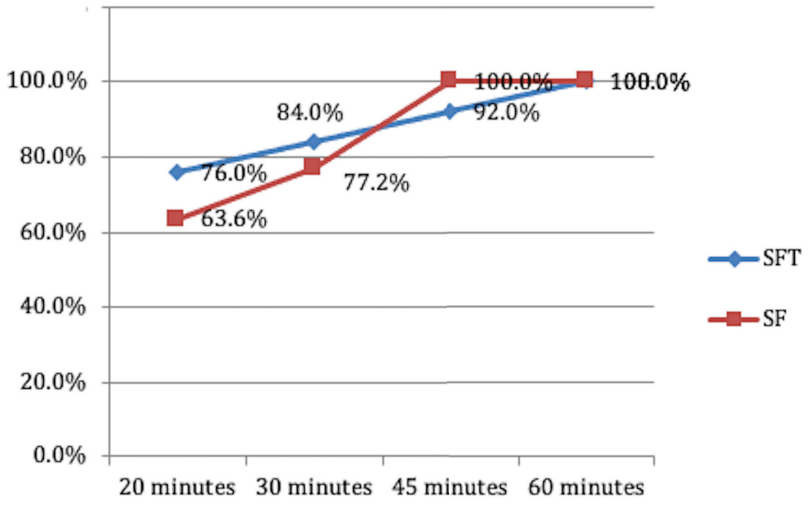

Figure 1.a Cumulative Percentage of Cycloplegic Peak Time Between SFT and SF

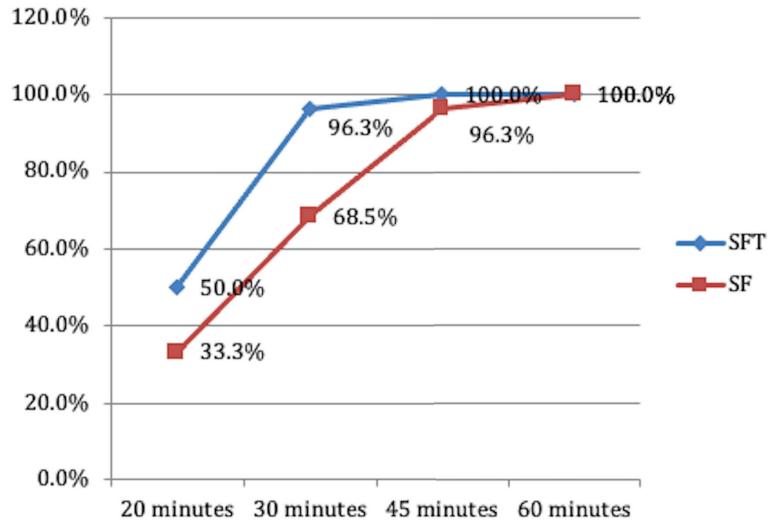

Figure 1.b Cumulative Percentage of Mydriasis Peak Time Between SFT and SF

milestone at 30 minutes.

This study compared the changes in blood pressure and heart rate to evaluate the systemic effects of various regimens in addition to their ocular effect. Table 2 shows that after drug administration in the SFT and SF regimens, the mean values of SBP, DBP, and HR increased. Systolic and diastolic blood pressure, as well as heart rate, were similar in both groups (p = 0.201; p=0.950) (p=0.521). However, as the systemic effect was only examined in this study at the 60th minute, fluctuations and variability could not be determined.

Figures 1.a and 1.b show the cumulative percentages of the cycloplegic and mydriasis peak times between two groups.

Discussion

This study demonstrated no significant difference in refractive power between the SFT and SF instillation methods. Cyclopentolate primarily acts on M1 muscarinic receptors,

while tropicamide affects M1, M2, and M4 receptors. When used together, tropicamide may enhance cyclopentolate's effect by suppressing M4 and M2 receptors, potentially leading to a more pronounced antimuscarinic effect overall. Despite these pharmacological interactions, the mean change in refractive power with SFT (0.13 D) was greater than with SF, but this difference was not statistically significant.[5,7,13.]

Results of this study was similar to that of Sherman[5] et al., which demonstrated that changes in refractive power caused by SFT and SF were not significantly different in the dark and light iris. Yoo et al.[9] compared a regimen consisting of 0.5% tropicamide, 0.5% phenylephrine combined with 1% cyclopentolate versus 1% cyclopentolate alone. The study showed that among hyperopic children aged 6 to 14 years, the two regimens did not significantly differ in their ability to produce cycloplegic symptoms. However, a cyclopentolate regimen alone produced a larger cycloplegic impact in children aged 5 and under than a combination of cyclopentolate with tropicamide and phenylephrine did, particularly in those with severe hyperopia or accommodative esotropia.[5,9] This study also shown that, despite a difference between SFT and SF during 30 and 45 minutes of observation, there was no discernible difference in the mean change in pupil diameter between the two groups. The SFT regimen produced pupils that were 0.72 mm and 0.47 mm larger than SF at 30 minutes and 45 minutes, respectively. When combined with cyclopentolate and phenylephrine, tropicamide has a quicker mydriasis effect because it penetrates the corneal epithelium more effectively than cyclopentolate.[13] Sherman[5] et al. demonstrated that SFT produced a pupil diameter that was 0.39 mm greater than SF in patients with dark irises, however the measurement was only made once, i.e., 30 minutes after installation.[5]

The peak timings of several cycloplegic drugs have also been investigated in several prior studies. Laojaroenwanit[6] et al. assessed the cycloplegic peak time of 3 drops of 1% cyclopentolate in Thai children and found that it took longer in participants with myopia—up to an hour—to reach the peak time (50 minutes). These studies were consistent to our findings, which demonstrated that most myopic participants had cycloplegic peak times in SFT and ST of 45 minutes.[6]

Contrary to this outcome, mydriasis peak time varied considerably between the two regimens. The SFT regimen induced mydriasis more rapidly than SF. Pupil diameter varied significantly during 30 and 45 minutes of observation. The mydriasis peak time was identified using 7.0 mm as the upper limit value because it is the optimum diameter for funduscopic examination.

Sherman et al.[5] investigated the effects of mydriasis in patients aged 4 to 32 years with dark irises, comparing two regimens: tropicamide 1% combined with phenylephrine 2.5% (TF) and tropicamide 1% combined with cyclopentolate 1% (TS). The study found that the TF regimen achieved a pupil diameter of 7 mm in an average of 32 minutes, while the TS regimen took an average of 52 minutes. Additionally, the study noted that younger patients required a longer time to reach the desired pupil diameter compared to older age groups.

This study also evaluated the safety of using the two combination regimens by comparing the likelihood of systemic effects on blood pressure and heart rate. The results showed no difference in heart rates or systolic and diastolic blood pressure between the two groups. The risk of adverse effects and costs can rise when using a range of medications. The higher volume of drops, stinging and burning sensations could induce trauma in children. Children become uneasy and less complaint throughout subsequent assessments. Additionally, cycloplegic refraction is carried out once the pupil has fully dilated and stopped responding to light. Because the maximum cycloplegic and mydriatic effects are uncertain, this prolongs waiting times. [5,12,17]

Based on the findings, the inclusion of tropicamide in the SFT regimen for pediatric cycloplegic refraction may not be necessary. Although tropicamide accelerates mydriasis, it does not significantly enhance the cycloplegic effect of the SFT regimen. Using only 2.5% phenylephrine can achieve adequate mydriasis without the additional systemic risks associated with higher concentrations of phenylephrine, such as tachycardia and elevated blood pressure, which is particularly relevant for infants and the elderly.[14]

The outcomes of this study suggest a more comfortable approach for cycloplegic evaluation in children. The effectiveness of two-drug regimens in inducing cycloplegia is comparable to that of three-drug regimens. As a result, using a two-drug regimen can reduce the discomfort associated with cycloplegic refractive examinations in children.

A limitation of this study is its focus primarily on myopic eyes, which may not fully represent the efficacy of the regimen for other refractive abnormalities. Further research is needed to

assess the benefits of this regimen for children with extreme hyperopia and accommodative esotropia. Additionally, exploring the effectiveness of drug combinations when synthesized into a single drop could provide further insights into optimizing cycloplegic treatments.

In conclusion, while mydriasis develops more rapidly with the SFT regimen, there is no significant difference in cycloplegic effects between the two groups. Both treatment regimens are systemically safe for children. The SF regimen may be a more practical option for cycloplegic refraction in children with refractive errors.

References

1. Dhaneshа U, Polack S, Bastawrous A, Banks LM. Prevalence and causes of visual impairment among schoolchildren in Mekelle, Ethiopia. Cogent Med. 2018;5:1554832.
2. Harrington SC, Stack J, Saunders K, O'Dwyer V. Refractive error and visual impairment in Ireland schoolchildren. Br J Ophthalmol. 2019;103(8):1112–8. doi:10.1136/bjophthalmol-2018-312573
3. WHO. World Report on Vision. Geneva: World Health Organization; 2019.
4. Halim A, Suganda R, Sirait NS, Memed FK, Syumarti, Rini M, et al. Prevalence and associated factors of uncorrected refractive errors among school children in suburban areas in Bandung, Indonesia. Cogent Med. 2020;7(1):1737354.
5. Sherman AE, Shaw MM, Ralay-Ranaivo H, Rahmani B. Tropicamide has limited clinical effect on cycloplegia and mydriasis when combined with cyclopentolate and phenylephrine. J AAPOS. 2019:2.e1-30.e5.
6. Laojaroenwanit S, Layanun V, Praneeprachachon P, Pukrushpan P. Time of maximum cycloplegia after instillation of cyclopentolate 1% in children with brown irises. Clin Ophthalmol. 2016;10:897–902.
7. Kyei S, Nketsiah AA, Asiedu K, Awuah A, Owusu-Ansah A. Onset and duration of cycloplegic action of 1% cyclopentolate – 1% tropicamide combination. Afr Health Sci. 2017;17(3):923–32. doi:10.4314/ahs.v17i3.36
8. Yazdani N, Sadeghi R, Momeni-Moghaddam H, Zarifmahmoudi L, Ehsaei A. Comparison of cyclopentolate versus tropicamide cycloplegia: A systematic review and meta-analysis. J Optom. 2018;11:135–43.
9. Yoo SG, Cho MJ, Kim US, Baek S-H. Cycloplegic refraction in hyperopic children: Effectiveness of a 0.5% tropicamide and 0.5% phenylephrine addition to 1% cyclopentolate regimen. Korean J Ophthalmol. 2017;31(3):249.
10. American Academy of Ophthalmology. Pediatric Eye Evaluations Preferred Practice Pattern®. San Francisco; Elsevier Inc.; 2017.
11. Minderhout HM, Joosse M V, Grootendorst DC, Schalij-Delfos NE. A randomized clinical trial using atropine, cyclopentolate, and tropicamide to compare refractive outcome in hypermetropic children with a dark iris; skin pigmentation and crying as significant factors for hypermetropic outcome. Strabismus. 2019;27(3):127–38. doi:10.1080/09273972.2019.1629466
12. Liewellyn S, Khandelwal P, Glaze S, Thomas P, Dahlmann-Noor A. Time to drop the phenylephrine from the paediatric cycloplegia protocol: informing practice through audit. Eye. 2019;33:337–8. doi:10.1038/s41433-018-0246-5
13. Gupta SK. Mydriatics and cycloplegics. In: Gupta SK, Agarwal R, Srivastava S, eds. Textbook on Clinical Ocular Pharmacology and Therapeutics. 1st ed. New Delhi: Jaypee Brothers Medical Publishers; 2014. p. 87–95.
14. Esteve-Taboada JJ, Del Aguila-Carrasco AJ, Bernal-Molina P, Ferrer-Blasco T, Lopez-Gil N, Montes-Mico R. Effect of phenylephrine on the accommodative system. J Ophthalmol. 2016;2016:1–13. doi:10.1155/2016/7968918