Original Article

Effectiveness of cyclopentolate 1% compared to the combination of cyclopentolate 1%, tropicamide 1%, and phenylephrine 10% in cycloplegic refractive examination

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Context: Refractive errors in children require appropriate eyeglass correction. Cycloplegic refraction is a method used to determine eyeglass prescriptions in children due to their high accommodative power. Drugs such as cyclopentolate, tropicamide, and phenylephrine are often used in performing cycloplegic refraction. **Aims:** This study aims to compare the effectiveness of cyclopentolate 1% (C) and a combination of cyclopentolate 1%, tropicamide 1%, and phenylephrine 10% (CTP). **Settings and Design:** This is a cross-sectional study using medical records from using medical records from a private hospital in Surabaya, Indonesia, obtained through consecutive sampling (January 2021–July 2024). **Subjects and Methods:** Subjects were grouped based on the agents used, C and CTP. Refractive values before and after drug administration, as well as the differences, were compared. **Statistical Analysis Used:** Data were analyzed using Jamovi 2.4.11. **Results:** The data obtained were from children aged 6–17 years. Of the 64 samples, 34 (53.1%) were female, and 30 (46.9%) were male. The most common age group was 6–9 years (60.9%). Significant differences in refraction were found before and after drug administration in both the C group ($P < 0.05$) and the CTP group ($P < 0.05$). However, no significant differences in refraction were found between the two groups after drug administration for both the left eye ($P = 0.21$) and the right eye ($P = 0.88$). **Conclusions:** There were significant differences in the changes in refraction results in both groups, while no differences in effectiveness were found between the two groups.

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Introduction

Cycloplegic refraction is the gold standard examination for correcting refractive errors in children. Cycloplegic examination is recommended to determine the appropriate lens power to correct refractive errors in children due to their stronger accommodative ability. Strong accommodation power, if not minimized, will result in misdiagnosis of refractive errors in children.[1,2] The inaccurate correction of refractive errors in children may result in the development of amblyopia.[3] According to the World Health Organization, there are approximately 2.2 billion people worldwide with visual impairment, both near and far. It is reported that the leading causes of distance vision impairment or blindness include cataracts in 94 million people and refractive errors in 88.4 million people.[4] In Saudi Arabia, refractive errors in children aged 5–15 years are reported to be around 12.8 million people.[5] Furthermore, data on refractive error and blindness in Southeast Asia countries such as Thailand is around 0.3%, India 0.7%, and Bangladesh 1%. However, data in Indonesia shows that refractive error is the most common disorder. Approximately 25% of the population, or around 55 million individuals, have the condition. There is an increase in the prevalence of refractive error and blindness in Indonesia of 1.5%, which is the highest rate compared to other Asian countries.[6] In 2023, refractive error in school-age children was around 23% in the Pangandaran sub-district.[7] This number increased compared to 2012 (24.7%), especially after the COVID-19 pandemic (35%–40%).[8]

Cycloplegic refraction is a refractive examination performed after administering drugs that can temporarily paralyze the accommodative function. This paralytic effect occurs through the blockade of acetylcholine receptors on the ciliary body, with agents such as atropine sulfate, homatropine hydrobromide, cyclopentolate, and tropicamide.[1] Atropine is the gold standard in cycloplegic refraction. However, its use is limited due to its severe side effects, slow onset, long recovery time, and prolonged blurring effect. As a result, cyclopentolate and tropicamide are preferred for use in children.[9-11] It is important to note that the administration of cyclopentolate in excessive doses has the risk of causing systemic toxicity. Therefore, to prevent this, it is recommended to combine this drug with other drugs to ensure that the dose required

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to achieve a cycloplegic effect is not exceeded.[12] Nowadays, many clinicians use a combination of cyclopentolate and tropicamide, sometimes with the addition of sympathomimetic agents such as phenylephrine, to achieve maximal pupillary mydriatic effects. However, there is still no optimal regimen for use in pediatric patients.[9]

Caputo and Lingua reported that combining cyclopentolate 1.3%, tropicamide 0.16%, and phenylephrine 1.6% could lead to faster mydriasis and cycloplegia effects. This combination is comparable to atropine, and no significant side effects were found.[13] Currently, limited studies are comparing cyclopentolate 1% with a combination of cyclopentolate 1%, tropicamide 1%, and phenylephrine 10% (CTP). This study aims to compare the effect of using cyclopentolate 1% with this combination on pediatric refractive examination.

Subjects and Methods

The method used in this study was cross-sectional. Data were collected from medical records of pediatric patients who sought treatment at the outpatient eye clinic of Husada Utama Hospital in Surabaya, from January 2021 to July 2024. The inclusion criteria for this study are pediatric patients aged 6–7 years, diagnosed with refractive error (myopia, hypermetropia, or astigmatism), and who underwent cycloplegic refractive examination with cyclopentolate 1% or a combination of CTP. This study has obtained ethical approval from the ethics committee of Husada Utama Hospital (No. 23/KEP-RSHU/VII/2024).

Sampling data was collected from June to July 2024. This study used a consecutive sampling method. Samples that met the research criteria were divided into two groups. The first group underwent refractive examination using cyclopentolate 1% (C), whereas the second group used a combination of CTP. Data processing and analysis were performed using Jamovi version 2.4.11 (The Jamovi Project, Sydney, NSW, Australia). Refractive values, represented by spherical equivalent (SE), before and after drug administration, were compared. SE values before and after drug administration were assessed using paired *t*-test, while differences in SE changes between the two groups were analyzed using the Mann–Whitney *U*-test. Statistical significance was determined at $P < 0.05$.

Results

As shown in Figure 1, 64 samples met the research criteria. Five samples were excluded due to incomplete medical record data. Table 1 presents the characteristics of the samples in this study. Sample characteristics are divided by gender, age, and refractive errors in both groups (C and CTP). Both groups have a similar gender distribution, with slightly more females in the CTP group. The C group has a higher percentage of participants in the 6–9-year age category (25%), whereas the CTP group has the highest in the same category (35.9%). Composite myopia astigmatism is the most common refractive error in both groups, with a higher prevalence in the CTP group (24%).

Table 2 presents the distribution of refractive error types before and after cycloplegic agents administration in both groups. A noticeable shift in refractive error status was observed following the use of cycloplegic agents. Before cycloplegic refraction was conducted, the most commonly found refractive error was compound myopic astigmatism. However, after cycloplegic administration, hypermetropia became the most frequently identified refractive error.

Based on the data obtained, the results of refractive error correction before and after the cycloplegic agents used in each group changed. The data in Table 3 show a statistically significant improvement in refractive correction after drug administration in both Group C and Group CTP (all $P = 0.001$).

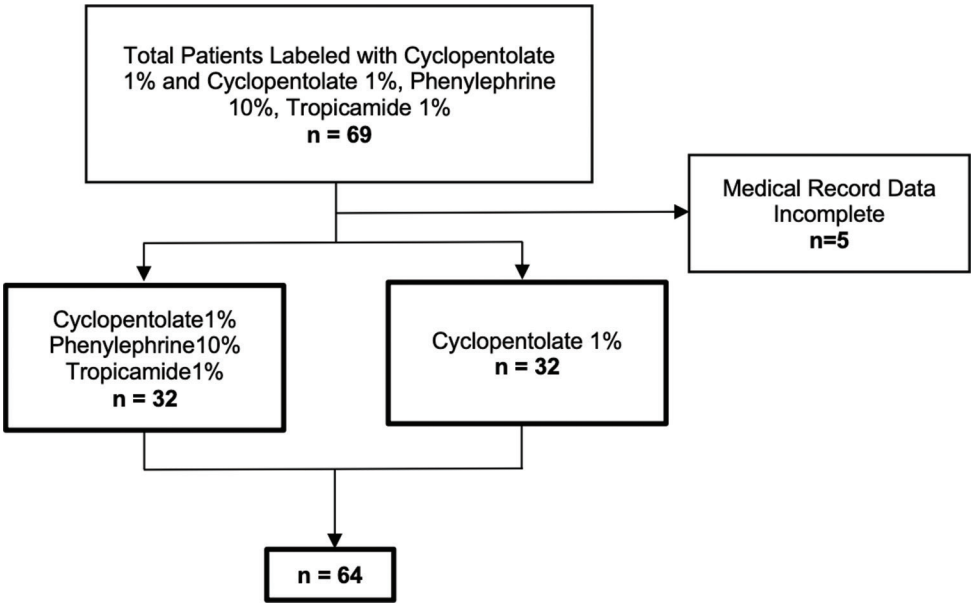

Figure 1: Enrollment and sample selection

Table 4 presents the differences in refractive error correction between group C and CTP. The changes in refractive error correction results between these groups were similar for both the right eye (VOD) and left eye (VOS). The median differences in refractive error were comparable, with no significant difference ($P = 0.88$ and 0.87, respectively).

Discussion

Cycloplegic agents are used to obtain accurate refraction results by reducing accommodation power in children. Optimal reduction of accommodation can be attained using either a single cycloplegic agent or a combination of drugs. However, the specific agents used in cycloplegic refraction may vary between clinicians. Multiple factors influence this variability, including the choice of drug or combination, dosage, mode of administration, and the side effect profile. The combinations used may consist of two to four drugs and can also vary in terms of dosage and method of administration.[14] There is still a lack of guidelines regarding the optimal drug regimen for cycloplegic refraction examinations.

Drugs exhibiting cycloplegic effects include atropine, homatropine, scopolamine, cyclopentolate, and tropicamide.[1] Atropine was the first cycloplegic agent used and the gold standard in cycloplegic refractive examination. Compared to other drug regimens, the cycloplegic and mydriasis effects of atropine can last up to 14 days. Scopolamine and homatropine have a shorter effect, up to 3 days in scopolamine and one to 3 days in homatropine. Based on their onset of action, scopolamine and homatropine require approximately 1 h to take effect, whereas cyclopentolate has a shorter onset of around 30 min. Furthermore, the cycloplegic effect produced by cyclopentolate can last up to 24 h.[15,16] Tropicamide is also commonly used, although its cycloplegic effect is not as strong as other regimens. The cycloplegic effect of tropicamide can last 1–2 h after drug administration.

Among these cycloplegic agents, cyclopentolate is the most commonly used drug in children due to its significant cycloplegic effect with a maximum duration of action (24 h) and better safety profile than atropine.[9-11] This drug is an antagonist of muscarinic receptors, particularly M3, found

Table 1: Sample characteristics

Variable	Group	
	C, *n* (%)	CTP, *n* (%)
Gender		
Female	16 (25)	18 (28.1)
Male	16 (25)	14 (21.9)
Age category (years)		
6–9	16 (25)	23 (35.9)
10–13	14 (21.9)	8 (12.5)
14–17	2 (3.1)	1 (1.6)
Refractive errors (eye)		
Simple myopic astigmatism	0	2 (1.6)
Simple hyperopic astigmatism	6 (4.7)	2 (1.6)
Compound myopi astigmatism	26 (20.3)	31 (24)
Compound hyperopic astigmatism	18 (14.1)	7 (5.5)
Mixed astigmatism	9 (7)	18 (14.1)
Myopia	1 (0.8)	2 (1.6)
Hyperopia	4 (3.1)	2 (1.6)

Table 2: Types of refractive error before and after cycloplegia

Types of refractive errors	C		CTP	
	Before, *n* (%)	After, *n* (%)	Before, *n* (%)	After, *n* (%)
Simple myopic astigmatism	3 (4.7)	0	4 (6.3)	2 (3.1)
Simple hyperopic astigmatism	3 (4.7)	6 (9.4)	0	2 (3.1)
Compound myopic astigmatism	34 (53.1)	26 (40.6)	41 (64.1)	31 (48.4)
Compound hyperopic astigmatism	2 (3.1)	18 (28.1)	5 (7.8)	7 (10.9)
Mixed astigmatism	15 (23.4)	9 (14.1)	10 (15.6)	18 (28.1)
Myopia	2 (3.1)	1 (1.6)	3 (4.7)	2 (3.1)
Hyperopia	5 (7.8)	4 (6.3)	1 (1.6)	2 (3.1)
Total	64	64	64	64

Table 3: Refractive correction results before and after drug administration

Refraction	Pre, average±SD	Post, average±SD	Mean difference (95%CI)	*P*
Group C				
SE VOD	−1.57±1.92	−0.80±0.25	−0.77 (−1.08–−0.47)	0.001*
SE VOS	−1.30±1.82	−0.66±2.07	−0.63 (−0.85–−0.41)	0.001*
Group CTP				
SE VOD	−2.19±2.13	−1.38±2.24	−0.81 (−1.07–−0.55)	0.001*
SE VOS	−1.98±1.95	−1.34±2.20	−0.63 (−0.83–−0.44)	0.001*

*Paired *t*-test. SD: Standard deviation, SE: Standard error

Table 4: Differences in changes in refractive error correction results between the two groups

Refraction changes	C, median (minimum–maximum)	CTP, median (minimum–maximum)	*P*
ΔSE VOD	0.75 (−0.25–3)	0,75 (−0.75–2.75)	0.88
ΔSE VOS	0.63 (−0.75–2)	0,5 (−0.25–1.75)	0.87

*Mann–Whitney. SE: Standard error

in the iris sphincter and ciliary muscle. Inhibition of the muscarinic receptors in the iris sphincter causes pupil dilation (mydriasis). Meanwhile, inhibition of the muscarinic receptors in the ciliary muscle results in loss of the eye's ability to accommodate, as the ciliary muscle can no longer contract to change the shape of the lens.[15]

The use of cyclopentolate 1% may be associated with systemic toxicity, which is of particular concern in children.[12] The administration of multiple doses of cyclopentolate has been reported to frequently cause adverse events in young children with a low body mass index (BMI). This is due to children's higher skin perfusion and reduced tissue density, allowing for more rapid and greater systemic absorption of cyclopentolate.[17] However, the drug is relatively safe in pediatric patients with greater BMI.

Previous studies have also reported changes in the diagnosis of refractive errors after cycloplegic refraction.[18] The use of cycloplegic agents results in changes in refractive error diagnosis by inducing maximum relaxation of the ciliary muscle. This eliminates the influence of accommodation, allowing for a more accurate assessment of the eye's true refractive power.[14]

Based on the analysis, both groups (C and CTP) had a significant difference in refraction pre-and post-drug administration [Table 3]. A study that was conducted by Doherty and Boengas also reported similar results.[18-20] This study also confirmed that children have greater accommodation power than adults. In the refractive examination with a distance of 6 m in children without cyclopegic drugs, the ciliary muscle is still contracting, resulting in a less accurate examination in children.[1] Hence, cycloplegic agents should be used in refractive examination in children to improve diagnosis accuracy.[10,21]

Although previous studies have compared the cycloplegic and mydriatic effects of these agents, the results remain variable. One study in children under 5 years of age comparing the effects of cyclopentolate 1% with a combination of cyclopentolate 1% and tropicamide 0.5% showed that the cyclopentolate alone regimen gave greater effects than the combination. However, in children aged 6–14 years, there was no significant difference between these two.[22] Furthermore, according to Ebri, the combination of cycloplegic agents has a greater effect than cyclopentolate alone.[23] Caputo and Lingua reported that the combination of cyclopentolate 1.3%, tropicamide 0.16%, and phenylephrine 1.6% was comparable to atropine, and no significant side effects were found after administration of this combination.[13] Similarly, a study conducted by Sherman compared the effects of a combination of cyclopentolate 1%, tropicamide 1%, and phenylephrine 2.5% against a combination of cyclopentolate 1% and phenylephrine 2.5%, showing no significant difference between these two combinations.[9]

This study showed that adding phenylephrine and tropicamide did not result in significant differences because phenylephrine is a sympathomimetic agent that causes mydriasis and has little cycloplegic effect. Phenylephrine is often combined with other cycloplegic agents such as cyclopentolate or tropicamide to enhance pupillary dilation while maintaining adequate cycloplegia.[10] Tropicamide has a rapid cycloplegic onset with a shorter duration of action than cyclopentolate. The cycloplegic effect of tropicamide is smaller than that of cyclopentolate. Therefore, administering cyclopentolate alone may result in a more substantial cycloplegic effect.[24] Although the addition of phenylephrine and tropicamide provides minimal additional cycloplegic effect, the addition of these agents is reported to reduce the toxicity and systemic absorption of cyclopentolate 1%. Administering three agents in a combination is safer than a single agent, as the amount of cyclopentolate in the combination is limited to just one drop, compared to larger doses when cyclopentolate is used alone.[12] This study did not assess the adverse effects, which limits the understanding of the safety profile of the intervention. Future research should include a comparison of the side effect profiles between the fixed drug combination and cyclopentolate alone to provide a more comprehensive evaluation of their overall benefit.

This study also has a limitation of not assessing the iris color of the patient. A study conducted by Ebri reported that iris color is a factor that influences the effect produced by cycloplegic agents. Melanocytes in the dark iris contain a higher amount of melanin. The higher the melanin content, the more drug substance binds to the iris pigment, reducing free drug that could bind to the ciliary receptor, resulting in a smaller pharmacological effect.[23]

Conclusion

This study demonstrated significant differences between cycloplegic and noncycloplegic refraction, supporting the use of cycloplegic agents for more accurate diagnosis in children. However, no significant difference was found between cyclopentolate 1% alone and the combination of CTP.

Data availability statement

The data supporting the findings of this study will be made available upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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