SYSTEMATIC REVIEW

The Efficacy of Combination Therapy Using Atropine and Orthokeratology in Limiting Myopia Progression in Comparison to Atropine and Orthokeratology Monotherapy—A Systematic Review

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Abstract

The growing incidence rate of myopia in the global population has heightened concerns over how to effectively manage it. This systematic review evaluates the efficacy of a combination therapy using atropine and orthokeratology to limit myopia progression compared to atropine and orthokeratology monotherapy. We accessed PubMed, Web of Science, and other databases to search for articles that addressed the effectiveness of the combined therapy. Data were accessed on 22 August 2024, and collected systematically from eight studies on combination therapy, six on orthokeratology alone, and five on atropine monotherapy. All studies focused on changes in axial length of the individuals who underwent the prescribed therapies. Statistical analysis was completed using Review Manager 5.4.1 and Python, Pandas Scikit Learn, SciPy, and MatPlotLib for data visualization, accuracy, and efficiency to obtain valid test results. Our analysis revealed that combination therapy resulted in a mean reduction in elongation of the axial length of 0.10 mm to 0.28 mm, significantly outperforming atropine monotherapy (0.17 mm to 0.87 mm) and orthokeratology alone (0.19 mm to 0.36 mm). The pooled mean difference in combination therapy (atropine + ortho-k) studies between the treatment (combination therapy) and control groups (monotherapy) was -0.10 mm (95% CI: -0.12 to -0.07 mm, $p < 0.00001$) and favored the treatment group. The results were homogeneous, showing consistency among different studies included in combination therapy., This review highlights the potential of combination therapy as a superior approach to myopia management, advocating its consideration in clinical practice to mitigate the growing burden of myopia. However, variability in study designs and the limited availability of long-term data reinforce the need for further research.

KEYWORDS:
Myopia management, atropine, orthokeratology, combination therapy

INTRODUCTION

The incidence rate of myopia has significantly increased over the past few decades, making it the most common ocular disorder worldwide.[1,2] It is predicted that by 2050 nearly half of the global population will be myopic.[3] The estimated incidence of myopia in school-going children in certain regions of East Asia is already as high as 90%, while more than 30% of the European and United States population is myopic.[4,5] Recent studies have shown that the incidence rate of myopia continues to rise, particularly among younger populations, with some regions reporting epidemic-like trends. Studies highlight the association between various factors and myopia development, including genetic predisposition, educational intensity, increased near work, and reduced outdoor activities, with some studies suggesting that a family history of myopia may be the strongest predictor of myopia development, even when accounting for environmental factors.[6] The genetic influence is particularly strong in cases where both parents are myopic, increasing a child's risk significantly compared to those with non-myopic parents.[7] This genetic predisposition interacts with environmental factors, such as educational intensity and near work, to further elevate the risk of myopia progression.[7]

MANAGEMENT OF MYOPIA

Given the global increase in myopia incidence, researchers have concentrated on developing techniques to slow its progression. These methods include optical interventions, pharmacological treatments, and environmental modifications. Optical approaches, such as daily disposable contact lenses and defocus-incorporated multiple segment lenses (DIMS), have shown promise in controlling myopia progression. Environmental factors, particularly increasing outdoor activities, have also been associated with reduced progression rates in children.[8-11]

Among pharmacological treatments, atropine eye drops stand out as the most effective approach currently available.[12] Numerous studies have demonstrated the efficacy of atropine in slowing axial length elongations.[13] Orthokeratology (ortho-k), which reshapes the cornea overnight, has also proven to be an effective strategy for myopia control.[14,15]

ATROPINE

Atropine is a widely studied pharmacological agent for myopia control, primarily through its action on muscarinic receptors.[16] These receptors, part of the G protein-coupled receptor family, are distributed across various ocular structures, including the retinal pigment epithelium, scleral fibroblasts, iris, and ciliary body.[17-19] Muscarinic receptors are believed to play a significant role in ocular growth and retinal development, making them key targets in myopia progression.[20] However, because atropine is not selective in which receptors are targeted, it has many side effects.

The mechanism of action of atropine in myopia control involves blockading acetylcholine receptors, specifically muscarinic receptors, which leads to the inhibition of ocular elongation.[21] However, some studies posit that atropine may exert effects on non-muscarinic pathways, including α2A-adrenergic receptors and γ-aminobutyric acid receptors, which could further modulate ocular growth.[21,22] In addition to its action on receptors, atropine has been shown to inhibit proliferation of epidermal growth factor (EGF), a factor that stimulates the growth of scleral fibroblasts, further contributing to its anti-myopic effects.[18,22]

Clinical studies, including the landmark ATOM1 and ATOM2 trials, have demonstrated the efficacy of atropine in controlling myopia progression, with higher concentrations (e.g., 1%) yielding stronger effects but also more side effects, such as photophobia and blurred vision. Recent interest has focused on low-dose atropine (e.g., 0.05%), which offers a more favourable balance between efficacy and reduced side effects.[12,13] These studies highlight atropine's role as one of the most effective pharmacological treatments for slowing myopia progression.

ORTHOKERATOLOGY

In 1962, George Jessen introduced the concept of "ortho-focus" at a meeting of the International Society of Contact Lens Specialists. Using rigid polymethyl methacrylate (PMMA) lenses, Jessen proposed reshaping the cornea over time to eliminate the need for glasses or corrective lenses. This idea laid the foundation for modern orthokeratology (ortho-k), a technique that temporarily reshapes the cornea using specially designed hard contact lenses to reduce refractive errors.[23,24]

Modern ortho-k lenses utilize high-oxygen-permeable materials and reverse geometry designs, which allow for faster and more effective corneal reshaping.[25] These lenses flatten the central cornea while steepening the peripheral cornea, creating a clear central vision zone and inducing myopic peripheral defocus. This peripheral defocus is believed to reduce the stimulus for axial elongation, which is a key factor in the progression of myopia.[26,27]

Numerous clinical studies have demonstrated the efficacy of ortho-k in slowing myopia progression, particularly in children, where reductions in axial elongation of up to 50% have been reported.[28] Despite its benefits, ortho-k is not without risks, such as an increased likelihood of microbial keratitis.[29] Proper lens hygiene, patient compliance, and regular follow-up are crucial for maintaining the safety and effectiveness of the treatment.

THE EFFECT OF LOW-DOSE ATROPINE IN MYOPIA CONTROL

Wei et al. conducted the ATOM 1 in Singapore, evaluating the efficacy of 1% atropine in myopia control over a period of 2 years and found a significant reduction in axial length elongation compared to the control group.[30] Subsequently, in 2012, Chia et al. evaluated the efficacy of three different concentrations of atropine (0.5%, 0.1%, 0.01%) in myopia control, compared the results with the ATOM 1 study, and found that higher concentrations of atropine were more effective in controlling myopia (spherical equivalent) progression and elongation of axial length.[31] In the earlier study, higher concentrations of atropine (0.5%, 1.0%, 2.0%) were found to be more effective in controlling myopia progression in the short term, whereas in the subsequent long-term study, lower concentrations (0.01%) showed sustained efficacy with fewer side effects, making them preferable for extended use.[32,33]

Yam et al. conducted a large-scale study evaluating the safety and efficacy of lower concentrations of atropine at 0.05%, 0.025% and 0.01% against a placebo group. A total of 438 participants were followed over 1 year, and data demonstrated that 0.05% atropine was the most effective in controlling myopia progression.[34] This study was extended for a further 2 years and later to 3 years, and the data reinforced 0.05% atropine as the optimal dose for long-term myopia control.[35,36]

EFFECT OF ORTHOKERATOLOGY ON MYOPIA CONTROL

Numerous clinical studies have confirmed the efficacy of modern overnight orthokeratology (ortho-k) in slowing myopia progression in children. One of the earliest significant studies was conducted by Cho et al. who ran a 2-year pilot study showing that children in the ortho-k treatment group experienced significantly less axial elongation compared to controls.[37] A 2-year randomized clinical trial in 2012 reinforced these findings.[38]

In a study by Chen et al. in 2013, ortho-k was shown to slow axial length elongation by 52% compared to a control group, highlighting its effectiveness in reducing myopia progression.[15] Similarly, Charm et al. found that partial reduction (PR) ortho-k lenses reduced myopia progression by 63% compared to children wearing spectacles.[39]

Long-term efficacy and safety were further supported by Hiraoka et al. whose study demonstrated positive outcomes over extended periods of ortho-k use, including sustained control of axial elongation and a low incidence of adverse events.[40] Likewise, a study by Jakobsen et al. confirmed these findings in a Scandinavian cohort where children using ortho-k lenses had significantly less axial elongation compared to children wearing single-vision lenses.[41]

Taken together, these studies provide strong evidence that ortho-k is an effective treatment for slowing the progression of myopia in children, with reductions in axial elongation ranging from 50–63% across different studies. The peripheral defocus the ortho-k lenses induced likely played a key role in reducing the stimulus for axial growth, which is critical in managing myopia progression.

EFFECT OF LOW-DOSE ATROPINE COMBINED WITH ORTHOKERATOLOGY IN MYOPIA CONTROL

As discussed above, numerous studies have demonstrated the individual efficacy of atropine and orthokeratology (ortho-k) in myopia control. However, some researchers combined the two forms of therapies, with Kinoshita et al. being the first to assess the efficacy of combination therapy (ortho-k with 0.01% atropine) in 2018. Their study lasted 1 year and revealed that combination therapy was significantly more effective in controlling myopia compared to monotherapy (only ortho-k).[42] This was closely followed by a study by Tan et al. in 2019, which yielded different outcomes. They discovered that the addition of 0.01% atropine did not improve outcomes in patients who were previously on ortho-k monotherapy. They did, however, conclude that further investigations were necessary and that a longer trial (minimum of 2 years) would be needed to further assess the effectiveness of combination therapy.[43]

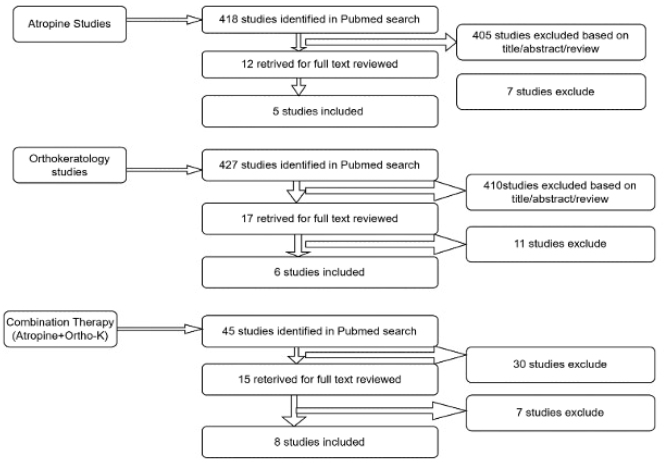
In contrast to Tan at al.'s study, data from a more robust study by Chen et al. demonstrated a reduction in the progression of axial length in patients using combination therapy (ortho-k with 0.01% atropine) compared to when the same patients were on ortho-k monotherapy. It is, however, important to note that they added atropine in patients with faster myopia progression who were already on ortho-k treatment.[44] Similarly, Vincent et al.[45], and Yu at al.[46] found combination therapy (ortho-k with 0.01% atropine) considerably more effective in controlling axial elongation and hence myopia control compared to ortho-k alone. A summary of the key outcomes from these studies, including reductions in axial length progression, can be found in Table 1. These findings indicate that combination therapy using atropine and ortho-k is more effective than monotherapy in controlling myopia, particularly in patients with faster progression.[42-49]

METHODS

We conducted an extensive literature search in PubMed using the terms "myopia control," "atropine," "orthokeratology," and "atropine with orthokeratology in combination." Studies were considered if they were available in full text, written in English, and focused on myopia control.

Two authors independently screened titles and abstracts for relevance, resolving discrepancies through discussion with additional experts. Data were extracted from five studies on atropine, six on orthokeratology, and eight on combination therapy (atropine ± ortho-k). We also performed a manual search of references. The study selection process is illustrated in the PRISMA flow diagram (Figure 1). All eligible observational studies were included in this review to assess the effectiveness of these treatments in controlling myopia progression.

Figure 1: *Diagram Showing Data Collection Procedure*



STATISTICAL ANALYSIS

We evaluated the efficacy of various treatment options for myopia control using comprehensive statistical analyses of the atropine monotherapy, orthokeratology, and combination therapy studies we selected. The primary outcome measured was the change in axial length (AL) in millimetres (mm).

We conducted the data analysis using Python, leveraging libraries such as Pandas for data manipulation, SciPy for statistical tests, sci-kit-learn for regression analysis, and Matplotlib for visualization. These tools provided a comprehensive suite for efficient and accurate data analysis. We also used Review Manager 5.4.1 to analyze the efficacy of combination therapy (atropine ± ortho-K) in myopia.

We assessed and confirmed normality of the data. We used one-way ANOVA and Kruskal–Wallis tests to evaluate differences in ΔAL among the atropine, orthokeratology, and combination therapy groups. We performed post hoc analysis using Tukey's HSD test to identify pairwise differences. For the meta-analysis of combination therapy studies (Table 3), we calculated pooled mean differences in ΔAL and assessed heterogeneity using I^2, Tau^2, and Chi^2 statistics. To achieve homogeneity, we conducted sensitivity analysis.

RESULTS

Descriptive statistics of the three treatment groups showed the mean axial length change in the low-dose atropine group was 0.4125 ± 0.3228 mm (n=12), indicating a moderate reduction. The mean AL change in the orthokeratology group was 0.2680 ± 0.2366 mm (n=6), and the combination group achieved a mean AL change of 0.0963 ± 0.1394 mm (n=8). These findings suggest that the combined treatment approach may provide a more effective reduction in myopia progression compared to monotherapy atropine or orthokeratology.

Figure 2: *Mean Axial Length in Monotherapy and Combination Therapy Groups*

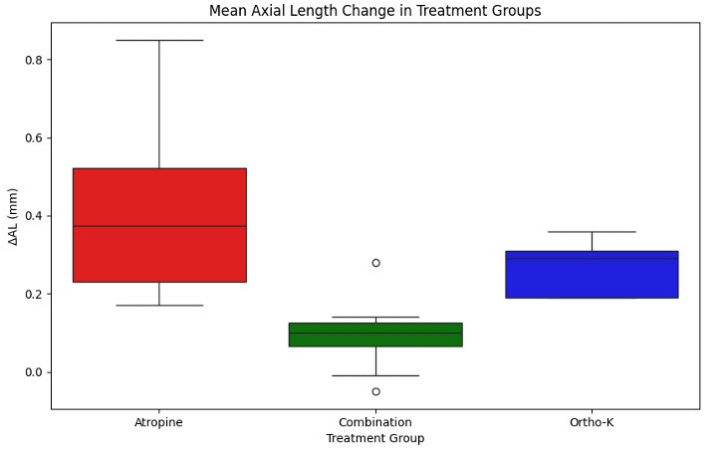


Table 1: *Atropine Monotherapy in Myopia Control*

Legend: ΔAL (mm): mean axial length, SE: spherical equivalent, ortho-k: orthokeratology

Author	Subjects (n)	Study Duration (Years)	Atropine Concentration	Treatment Group		Control Group	
				ΔAL (mm)	ΔSE (D)	ΔAL (mm)	ΔSE (D)
Chia A et al. (ATOM2) 2012 [31]	400	2	0.01%	0.41±0.32	-0.49±0.63	This study was done to compare the results of ATOM-1	
Chia A et al. 2015 [32]	400	5	0.1%	0.85±0.53	-1.83±1.16		
			0.01%	0.75±0.48	-1.38±0.98		
Yam JC et al. (LAMP1) 2019 [34]	438	1	0.05%	0.20±0.25	-0.27±0.61		
			0.025%	0.29±0.20	-0.46±0.45		
			0.01%	0.36±0.29	-0.59±0.61	0.41±0.22	-0.81±0.53
Yam JC et al. (LAMP2) 2020 [35]	383	2	0.05%	0.39±0.35	-0.55±0.86		
			0.025%	0.50±0.33	-0.85±0.73		
			0.01%	0.59±0.38	-1.12±0.85		
Yam JC et al. (LAMP3) 2022 [36]	326	3	0.05%	0.17±0.14	-0.28±0.42	0.33±0.17	-0.68±0.49
			0.025%	0.20±0.15	-0.35±0.37	0.29±0.14	-0.57±0.38
			0.01%	0.24±0.18	-0.38±0.49	0.29±0.15	-0.55±0.40

Table 2: *Orthokeratology (Ortho-K) Monotherapy in Myopia Control*

Legend: 2 AL: axial length, SE: spherical equivalent, ortho-k: orthokeratology, NR not reported

Author	Subjects (n)	Study Duration (Years)	Treatment With Ortho-K		Control Group	
			Δ AL (mm)	Δ SE (D)	Δ AL (mm)	Δ SE (D)
Cho P et al. 2005 [37,38]	35	2	0.29±0.27	NR	0.54±0.27	NR
Cho P et al. 2012 [38]	78	2	0.36±0.24	NR	0.63±0.26	NR
Chen C et al. 2013 [15]	58	2	0.31±-.27	NR	0.64±0.31	NR
Charm J et al. 2013 [39]	52	2	0.19±0.21	0.13	0.51±0.32	1.00
Hiraoka T et al. 2018 [40]	92	10	NR	-1.26±0.98	NR	-1.79±1.24
Jakobsen TM et al. 2021 [41]	47	1.5	0.19±0.18	NR	0.43±0.23	NR

Normality tests showed a normal distribution in all atropine, orthokeratology, and combination therapy groups. The one-way ANOVA revealed a statistically significant difference in ΔAL among these groups ($F = 8.36$, $p = 0.002$). To validate the findings, a non-parametric Kruskal–Wallis test confirmed the significance of the differences ($H = 13.99$, $p < 0.001$). To pinpoint the specific pairs of treatment groups with significant mean differences, we employed Tukey's Honestly Significant Difference (HSD) test. The results indicated significant differences in

ΔAL between the three treatment groups. Combination therapy demonstrated a significantly smaller ΔAL than atropine (mean difference = 0.3163, p = 0.017). However, there was no significant difference in ΔAL between atropine and orthokeratology (p = 0.489), nor between orthokeratology and combination therapy (p = 0.328), which supports the superiority of combination therapy in myopia.

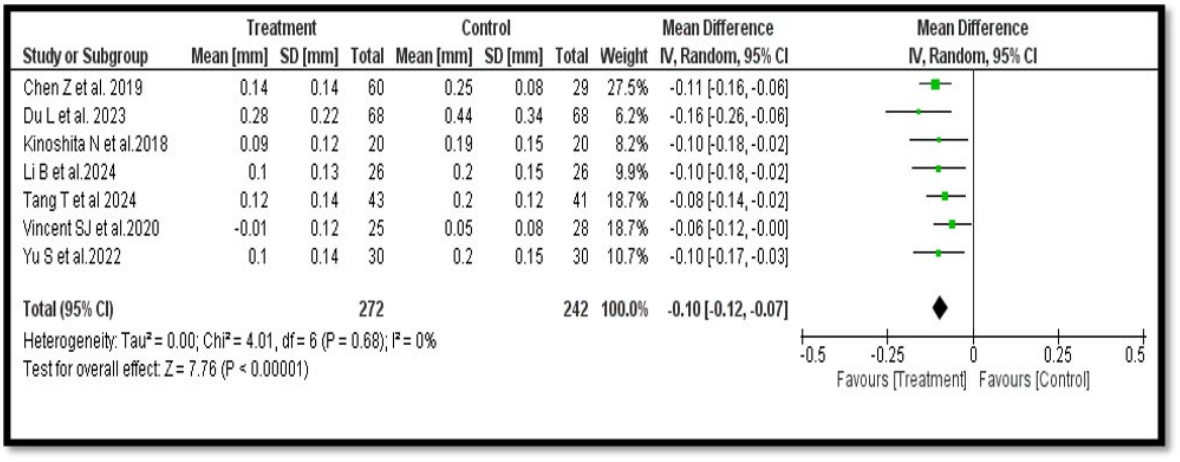
We performed the meta-analysis on combination therapy (atropine ± ortho-k) studies data (Table 3) to find the efficacy of the treatment group in controlling myopia progression in terms of AL change. We found the pooled mean difference in AL change between the treatment group (combination therapy) and the control group (monotherapy) to be -0.10 mm (95% CI: -0.12 to -0.07 mm, p < 0.00001) favoring the combination therapy (treatment group). Heterogeneity was high I^2 = 94%. We then performed sensitivity analysis to reduce the heterogeneity. After removing one study (Tan Q et al. 2019), we secured homogenous results I^2 = 0%. Heterogeneity analysis showed no substantial variability among the included studies (Tau^2 = 0.00, Chi^2 = 4.01, df = 6, p = 0.68, I^2 = 0%) as shown in the forest plot in Table 4 below.

Table 3: *Combination Therapy (Atropine ± Ortho-K) in Myopia Control*

Legend: AL: axial length, SE: spherical equivalent, OK: orthokeratology,

Author	Subjects (n)	Study Duration (Years)	Treatment Group		Control Group	
			Combination Therapy	ΔAL (mm)	Therapy	Δ AL (mm)
Kinoshita N et al.2018 [42]	20+20	1	0.01% AT + ortho-k	0.09±0.12	ortho-k	0.19±0.15
Tan Q et al. 2019 [43]	30+34	1	0.01% AT + ortho-k	-0.05±0.05	ortho-k	-0.02±0.03
Chen Z et al. 2019[44]	60+29	2	0.01% AT + ortho-k	0.14±0.14	ortho-k	0.25±0.08
Vincent SJ et al.2020 [45]	25+28	0.5	0.01% AT + ortho-k	-0.01±0.12	ortho-k	0.05±0.08
Yu S et al.2022 [46]	30+30	1	0.01% AT + ortho-k	0.10±0.14	ortho-k	0.20±0.15
Du L et al. 2023[47]	68+68	2	0.01% AT + ortho-k	0.28±0.22	ortho-k	0.44±0.34
Tang T et al 2024 [48]	43+41	1	AT + ortho-k	0.12±0.14	ortho-k	0.20±0.12
Li B et al.2024 [49]	26+26	1	0.01% AT + ortho-k	0.10±0.13	ortho-k	0.20±0.15

Table 4: *Forest Plot Showing the Meta-Analysis on Myopia Control Studies*



DISCUSSION

The main aim of this review was to evaluate the efficacy of orthokeratology and atropine in limiting myopia progression, and it was very clearly established that combination therapy—atropine use alongside orthokeratology—was far superior in controlling axial length progression compared to monotherapy with either atropine or orthokeratology. The enhanced effectiveness of combination therapy suggests a synergistic effect that could redefine current myopia management strategies. Combining atropine's pharmacological ability to inhibit axial length elongation with the mechanical reshaping effects of orthokeratology lenses might result in a compounded effect that optimally reduces myopic progression, hence providing a more robust intervention for patients at high risk of rapid myopia progression. It is also important to note that combination therapies involving atropine and other optical interventions, such as multifocal or bifocal contact lenses, have shown similar efficacy in slowing myopia progression.[48] Comparing these different approaches could guide clinicians in selecting the most appropriate intervention based on patient-specific factors.

Atropine is an anticholinergic agent that also blocks the production of epidermal growth factors that would otherwise contribute to the elongation of the eyeball, hence reducing the progression of myopia.[17] Numerous research studies have demonstrated the efficacy of atropine in myopia control Thus, atropine stands out as a leading pharmacological option for myopia management.[31-36] A review of 10 randomized controlled trials found that atropine significantly slows myopia progression (MD = -0.80) and axial elongation (MD = -0.26) compared to controls.[50]

While we noted no significant difference in adverse events between ortho-k and controls in the meta-analysis,[28] it is important to monitor the risk of complications, particularly microbial keratitis, which has been associated with overnight contact lens use.[51,52] Further research is needed to assess the safety profile of combination therapy.

Huang explored the effects of combining defocus-incorporated multiple segments (DIMS) with atropine for myopia control, reporting a mean increase in axial length (AL) over 1 year of 0.28 ± 0.24 mm for the combination group (atropine ± ortho-k) compared to 0.41 ± 0.22 mm for the DIMS-only group and 0.52 ± 0.22 mm for the single-vision (SV) group.[53] In contrast, this study observed a mean change in AL of 0.0963 ± 0.1394 mm in the combination therapy group (atropine with orthokeratology), suggesting a more pronounced reduction in axial length compared to the combination of DIMS with atropine.

Jones reported that combining 0.01% atropine with soft multifocal contact lenses reduced myopia progression (SER -0.57) and axial length elongation (-0.37 mm), and they concluded that the addition of 0.01% atropine with SMCLs with ±2.50D add power did not show improved myopia control.[54] However, atropine with orthokeratology as a combination therapy shows greater efficacy in myopia control as proved in our review.

While this review provides comprehensive insights into combination therapy, limitations include potential publication bias, the variability in treatment protocols across various studies, and small sample sizes which may influence the credibility of the findings. Despite these limitations, the review's strength lies in its robust meta-analytical approach incorporating diverse populations and treatment regimens, thus offering a thorough evaluation of combination therapy's efficacy. Evidence suggests combination therapy should be considered a viable option for patients with rapidly progressing myopia, and clinicians can enhance patient outcomes by tailoring treatment plans that incorporate both pharmacological and orthokeratology interventions.

Using both atropine and ortho-k together might be more challenging for some patients (e.g., children or those uncomfortable with contact lenses). However, based on the scientific data, if combination therapy (atropine ± ortho-k) is applied, it can enhance the clinical outcome of myopia control in those patients by increasing pupil size and peripheral defocus area.

This review underscores the need for integrating combination therapy into mainstream clinical practice as a viable and effective strategy for children with rapidly progressing myopia. As clinicians, researchers, and policymakers increasingly recognize the global burden of myopia, advancing these treatment strategies will be critical in mitigating the long-term visual and public health consequences associated with high myopia. Ultimately, combination therapy may not only redefine myopia management but also significantly improve patient outcomes worldwide.

CONCLUSION

This review aimed to comprehensively evaluate the efficacy of orthokeratology and atropine in the management of myopia progression. Based on the extensive literature reviewed, both treatments have demonstrated significant individual efficacy in controlling axial length elongation and limiting myopia progression in children. However, the evidence strongly supports that **combination therapy** using low-dose atropine in conjunction with orthokeratology offers a superior approach, leveraging the strengths of each modality to achieve enhanced control over myopia progression. ●

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STUDY CONTRIBUTORS

All the authors were involved in conceptualizing, drafting, analyzing, interpreting, reviewing, and commenting and have approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest with any organization or person for this review article.

ETHICAL APPROVAL

Not required

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