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Efficacy and safety of diquafosol sodium eye drops for children with dry eye wearing orthokeratology lens

Li Zhongming, He Yongchuan, Wang Mengyao, Liu Ying, Ren Yi

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Chongqing Aier Children's Eye Hospital, Chongqing 400020, China

Correspondence to: Ren Yi. Chongqing Aier Children's Eye Hospital, Chongqing 404100, China. renxabu@icloud.com

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地夸磷索钠滴眼液对配戴角膜塑形镜的干眼患儿的疗效及安全性

李中明,何勇川,王孟尧,刘 颖,任 毅

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作者单位:(400020)中国重庆市,重庆爱尔儿童眼科医院
作者简介:李中明,毕业于西班牙马德里康普顿斯大学,硕士,副主任医师,研究方向:近视防控及斜弱视。
通讯作者:任毅,毕业于重庆医科大学,硕士,副主任医师,研究方向:角膜眼表病. renxabu@icloud.com

摘要

目的:评估3%地夸磷索钠滴眼液在配戴角膜塑形镜且患干眼病(DED)或有DED风险的儿童中的有效性和安全性。

方法:随机对照试验。纳入于2023年11月至2024年11月在重庆爱尔儿童眼科医院就诊的DED患儿或有DED风险的患儿,按1:1的比例随机分配受试者接受每日6次3%地夸磷索钠滴眼液或空白对照。主要指标为基线至第12 wk干眼问卷-5(DEQ-5)评分的变化。次要指标包括非侵入性泪膜破裂时间(NIBUT)、泪河高度、Schirmer试验、角膜荧光染色评分以及眼轴长度。

结果:共纳入80名受试者(80眼,两组各40眼),平均年龄为11.11±1.88岁,其中女43例(54%),男37例(46%),均完成试验。12 wk后,地夸磷索钠组与空白对照组的DEQ-5评分分别为1.88±2.02与2.88±2.79(P=0.079)。地夸磷索钠组在DEQ-5评分的干燥症状评分(-0.33±0.66 *vs* 0.05±0.81, P=0.023)及NIBUT(6.18±3.73 *vs* -1.09±4.40 s, P<0.001)在第12 wk显著改善。此外,地夸磷索钠组眼轴未出现增长,而空白对照组出现了眼轴增长(0.00±0.08 *vs* 0.05±0.10 mm, P=0.013)。次要指标均未观察到其他显著差异。试验期间未发生不良事件。

结论:虽然总体DEQ-5评分无显著改善,但与空白对照相比,3%地夸磷索钠滴眼液可显著改善干燥症状及NIBUT。

关键词:干眼病;角膜塑形镜;近视;儿童;地夸磷索钠;随机对照试验

Abstract

• AIM: To evaluate the efficacy and safety of 3% diquafosol sodium eye drops in children wearing orthokeratology lenses and with dry eye disease (DED) or at risk of DED.

• METHODS: Randomized controlled trials. Children with DED or at risk of DED were randomly assigned in a 1:1 ratio to receive either 3% diquafosol sodium eye drops 6 times daily or a blank control at Chongqing Aier Children's Eye Hospital from November 2023 to November 2024. The primary endpoint was the change in the Dry Eye Questionnaire-5 (DEQ-5) score from baseline at 12 wk. Secondary assessments included non-invasive breakup time (NIBUT), tear meniscus height, Schirmer's test, corneal fluorescein staining score, and axial length.

• RESULTS: A total of 80 participants (80 eyes) were enrolled (40 in each group), the average age of the participants was 11.11±1.88 years, with 43 females (54%) and 37 males (46%), and all completed the trial. After 12 wk, the DEQ-5 scores for the diquafosol sodium group and the blank control group were 1.88±2.02 and 2.88±2.79, respectively (P=0.079). The diquafosol sodium group demonstrated a significant improvement in DEQ-5 dryness symptom scores (-0.33±0.66 *vs.* 0.05±0.81, P=0.023) and NIBUT (6.18±3.73 *vs.* -1.09±4.40 s, P<0.001) at 12 wk. Additionally, the diquafosol sodium group showed no axial length elongation, in contrast to the blank control group, which exhibited elongation (0.00±0.08 *vs.* 0.05±0.10 mm, P=0.013). No other significant differences were found in the secondary endpoints. No adverse events occurred during the trial.

• CONCLUSION: Although no statistically significant improvements were noted in the overall DEQ-5 scores, the 3% diquafosol sodium eye drops significantly improved dryness symptoms and NIBUT when compared to the blank control group.

• KEYWORDS: dry eye disease; orthokeratology; myopia; children; diquafosol sodium; randomized controlled trial
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INTRODUCTION

Myopia, the most common refractive error[1], presents a major public health burden in China with a reported prevalence of 36.6% in pediatric populations[2]. Notably, an increased prevalence of myopia was observed following the COVID-19 lockdown, likely attributable to reduced outdoor activities and increased near-work demands[3]. Orthokeratology is a non-invasive therapeutic option for myopia control, utilizing reverse-geometry lens designs to temporarily reshape the corneal curvature during nocturnal wear, thereby providing unaided daytime visual acuity[4-5]. Moreover, orthokeratology lenses may reduce axial elongation compared with single-vision lenses in children with myopia[6] and are associated with higher vision-related quality of life[7]. These advantages have driven widespread clinical adoption of orthokeratology lenses in pediatric myopia management[8].

Dry eye disease (DED) is a multifactorial disorder characterized by disrupted tear film homeostasis, hyperosmolarity-driven inflammation, and neurosensory dysfunction[9]. Similar to myopia, the widespread use of electronic devices among children has led to a high prevalence of childhood DED (reaching 23.7%)[10]. Additionally, orthokeratology lenses may induce ocular discomfort, reduce tear film stability, and increase the risk of corneal epithelial injury and DED in children[11]. These findings highlight the imperative for evidence-based DED management strategies in this population.

Diquafosol sodium, a novel P2Y2 receptor agonist, addresses multiple components of DED pathophysiology by stimulating both mucin secretion from goblet cells and aqueous production from conjunctival epithelial cells[12-13]. Several studies have established its efficacy across diverse adult populations, including those with DED of unspecified etiology[14-15], as well as in specific patient cohorts such as post-cataract surgery patients[16-17], patients with meibomian gland dysfunction[18], and those with soft contact lens-associated DED[19]. However, evidence remains limited regarding its application in pediatric populations, particularly among orthokeratology lens wearers. A prospective cohort study demonstrated significant improvements in Dry Eye Questionnaire-5 (DEQ-5) scores and non-invasive breakup time (NIBUT) with 3% diquafosol treatment in children using orthokeratology lenses[20]. Nevertheless, the absence of controlled comparison necessitates validation through rigorous randomized controlled trials (RCTs). Therefore, this RCT aimed to evaluate the efficacy and safety of 3% diquafosol sodium eye drops in children wearing orthokeratology lenses and with DED or at risk of DED.

PARTICIPANTS AND METHODS

Ethical Approval The study was approved by the Ethics Committee of Chongqing Aier Children's Eye Hospital (No. 2023-001-02). Written informed consent was provided by the patient's legal guardians. This RCT enrolled patients with DED or at risk of DED at Chongqing Aier Children's Eye Hospital from November 2023 to November 2024. This study complied with the Good Clinical Practice, current regulations, and the Declaration of Helsinki. The study was approved by the Ethics Committee of Chongqing Aier Children's Eye Hospital (No.2023-001-02) and was registered on ChiCTR (ChiCTR2500099881). Written informed consent was provided by the patient's legal guardians. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Participants The inclusion criteria were: 1) age between 8 and 18 years; 2) myopia ranging from -1.00 to -6.00 D, with regular astigmatism <-1.75 D or irregular astigmatism <-0.75 D, and corneal curvature between 39.00 and 48.00 D; 3) first-time fitting of orthokeratology lens; 4) mild-to-moderate DED or at risk of DED, defined as NIBUT of <10 s and/or non-invasive tear meniscus height (TMH) of <0.20 mm; 5) willing for regular follow-up visits. The exclusion criteria were: 1) patients with a history of allergy to any component of the study drugs or tests (*e.g.*, diquafosol sodium and fluorescein); 2) patients who used 3% diquafosol sodium eye drops within 2 wk before enrollment; 3) patients planning to modify ocular medications during the observation period for reasons other than complications from orthokeratology lens wear; 4) patients who participated in or was participating in other clinical trials within 1 mo; 5) patients deemed unsuitable for study participation by the investigators.

During the baseline period, eligible eyes were designated as study eyes. If both eyes met the criteria, the eye with the shorter baseline NIBUT was selected. If both NIBUT values were the same, the right eye was chosen as the study eye.

Intervention The fitting procedures for orthokeratology lenses adhered to relevant standards and guidelines[21]. Participants were required to wear the lenses nightly for 6-10 h. The lens fitting personnel provided professional guidance on lens wear and care to both participants and their parents. Potential participants were screened at the lens dispensing visit. Eligible patients were then enrolled and randomized in a 1∶1 ratio into either the diquafosol sodium group or the blank control group, using a random number table.

Participants in the treatment group received 3% diquafosol sodium eye drops, administered 6 times daily, with one drop each time. Recommended administration times were 7:00 AM, 10:00 AM (post-breakfast), 1:00 PM (post-lunch), 4:00 PM, 7:00 PM (post-dinner), and 10:00 PM (before bedtime). Throughout the treatment period, dosage adjustments were permitted based on clinical conditions (*e.g.*, intolerance to 6 daily administrations), with modifications made as necessary. Patients were prohibited from using other medications to relieve DED.

Endpoints and Assessments The primary endpoint was the change in the DEQ-5 score from baseline at 12 wk for the treatment group compared to the blank control group. The DEQ-5 measures the frequency of watery eyes, discomfort,

and dryness (each scored 0-4 points based on occurrence), as well as the late-day (PM) intensity of discomfort and dryness (each scored 0-5 points based on severity), with a total possible score range of 0-22 points[22].

Secondary endpoints included DEQ-5 scores at 1 and 4 wk, as well as measurements of NIBUT, TMH, Schirmer's test (SIt), corneal fluorescein staining (CFS) score, and axial length at 1, 4, and 12 wk. Safety assessments involved monitoring adverse events (AEs), with AE data collected until 2 wk after participants completed the trial.

Sample Size Based on the investigators' estimates, the proportion of patients diagnosed with subjective symptoms and signs of DED at the outpatient department of Chongqing Aier Children's Eye Hospital was approximately 700 out of 1000. Using an expected event incidence rate ($P=0.7$), allowable error ($\delta=0.1$), type I error ($\alpha=0.05$), type II error (power; $1-\beta=0.8$), and a loss to follow-up rate of 15%, the calculated total sample size was 81.

Statistical Analysis Categorical data were described using frequency (n) and percentage (%), with inter-group comparisons performed using Chi-squared or Fisher's exact tests. Continuous data were tested for normal distribution using the Shapiro-Wilk test. Normally distributed data were presented as means±standard deviations (SD) and analyzed using Student's t-test; otherwise, they were presented as medians with interquartile ranges (IQRs) and analyzed using the Mann-Whitney U test. All statistical tests were two-sided, and $P<0.05$ were considered statistically significant. Statistical analysis was performed using R software (Version 4.4.0).

Efficacy analysis was conducted based on the full analysis set (FAS) and per-protocol set (PPS). The FAS included all randomized participants who received study drug therapy and had at least one post-treatment effectiveness evaluation. The PPS included all randomized participants who received study drug therapy, had at least one post-treatment evaluation, and exhibited no protocol deviations. The safety analysis used the safety set (SS), which included all randomized participants who received study drug therapy and had at least one safety assessment.

RESULTS

Baseline Characteristics From November 2023 to November 2024, 100 patients were screened, with 80 patients (80 eyes; 40 in each group) meeting the eligibility criteria and receiving at least one dose of the study drug. All participants completed the study without major protocol deviations; both the FAS and PPS included all 80 participants, which were revealed in Figure 1.

The baseline characteristics of the participants are summarized in Table 1. The average age of the participants was 11.11±1.88 years, with 43 females (53.8%) and 37 males (46.2%). The overall mean DEQ-5 total score was 2.69±2.19, showing comparable scores between the diquafosol sodium group (2.50±1.59) and the control group (2.88±2.66). Although baseline data were generally balanced, the DEQ-5 item subscores indicated that the diquafosol sodium group had lower discomfort symptom scores (0.60±0.59 *vs.* 0.95±0.75) but higher dry eye symptom scores (0.72±0.60 *vs.* 0.50±0.75) compared to the control group. Additionally, the diquafosol sodium group exhibited a shorter NIBUT (7.24±2.41 *vs.* 9.76±4.48 s) but higher SIt values (8.12±2.36 *vs.* 7.00±2.56 mm/5 s) than the control group.

Efficacy The efficacy evaluation results for the diquafosol sodium and blank control groups at 1, 4, and 12 wk are shown in Figures 2 and 3. After treatment for 12 wk, the DEQ-5 total scores (primary endpoint) for the diquafosol sodium and blank control groups were 1.88±2.02 and 2.88±2.79 ($P=0.079$), respectively (Figure 2). Compared with the baseline, the diquafosol sodium group showed a numerically greater improvement in DEQ-5 total scores than the control group (-0.62±1.61 *vs.* -0.00±2.66, $P=0.061$; Table 2).

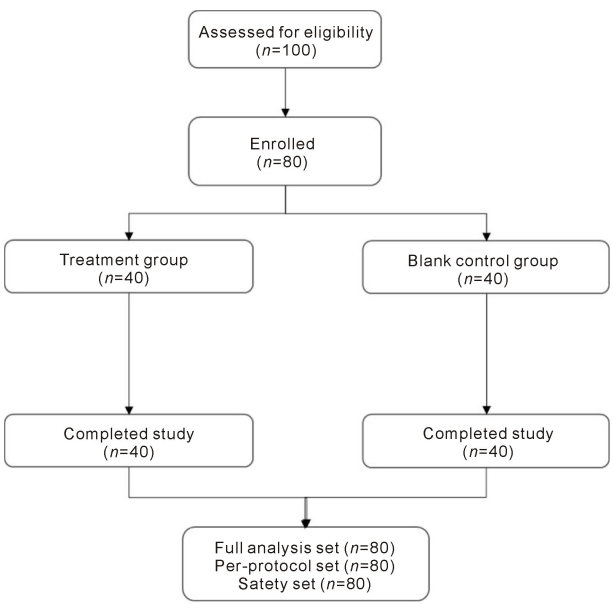

Figure 1 Participant flowchart during the trial.

Table 1 Baseline characteristics of the participants

Characteristics	All (n=80)	Blank control group (n=40)	Diquafosol sodium group (n=40)	P
Age ($\bar{x}\pm s$, years)	11.11±1.88	11.15±1.90	11.07±1.89	0.815
Sex (n, %)				0.262
Female	43 (54)	19 (48)	24 (60)	
Male	37 (46)	21 (52)	16 (40)	
Past and present medical history (n, %)				—
Yes	0	0	0	
History of allergy (n, %)				>0.999
No	79 (99)	39 (98)	40 (100)	
Yes	1 (1)	1 (2)	0	
DEQ-5 total score ($\bar{x}\pm s$, points)	2.69±2.19	2.88±2.66	2.50±1.59	0.953
Discomfort-frequency ($\bar{x}\pm s$, points)	0.78±0.69	0.95±0.75	0.60±0.59	0.034
Dryness-frequency ($\bar{x}\pm s$, points)	0.61±0.68	0.50±0.75	0.72±0.60	0.043
Watery eyes-frequency ($\bar{x}\pm s$, points)	0.62±0.74	0.65±0.80	0.60±0.67	0.983
Discomfort-PM intensity ($\bar{x}\pm s$, points)	0.36±0.68	0.47±0.85	0.25±0.44	0.330
Dryness-PM intensity ($\bar{x}\pm s$, points)	0.31±0.54	0.30±0.61	0.33±0.47	0.512
TMH($\bar{x}\pm s$, mm)	0.18±0.04	0.17±0.05	0.18±0.04	0.468
Corneal and conjunctival staining score ($\bar{x}\pm s$, points)	0.28±0.80	0.15±0.43	0.40±1.03	0.613
NIBUT ($\bar{x}\pm s$, s)	8.50±3.79	9.76±4.48	7.24±2.41	0.012
S I t ($\bar{x}\pm s$, mm/5 s)	7.56±2.51	7.00±2.56	8.12±2.36	0.035
Total axial length ($\bar{x}\pm s$, mm)	24.41±0.91	24.51±0.87	24.31±0.96	0.338

DEQ-5:Dry Eye Questionnaire-5; TMH: Tear meniscus height; NIBUT: Non-invasive breakup time; SIt: Schirmer's test.

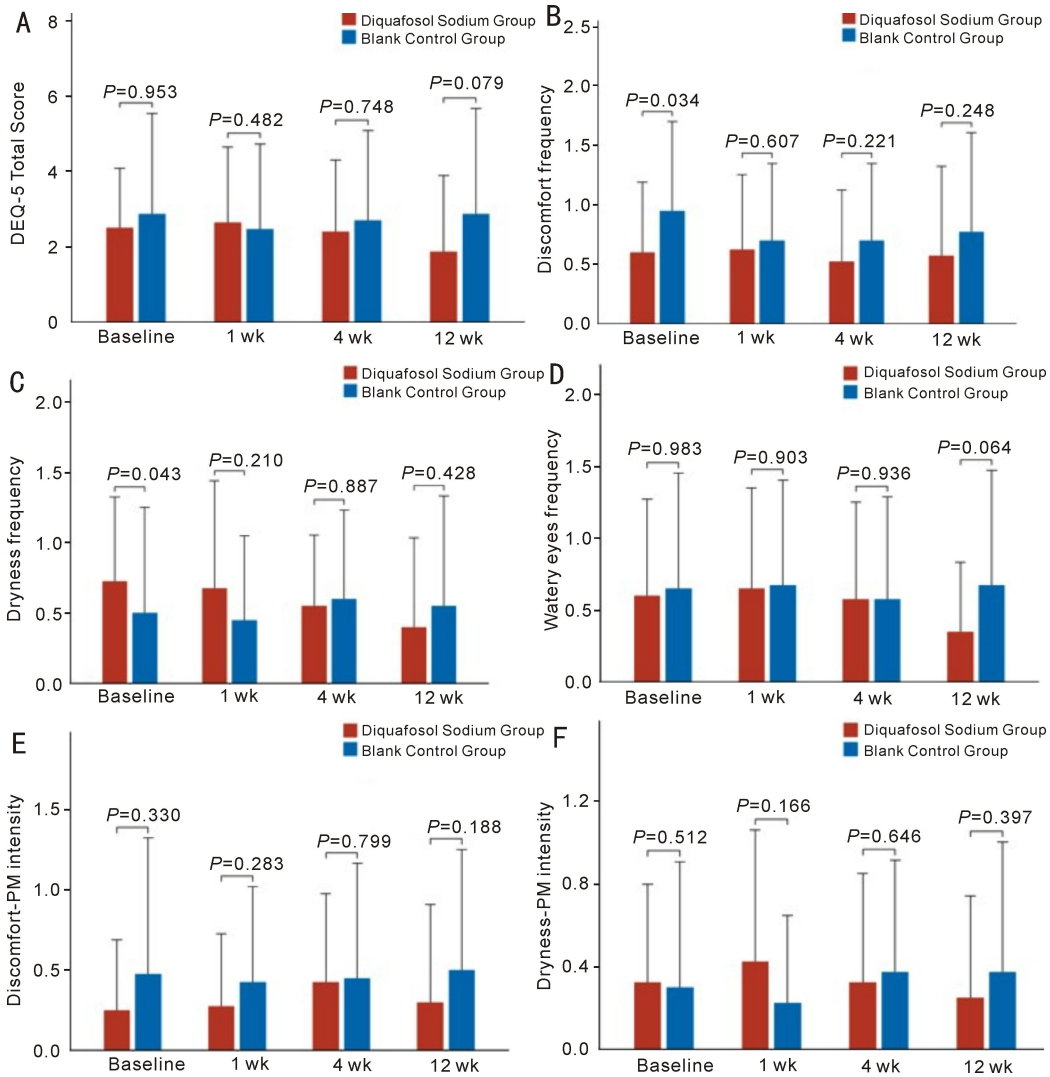

Figure 2 Dry Eye Questionnaire-5 scores. A: DEQ-5 total score; B-F: DEQ-5 item subscores.

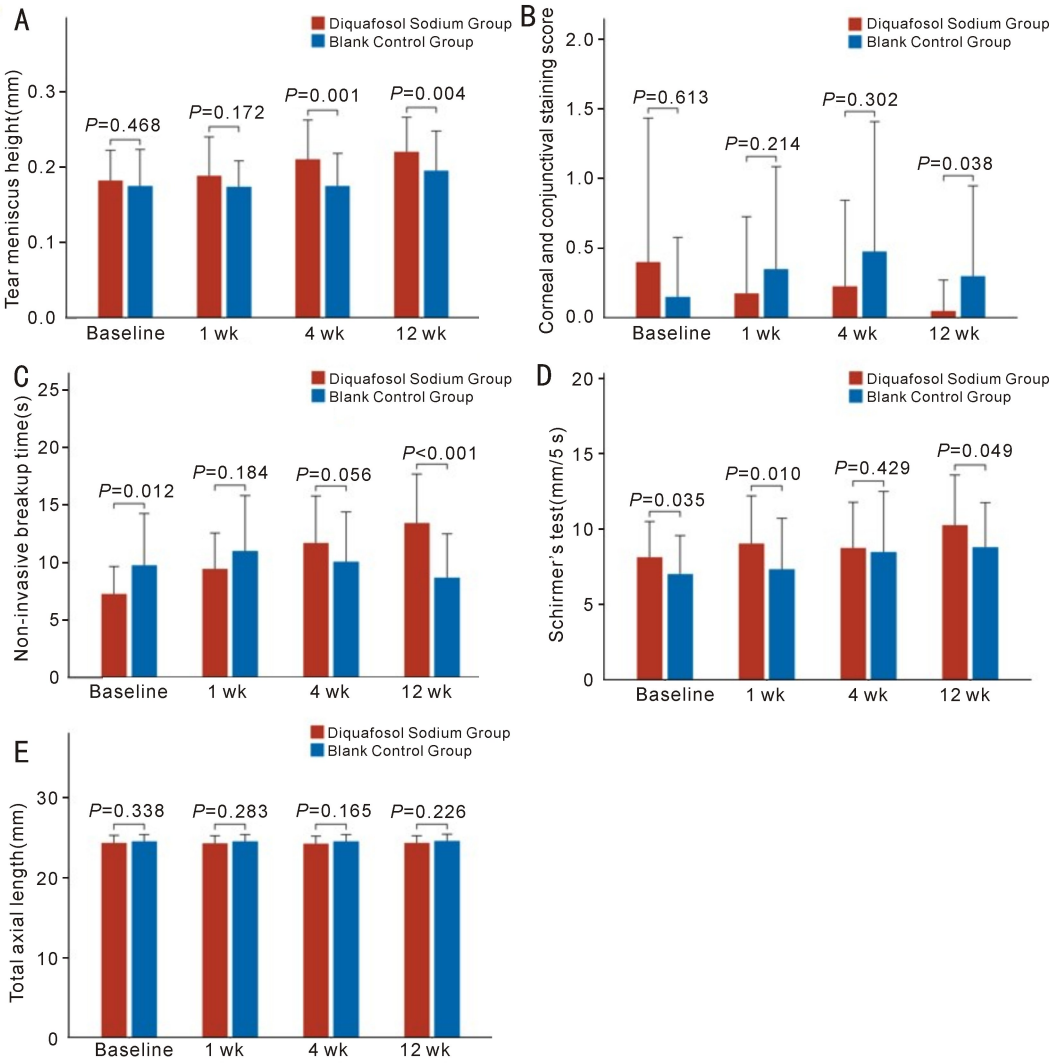

Figure 3 Other efficacy endpoints. A: Tear meniscus height; B: Corneal and conjunctival staining score; C: Non-invasive breakup time; D: Schirmer's test; E: Total axial length.

The diquafosol sodium group demonstrated significantly improved dryness symptoms and signs compared withthe baseline. At 4 wk, the diquafosol sodium group showed significantly greater improvement in DEQ-5 dryness symptom scores compared with the blank control group (diquafosol sodium group: -0.17 ± 0.59; blank control group: 0.10 ± 0.81; $P=0.046$). At 12 wk, the diquafosol sodium group exhibited further improvement in DEQ-5 dryness symptom scores (diquafosol sodium group: -0.33 ± 0.66; blank control group: 0.05 ± 0.81; $P=0.023$). A similar improvement trend was observed in NIBUT measurements. At 4 wk, the diquafosol sodium group showed a NIBUT improvement of 4.46 ± 3.48 s from baseline, while the blank control group showed 0.30 ± 4.92 s ($P<0.001$). At 12 wk, the improvements were 6.18 ± 3.73 s and -1.09 ± 4.40 s for the two groups, respectively ($P<0.001$; Table 2).

Significant differences were observed between the two groups in slowing the growth of total axial length. Compared with baseline, neither group showed noticeable axial elongation at 1 wk, with changes of -0.03 ± 0.03 mm in the treatment group and -0.01 ± 0.02 mm in the blank control group ($P<0.001$ between the two groups). At 4 and 12 wk, the diquafosol sodium group exhibited no significant axial elongation, whereas the blank control group showed an increased axial length (both $P<0.05$; Table 2).

There were no significant differences at 12 wk between the two groups regarding discomfort frequency, watery eye frequency, discomfort PM intensity, dryness PM intensity, TMH, or corneal and conjunctival staining scores (all $P>0.05$; Table 2). No AEs occurred during the study.

DISCUSSION

This study represents the first RCT evaluating the efficacy and safety of 3% diquafosol sodium eye drops in children who wearing orthokeratology lenses and presented with DED or were at risk of DED. While the diquafosol sodium group demonstrated numerical improvements in DEQ-5 total scores compared to the control group, these changes did not achieve statistical significance. The diquafosol sodium group exhibited numerical improvements in DEQ-5 total scores; however, these changes did not reach statistical significance. However, several secondary endpoints showed favorable outcomes, including DEQ-5 dryness symptom scores, NIBUT, and axial length elongation. Additionally, no AEs were reported during the trial or the 2-week post-trial safety period, supporting the

Table 2 Changes from baseline to each follow-up time point in efficacy endpoints between the two groups $\bar{x}\pm s$

Characteristics	Blank control group($n=40$)	Diquafosol sodium group($n=40$)	P
DEQ-5 total score (points)			
Baseline	2.88±2.66	2.50±1.59	0.953
1 wk	-0.40±1.58	0.15±1.12	0.170
4 wk	-0.17±1.74	-0.10±1.22	0.964
12 wk	0.00±2.66	-0.62±1.61	0.061
Discomfort-frequency (points)			
Baseline	0.95±0.75	0.60±0.59	0.034
1 wk	-0.25±0.59	0.03±0.42	0.025
4 wk	-0.25±0.87	-0.07±0.57	0.218
12 wk	-0.17±0.98	-0.03±0.70	0.540
Dryness-frequency (points)			
Baseline	0.50±0.75	0.72±0.60	0.043
1 wk	-0.05±0.68	-0.05±0.60	0.893
4 wk	0.10±0.81	-0.17±0.59	0.046
12 wk	0.05±0.81	-0.33±0.66	0.023
Watery eyes-frequency (points)			
Baseline	0.65±0.80	0.60±0.67	0.983
1 wk	0.03±0.70	0.05±0.45	0.725
4 wk	-0.07±0.69	-0.03±0.62	0.581
12 wk	0.03±0.92	-0.25±0.67	0.149
Discomfort-PM intensity (points)			
Baseline	0.47±0.85	0.25±0.44	0.330
1 wk	-0.05±0.60	0.03±0.28	0.739
4 wk	-0.03±0.53	0.17±0.45	0.078
12 wk	0.03±0.80	0.05±0.64	0.877
Dryness-PM intensity (points)			
Baseline	0.30±0.61	0.33±0.47	0.512
1 wk	-0.07±0.42	0.10±0.59	0.236
4 wk	0.07±0.47	0.00±0.60	0.549
12 wk	0.07±0.80	-0.07±0.57	0.220
TMH (mm)			
Baseline	0.17±0.05	0.18±0.04	0.468
1 wk	-0.00±0.05	0.01±0.05	0.521
4 wk	0.00±0.06	0.03±0.06	0.043
12 wk	0.02±0.06	0.04±0.06	0.057
Corneal and conjunctival staining score (points)			
Baseline	0.15±0.43	0.40±1.03	0.613
1 wk	0.20±0.88	-0.23±1.10	0.260
4 wk	0.33±0.94	-0.17±1.28	0.221
12 wk	0.15±0.80	-0.35±1.05	0.067
NIBUT (s)			
Baseline	9.76±4.48	7.24±2.41	0.012
1 wk	1.24±5.04	2.19±2.14	0.277
4 wk	0.30±4.92	4.46±3.48	<0.001
12 wk	-1.09±4.40	6.18±3.73	<0.001
SⅠt (mm/5 s)			
Baseline	7.00±2.56	8.12±2.36	0.035
1 wk	0.33±3.38	0.90±2.31	0.284
4 wk	1.48±4.22	0.60±2.91	0.699
12 wk	1.80±3.41	2.12±3.46	0.480
Total axial length (mm)			
Baseline	24.51±0.87	24.31±0.96	0.338
1 wk	-0.01±0.02	-0.03±0.03	<0.001
4 wk	0.01±0.05	-0.08±0.51	0.005
12 wk	0.05±0.10	0.00±0.08	0.013

DEQ-5: Dry eye questionnaire-5; TMH: Tear meniscus height; NIBUT: Non-invasive breakup time; SⅠt: Schirmer's test.

favorable safety profile of diquafosol sodium in this population. These findings provide clinically relevant insights into DED management for pediatric orthokeratology lens wearers.

The lack of statistically significant differences in DEQ-5 total scores may be attributed to the inclusion of treatment-naïve orthokeratology lens wearers. In a prospective investigation evaluating diquafosol sodium in pediatric orthokeratology lens wearers, DEQ-5 total scores decreased significantly from baseline to 1 mo (5.54±3.25 to 3.85±2.98 s, $P<0.001$) in children wearing orthokeratology lenses. However, subgroup analysis revealed DEQ-5 improvements were statistically significant only in patients who had used orthokeratology lenses for one year, whereas new wearers exhibited improvement only in watery eye frequency (0.88±0.99 *vs.* 0.54±0.81, $P=0.03$)[20]. Our RCT, performed in children, which exclusively enrolled treatment-naïve orthokeratology lens wearers, similarly showed non-significant between-group differences in total DEQ-5 scores despite numerical improvements. These collective findings suggest that measurable improvements in comprehensive dry eye symptoms may require extended orthokeratology lens wear duration. Future RCTs focusing on the effects of diquafosol sodium in children with DED in long-term orthokeratology lens wearers would be necessary to refine the results. Nevertheless, in the current study, diquafosol sodium demonstrated significant improvements in alleviating DEQ-5 dryness subscore compared to the control. These findings suggest that 3% diquafosol sodium eye drops may effectively target dryness-related manifestations of DED, though they do not appear to broadly address all DED symptoms.

Notably, the diquafosol sodium group achieved statistically significant improvements in both subjective dryness symptoms (measured by DEQ-5) and objective tear film stability (measured by NIBUT). These findings aligned with previous diquafosol studies. In the aforementioned study, children with DED who were first-time wearers of orthokeratology lenses showed a baseline average NIBUT of 8.65±5.24 seconds, which increased to 12.65±6.33 seconds after 1 mo ($P=0.00$)[20]. Furthermore, consistent with previous investigations of diquafosol sodium in DED management[10,16], this study demonstrated a similar trend showing more pronounced clinical improvement in dry eye signs with extended diquafosol sodium treatment. Therefore, this study demonstrated that 3% diquafosol sodium ophthalmic solution effectively improved both subjective symptoms and objective signs of ocular dryness in pediatric orthokeratology lens wearers, with improved efficacy appearing with extended treatment durations.

Another intriguing finding was the difference in axial length progression between groups. In the present study, participants in the diquafosol sodium group showed no changes in axial length, while the blank control group showed axial length elongation. This observation aligns with previous cross-sectional data demonstrating a significant relationship between tear film stability and axial length ($\beta=-0.067$, $P=0.004$)[23]. However, it is critical to emphasize that the current RCT was designed to establish causal relationships between NIBUT and axial length changes. Further mechanistic investigations are warranted to clarify this association, particularly given the multifactorial nature of axial elongation control[24].

This study has several limitations. First, the single-center design introduces potential selection bias and limits generalizability. Second, this study used a blank control as a comparator, rather than an active comparator. This design does not isolate the effect of the active drug from that of the formulation vehicle, whose physical properties may independently influence ocular surface parameters. As a result, the observed difference between groups may reflect a combination of active drug plus vehicle effects, making it difficult to attribute benefits solely to diquafosol. This design may overestimate the clinical relevance of diquafosol in real-world practice, where patients typically receive some form of lubricating or vehicle-containing drop rather than no active treatment at all. Hence, the absence of active comparator arms (*e.g.*, artificial tears) precludes comparative effectiveness assessments. Furthermore, the 12-week duration may have been insufficient to capture longitudinal changes in DEQ-5 scores, particularly in treatment-naïve orthokeratology lens users. Future multicenter trials with extended follow-up periods and active controls are needed to validate these findings.

In conclusion, although the diquafosol sodium group showed numerically greater improvement in DEQ-5 total scores than the control group, no statistically significant inter-group differences were observed. On the other hand, improvements were observed with diquafosol sodium regarding DEQ-5 dryness symptoms and NIBUT compared with the control group, without safety events. The diquafosol sodium group showed no elongation in axial length.

Conflicts of Interest: Li ZM, None; He YC, None; Wang MY, None; Liu Y, None; Ren Y, None.

Authors' contributions: Ren Y, He YC and Li ZM conceptualized the manuscript; Ren Y, He YC and Li ZM designed methodology, acquired the funding support and resources, and supervised the work; Li ZM, Wang MY and Liu Y formally analyzed and investigated the manuscript, and wrote the original draft; Ren Y and He YC reviewed and edited the manuscript. All authors read and approved the manuscript for publication.

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