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Meta-analysis

The effect of 3% diquafosol on the improvement of ocular surface post cataract surgery: A meta-analysis for time of intervention

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ABSTRACT

Purpose: The effect of interventional time for 3% Diquafosol reatment in post-cataract surgery has not been well established. A meta-analysis was performed to evaluate the improvement of ocular surface condition in post-cataract surgery patients who received 3% DQS for various treatment durations.

Methods: Studies were performed based on 5 databases: PubMed, Cochrane Library, Web of Science, Embase, and China National Knowledge Infrastructure. Data on changes in Schirmer's test, tear breakup time (TBUT), corneal staining score, and OSDI score were collected for meta-analysis.

Results: A total of 621 affected eyes from 9 independent clinical studies were included. 6 studies conducted Schirmer's test after the application of 3% DQS. Meta-analysis showed that the difference between 3% DQS and control groups was not statistically significant for short-term application (less than or equal to 1 month) (WMD = 0.14, $P = 0.27$, 95% CI:-0.11 to 0.39), but was statistically different for long-term application (longer than or equal to 3 months) (WMD = 0.76, $P = 0.03$, 95% CI:0.08 to 1.45). For the corneal fluorescence staining score, the data from 6 studies indicated that the improvement was statistically significant for short-term application (WMD = -0.40, $P < 0.00001$, 95% CI:-0.72 to -0.08) and but not long-term application (WMD = -0.21, $P = 0.26$, 95% CI:-0.57 to 0.15). For TBUT, the data from 9 studies indicated that both short-term and long-term application showed significant improvement (WMD = 1.70, $P < 0.00001$, 95% CI:1.38 to 2.03; WMD = 1.52, $P < 0.00001$, 95% CI:1.09 to 1.95). Similar results were observed in data from 5 studies with OSDI scores, where both short-term and long-term application showed statistically significant improvements (WMD = -5.41, $P < 0.00001$, 95% CI: -7.02 to -3.81; WMD = -6.10, $P < 0.00001$, 95% CI:-8.52 to -3.67).

Conclusions: The application of 3% DQS in post-operative cataract patients has a positive effect on improving the ocular surface conditions. Short-term application resulted in lower corneal staining scores, prolonged TBUT, and improved OSDI scores. Long-term application improved Schirmer's test results, TBUT, and subjective symptoms.

Key messages: The updated article suggests that 3% Diquafosol is less effective in the short term after cataract surgery, and that application over three months can improve the patient's ocular surface condition.

1. Introduction

Cataracts are still the leading cause of blindness in the world. Current surgical cataract treatment achieves good prognosis and greatly improves vision. However, due to intraoperative ocular surface irrigation, ultrasound energy, and eye drops applied on the ocular surface during the perioperative period,[1,2] most postoperative cataract patients experience distinct ocular surface abnormalities. Moreover, the application of NSAID drugs in the eyes after cataract surgery can reduce the density of conjunctival goblet cells, which aggravates the ocular surface damage of patients after cataract surgery.[3] These result in symptoms such as soreness, stinging sensation, foreign body sensation, burning sensation, and visual fatigue, which adversely affect patients' quality of life after surgery.[4] Artificial tears are now commonly used in clinics to improve patients' post-operative ocular surface symptoms. However, traditional artificial tears, which mainly replenish aqueously, are unable to improve complex symptoms.

Diquafosol sodium is a P2Y2 receptor agonist that promotes the secretion of aqueous fluid and mucin from ocular surface tissues and encourages corneal epithelial repair. Currently, diquafosol sodium is commonly used to improve dry eye symptoms.[5–7] Studies have used this

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drug in the treatment of post-operative dry eye or suspected dry eye in cataract patients, and some clinical studies have suggested that diquafosol sodium can be routinely used for post-cataract surgery patients. However, there are no clear conclusions on the association between the therapeutic effects and the application period of this drug in post-cataract surgery patients. Available meta-analyses have also failed to clearly characterise the relationship between the ocular surface condition after cataract surgery and the duration of application of the drug, and few studies were included.[8]

In this meta-analysis, we evaluated recent clinical studies on the use of 3% diquafosol sodium eye drops (3% DQS) for improving the post-operative ocular surface conditions of cataract patients. We then analysed the therapeutic effects of 3% DQS compared to traditional artificial tears applied at different stages of postoperative cataract surgery using indicators including Schirmer's test, tear breakup time (TBUT), corneal staining, and OSDI score.

2. Materials and methods

2.1. Study selection

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The relevant available literature was acquired from PubMed, Cochrane Library, MEDLINE, and China National Knowledge Infrastructure up to 2021. “Cataract Extraction”, “Cataract Surgery”, and “diquafosol” were used as keywords or subject terms for searches. The following search terms were used: “diquafosol” AND “Cataract Extraction”, “diquafosol” AND “Cataract Surgery”. Moreover, the list of citations retrieved and the studies involved in the relevant meta-analyses available were reviewed.

2.2. Inclusion criteria

Participants were included in the study when they met the following criteria: adults with cataracts who had undergone conventional cataract surgery (including small incision cataract surgery and phacoemulsification) with confirmed normal upper and lower eyelid morphology and closure and without internal eye disease, history of ocular laser surgery and ocular trauma, or autoimmune disease. Intervention: application of 3% DQS for post-cataract surgery ocular surface management. Outcomes: Ocular surface index data at different times after surgery including at least one of Schirmer’s test, TBUT, corneal staining score, or OSDI score. Exclusion criteria: case reports, descriptive studies, animal studies, and randomised controlled trials involving too many confounding factors in the treatment.

2.3. Data extraction and quality assessment

Two reviewers conducted an independent search according to a predetermined search strategy, screening articles by title, abstract, and keywords. The full texts of articles that met the criteria were read and basic information was extracted, including author, year of publication, sample size, gender ratio, and treatment factors. According to the standards of the Cochrane manual, literature quality assessment and bias risk assessment were carried out. If these criteria were not cleared, a third person was introduced to conduct an independent full text assessment. Moreover, the Newcastle-Ottawa Scale (NOS) was used to perform quality assessment for retrospective studies.

2.4. Statistical methods

Statistical analysis was performed using Cochrane Review Manager (RevMan version 5.3) software. The 95% confidence intervals (95% CI) were calculated for continuous variables. Heterogeneity was tested across studies by the χ^2 test and the I^2 statistic. If I^2 <50%, heterogeneity between studies was not statistically significant and the fixed-effects model was selected. If I^2 > 50%, heterogeneity was statistically significant. In this case, sensitivity analysis was performed and the influence of a single study on the pooled effect was examined by removing 1 study at a time. If heterogeneity could not be eliminated, a random-effects model was chosen for analysis. In addition, funnel plots were used to evaluate publication bias. The entire sample was divided into groups for analyses according to the duration of drug application in the study, as either short-term application (duration of use less than or equal to 1 month) or long-term application (duration of use longer than or equal to 3 months).

3. Results

3.1. Characteristics of the studies

The selection process for the inclusion of studies in this meta-analysis is summarised in Fig. 1. Thirty-four potentially relevant studies were initially identified via database searches. After excluding duplicate studies and initial screening, ten full-text articles were selected. One out of ten was excluded due to incomplete data. Finally, nine eligible published articles were recruited to our meta-analysis,[9–17] including eight randomised controlled trials[9,11–17] and one retrospective study.[10] A total of 621 eyes were included, with 314 eyes in the control group and 307 eyes in the experimental group. The main characteristics of the literature included are displayed in Table 1.

3.2. Quality assessment

Randomised controlled trials and retrospective studies were evaluated separately according to the Cochrane Handbook and the NOS scale. The results of the randomised controlled trials evaluation are shown in the Supplemental Figs. 1 and 2. Of these, two studies ranked as high-quality and six studies failed to demonstrate clear blinding. One retrospective study was evaluated as a high-quality study according to the NOS scale (Table 2).

3.3. Analysis of Schirmer’s test

Six of the included studies performed Schirmer's test with short-term follow-up (duration of use less than or equal to 1 month) with the application of 3%DQS, including 209 eyes in the experimental group and 198 eyes in the control group. Long-term follow-up (duration of use longer than or equal to 3 months) was carried out in 5 of the studies, including 195 eyes in the experimental group and 188 eyes in the control group. Studies were divided into two groups according to short-term and long-term applications. Our analysis showed no statistical heterogeneity (I^2 <50%) between the studies and a fixed-effects model was used to perform the analysis.

Compared to the control group, short-term application of 3% DQS did not show a statistically significant difference (WMD = 0.14, P = 0.27, 95% CI: -0.11 to 0.39). However, after long-term application, the 3% DQS group showed statistically higher Schirmer’s test values than the control group (WMD = 0.76, P = 0.03, 95% CI: 0.08 to 1.45) (Fig. 2).

3.4. Analysis of corneal fluorescence staining score

Six of the included studies measured corneal fluorescence staining score after the application of 3% DQS, two of which tested patients with long-term application. Meta-analysis was performed based on their test results, with subjects grouped by short-term or long-term application. The results of the fixed-effects model showed statistical heterogeneity (I^2 >50%) across studies, with the use of a case-by-case exclusion and sensitivity analysis failing to reveal a significant source of heterogeneity. A random-effects model was applied to the analysis.

Corneal fluorescence staining scores were significantly lower after short-term 3% DQS application compared to the control group (WMD = -0.40, P <0.00001, 95% CI: -0.72 to -0.08), but there was no statistically significant

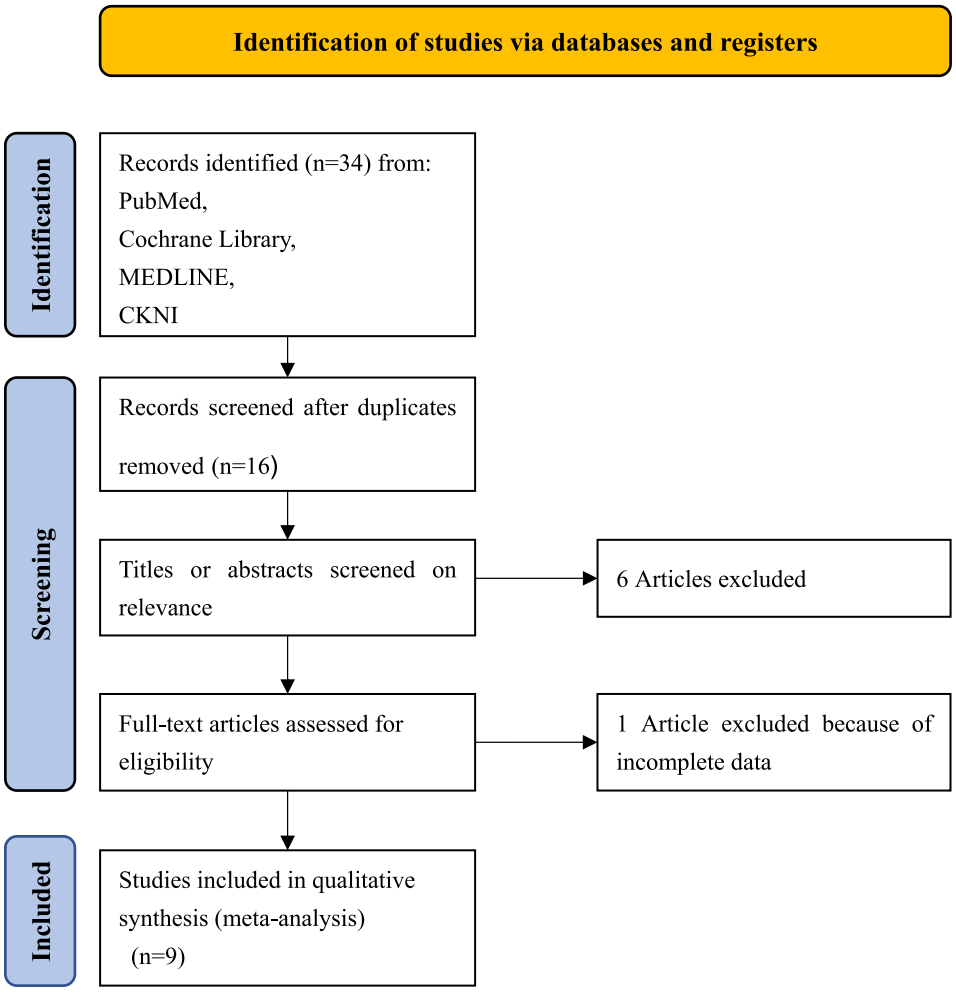

Fig. 1. Flow diagram of study selection.

Table 1
Main characteristics of studies included in this meta-analysis.

Auther	Design	Publication Year	Group size(eyes)		Gender radio (male/female)		Average age (years old)		Application Method		Follow-up period (postoperative)	Clinical Outcome
			Control	DQS	Control	DQS	Control	DQS	Control	DQS		
Beak	RCT	2016	32	32	10/22	10/22	67.66 ± 11.86	67.66 ± 11.86	AT	3% DQS	1–8 weeks	ABCDEG
Cui L	RCT	2017	44	50	16/28	18/32	63.39 ± 15.77	64.48 ± 16.75	AT	3% DQS	1–12 weeks	ABCDFG
Inoue Y	RCT	2017	33	26	7/15	10/10	70.6 ± 7.6	74.9 ± 8.1	AT	3% DQS	4–8 weeks	ABDFG
Kim S	RCT	2021	24	28	11/13	11/17	67.08 ± 7.73	69.57 ± 6.22	AT	3% DQS	1–15 weeks	ABDFG
Lee H	retrospective study	2017	33	31	10/23	10/21	66.7 ± 9.0	69.0 ± 10.9	None	3% DQS	1–12 weeks	ABDG
Park H	RCT	2016	49	45	10/39	17/28	65.37 ± 10.02	65.53 ± 11.15	AT	3% DQS	1–12 weeks	ABDFG
Miyake K	RCT	2017	79	75	23/56	30/45	70.3 ± 7.1	71.7 ± 7.4	AT	3% DQS	4–8 weeks	ABDG
Liu Y	RCT	2020	27	27	?	?	63.16 ± 8.7	62.85 ± 8.54	AT	AT+3% DQS	1–4 weeks	ABG
Jun I	RCT	2019	38	41	12/26	30/49	68.0 ± 7.6	69.72 ± 8.89	AT	3% DQS	1–3 months	ABDG

AT: Artificial Tears; **3% DQS:** 3% Diquafosol eye drop; **?:** unclear.
A: Schirmer's test (mm); **B:**TBUT; **C:**TCR (Tears clear rate); **D:**OSDI Score; **E:** Tear meniscus height (TMH) (mm); **F:** HO; **G:** Corneal staining scores.

Table 2
NOS scale of the retrospective study.

Auther	selection				Comparability		Exposure		Quality
	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Control for important factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Lee H	√	√	√	√	√		√	√	High

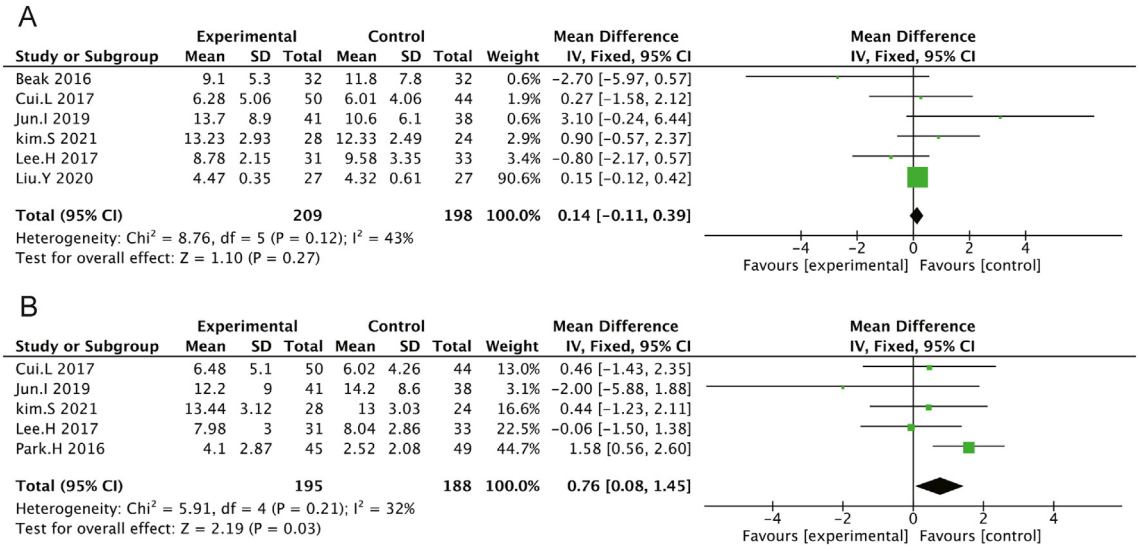

Fig. 2. Forest plot for the weighted mean difference of Schirmer's test. A. short-term 3% DQS B. long-term 3% DQS.

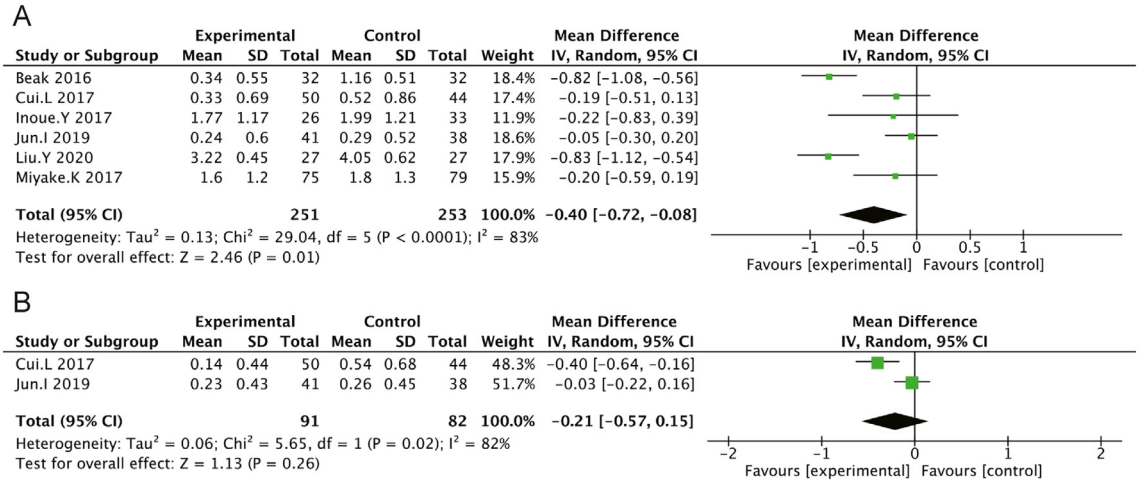

Fig. 3. Forest plot for the weighted mean difference of corneal staining score. A. short-term 3% DQS B. long-term 3% DQS.

difference between the experimental and control groups after long-term application (WMD = -0.21, $P = 0.26$, 95% CI: -0.57 to 0.15) (Fig. 3).

3.5. Analysis of TBUT

Nine of the studies included a TBUT test after 3% DQS application and five studies reported long-term application data; these were grouped according to short-term and long-term application. The results of the fixed-effects model showed statistical heterogeneity (I^2 >50%) within the long-term groups. Using the leave-one-out analysis, we found that Miyake's study was identified as the main source of heterogeneity. Fixed-effects model analysis was performed after Miyake's study was excluded.

Compared to the control group, TBUT values were significantly higher and statistically different in the experimental group compared to the control group for both short-term application and long-term application (WMD = 1.70, P <0.00001, 95% CI: 1.38 to 2.03; WMD = 1.52, P <0.00001, 95% CI: 1.09 to 1.95) (Fig. 4).

3.6. Analysis of OSDI score

Four of the studies included OSDI scores after short-term application, and five studies reported data following long-term application. Meta-analysis was performed based on their test results, with studies grouped by short-term or long-term application. The results of the fixed-effects model analysis showed statistical heterogeneity (I^2 >50%) among the long-term groups. After excluding the data from Cui. L's article using the

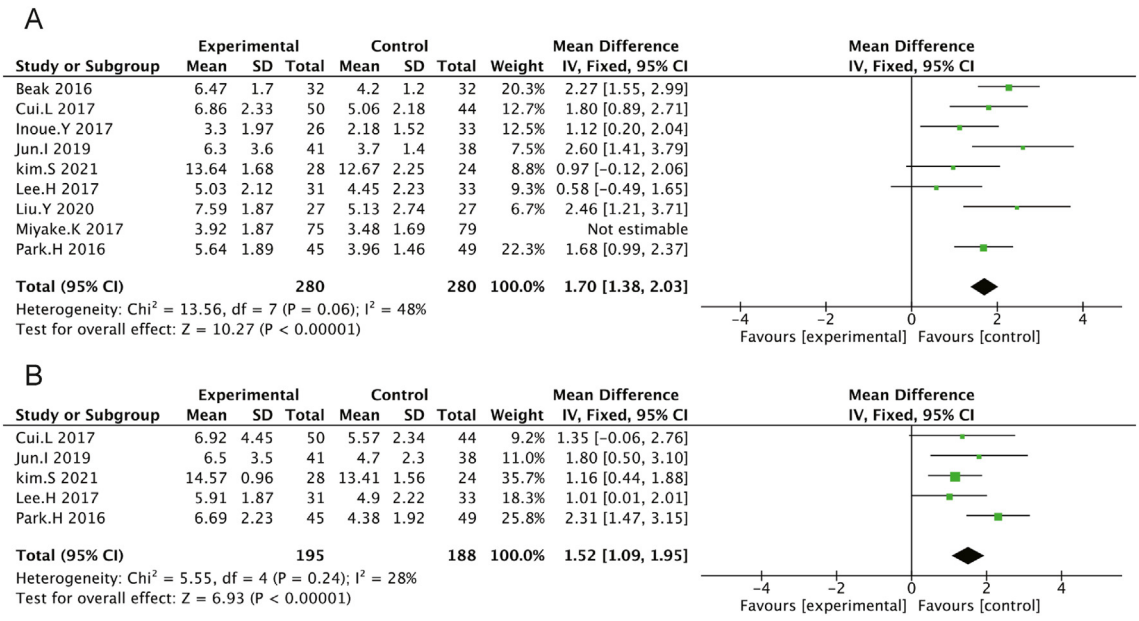

Fig. 4. Forest plot for the weighted mean difference of TBUT. A. short-term 3% DQS B. long-term 3% DQS.

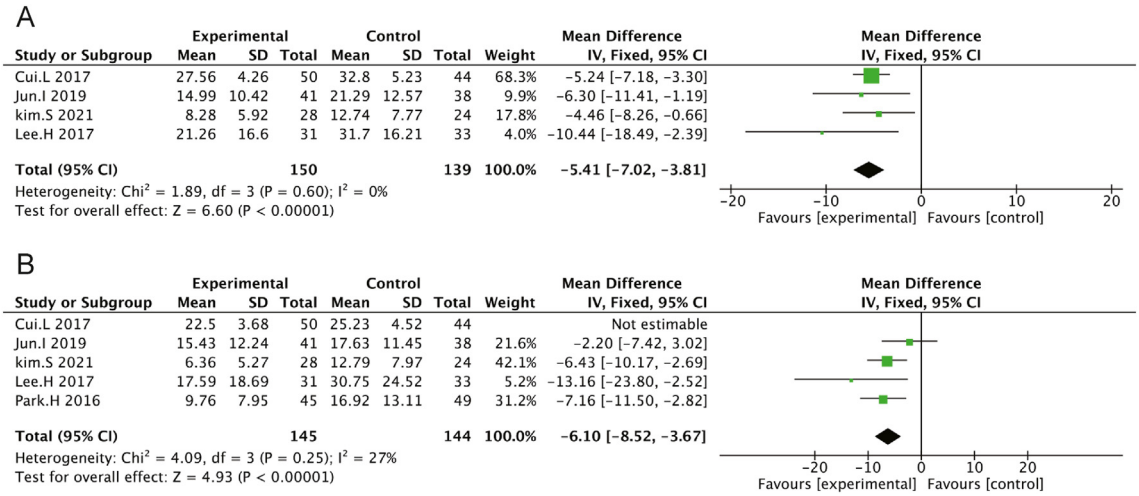

Fig. 5. Forest plot for the weighted mean difference of OSDI Score. A. short-term 3% DQS B. long-term 3% DQS.

leave-one-out analysis, the two groups had no statistical heterogeneity.

A fixed-effects model analysis showed a statistically significant reduction in OSDI scores with both short-term application and long-term application (WMD = -5.41, $P < 0.00001$, 95% CI: -7.02 to -3.81; WMD = -6.10, $P < 0.00001$, 95% CI:-8.52 to -3.67) compared to the control group (Fig. 5).

3.7. Sensitivity analysis and publication bias

Sensitivity analyses were conducted using a leave-one-out analysis. No evidence of publication bias was revealed by visual inspection of the funnel plot (Supplemental Fig. 3).

4. Discussion

Diquafosol sodium is a P2Y2 agonist that promotes the secretion of aqueous fluid and mucin from the ocular surface, which improves the composition and the stability of the tear film. Artificial tears are commonly used in clinics to improve the ocular surface of cataract patients who often have ocular surface problems after surgery. Many studies have demonstrated positive effects of 3% diquafosol on the ocular surface condition. A previous meta-analysis has been performed for 3% diquafosol in patients with post-cataract surgery dry eyes,[8] but earlier studies on this drug are scarce. We have expanded the scope of analysis because postoperative dry eye symptoms that are clearly diagnosed are not widespread. Our study also led to the new conclusion that the role of 3% diquafosol varies according to different durations of administration in the postoperative period.

In this meta-analysis, we evaluated the short-term and long-term improvement of the ocular surface condition in post-operative cataract patients by comparing several common clinical ocular surface indices. We found that 3% diquafosol sodium eye drops applied after cataract surgery had positive effects on Schirmer's test, corneal fluorescence staining and TBUT, as well as the OSDI score which represents the subjective symptoms of the patients. For Schirmer's experiment, the improvement mainly manifested itself in long-term application, with a poor short-term effect, which may indicate that it takes time for diquafosol sodium to promote tear secretion. The short-term impact of 3% DQS on corneal fluorescence staining was most pronounced, while corneal fluorescence staining in patients treated for more than three months was

not statistically different from the control group. For most patients who undergo cataract surgery, corneal damage gradually normalises after surgery, which may explain why there were no statistically significant differences in corneal staining score over three months after surgery. Its effect was most pronounced for TBUT, with significant improvement when applied over both the short-term and long-term. The OSDI scale is generally used for the investigation of dry eye conditions and assesses patients' subjective symptoms in the form of a questionnaire. Our analysis shows that the 3% DQS also has a positive effect on improving patients' OSDI scores, both short- and long-term. In addition, the patients involved in the study of Inoue Y received Diclofenac eye drops after cataract surgery. Although the researchers did not discuss the effect of NSAID drugs in-depth, the conclusion was consistent with the current study, which provides further evidence that 3% DQS can counter the effect of NSAID drugs on the density of conjunctival goblet cells in post-cataract surgery patients to some extent, which is conducive to the recovery of the ocular surface. However, further research is needed to prove this. We also referred to the existing meta-analysis associated with 3% DQS. Compared to this study, we analysed the effects of this drug on the ocular surface of post-cataract surgery patients in greater detail and obtained different and more accurate conclusions after including newly published studies from recent years. Overall, an improvement in the postoperative ocular surface conditions of the patients was evident with postoperative 3% DQS application. This may provide guidance for the postoperative use of medication in cataract patients and a basis for adjusting dosing regimens in different stages.

3% diquafosol sodium eye drops are a drug that has been marketed in recent years yet lacks substantial research; therefore, the number of included studies is small. Of all the literature that has been included, the longest follow-up period was 15 weeks and there was a lack of data on longer follow-up periods. Another limitation of this study is the absence of standards guiding the study of post-cataract surgery follow-up processes.

5. Conclusions

In conclusion, this meta-analysis evaluated the improvement of ocular surface conditions in post-cataract surgery patients who received 3% DQS over various interventional times. Our results showed improvement with both short-term and long-term application. Although Schirmer's test failed to show results after short-term application, it demonstrated improvements after long-term application. Hence, continuous application of DQS for at least three months after cataract surgery may be a better choice. However, more randomised and prospective studies are required to verify our conclusions. Application of these data may offer improved clinical insight into the ocular surface management of post-cataract surgery patients and help us optimise treatment strategy.

Study approval

This study was derived from open and available research data.This study was granted exemption by the ethics committee of Zhengzhou university. We certify that the study was performed in accordance with the 1964 declaration of HELSINKI and later amendments.

Author contributions

Conception and design of study: YZ and FZ; Data collection, analysis and interpretation: YZ and XX; Article drafting: YZ; Final approval of the version to be published: YZ, YQ, XX and FZ. All authors revised the article critically for important intellectual content. All authors read and approved the final manuscript.

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Declaration of completing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

DQS	Diquafosol
TBUT	Tear breakup time
OSDI score	Ocular Surface Disease Index score
PRISMA	Systematic Reviews and Meta-analyses
NOS	Newcastle-Ottawa Scale
RCT	Randomised controlled trials
NSAID	Non-steroidal anti-inflammatory drugs

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2022.100063.

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