Tropical Journal of Pharmaceutical Research July 2024; 23 (7): 1165-1178
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i7.16

Original Research Article

A meta-analysis of the efficacy of combining diquafosol tetrasodium with conventional therapy for dry eye disease

Fengjiao Yang[1], Xiang Li[2]*

[1]Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 610075, [2]Department of Ophthalmology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 610072, China

For correspondence: **Email: jeannelxiang@cdutcm.edu.cn*

Sent for review: 25 August 2023 *Revised accepted: 29 June 2024*

Abstract

Purpose: *To evaluate the safety and effectiveness of combining 3 % diquafosol tetrasodium (DQS) with conventional treatment in addressing dry eye disease (DED).*
Methods: *A comprehensive search was conducted in databases, including CNKI, VIP, WANFANG, CBM, DUXIU, PubMed, Embase, Cochrane, Web of Science, Ovid MEDLINE, Scopus, and ProQuest up to June 5, 2023. Thirteen relevant randomized controlled trials (RCTs) were included in the analysis. Odds ratios (ORs) were used for binary categorical variables, and standardized mean difference (SMD) was employed for continuous variables and presented with 95 % confidence intervals (CI). Publication bias was assessed using funnel plot diagrams and the Egger test.*
Results: *Combined treatment with 3 % DQS had significantly better efficacy than control group (that received conventional treatment alone) in improving clinical efficacy, prolonging tear film break-up time, increasing tear secretion volume, and reducing corneal fluorescent staining ($p < 0.05$). Furthermore, the treatment demonstrated a favorable safety profile.*
Conclusion: *In the management of dry eye disease, the inclusion of 3 % DQS displays better therapeutic effects and safety when compared to other alternative approaches. This study underscores the potential of DQS as a promising intervention for addressing the complex pathogenesis of DED. However, its long-term effectiveness and safety still need to be further evaluated.*

Keywords: *Dry eye disease, Diquafosol tetrasodium, Efficacy, Safety, Meta-analysis*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Dry eye, known clinically as keratoconjunctivitis sicca is one of the most common eye diseases, with a 5 - 50 % case rate [1] and a high incidence in females [2]. These factors, including changes in work and lifestyles, dependence on electronics, the widespread use of corneal contact lenses, and the increasing prevalence of sleep disorders, led to an increasing trend in its incidence in different age groups. Dry eye disease causes abnormal tear secretion and abnormal tear composition, which leads to eye dryness burning, photophobia, eye congestion, vision fluctuations, foreign body sensation and irritant tears [3].

The pathological mechanism is that tear deficiency and evaporation loss lead to a further hyperosmotic state of the tear film. The

generated hyperosmotic stress response induces inflammation and leads to numerous inflammatory factors (IL-1, IL-6, IFN- γ, and TNF-α) emerging [4,5]. The inflammation release causes the loss of epithelial cells and goblet cells in the local tissue, reduces the surface wettability and the smoothness of the ocular surface, reduces the stability of local tear fluid, and shortens tear film breakup time. The vicious cycle further aggravates the deterioration of the hyperosmolar state [6,7]. The current methods used to treat the disease mainly involve relief of the patient's symptoms, inflammation management, epithelial protection, eyelid management and neurological treatment [8,9].

DQS is a P2Y2 receptor agonist that is distributed in the epithelium of the palpebral conjunctiva and bulbar conjunctiva, goblet cells and epithelial cells of the meibomian glands. It promotes water and mucin secretion in the tear film and aids in the horn conjunctival epithelial injury repairs by activating the P2Y2 receptor on the ocular surface [10-12]. The application of DQS in dry eye disease is extensive [13-14]. DQS relieves eye discomfort symptoms, enhances subjective sensations in the eyes, and shows great safety. Because of the complicated pathological mechanism of dry eye disease, it is difficult to obtain satisfactory efficacy by using only DQS. So, combining DQS with other conventional therapies is necessary to obtain satisfactory efficacy. This study attempts to systematically review the combinations of DQS with other alternative treatment options in the treatment of dry eye disease, to expand its application, and to provide a basis for its safety and effectiveness for use in treatment.

METHODS

Data collection

Published randomized controlled trials that evaluated the combination of 3 % DQS with other treatment option to manage dry eye disease were compiled. The design and implementation of this study followed the PRISMA [15,16] and Cochrane Handbook [17] guidelines. This study was approved by the Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (approval no. 2022KL-017). Signed written informed consent was obtained from the patients and/or guardians.

Inclusion criteria

The following criteria were required for publications to be included: subjects were diagnosed with dry eye disease; studies must be RCT; trial groups received DQS treatment; subjects had one of the following outcome indicators available: Schirmer I test (SIT), tear film breakup time (BUT), fluorescein staining score (FL), clinical effect, adverse events; 3 % DQS was not used in the 1 week before enrollment.

Exclusion criteria

Publications were excluded if the study type wasn't an RCT study, articles were repeatedly published, valid outcomes couldn't be fetched from target articles, or the types of articles were animal experiments, reviews, dissertations, case reports, internal reports, conference articles and so on; those data with obvious problems or outcome indicators without integrity; the full text cannot be obtained.

Search strategy

According to the system evaluation method of Cochrane collaboration network, CNKI, VIP, WANFANG, CBM, DUXIU, PubMed, Embase, Cochrane, Web of Science, Ovid MEDLINE, Scopus, and ProQuest databases were all assessed, with the search time from their establishment up to June 5, 2023. Subject words combined with free words were searched. The following headings (Mesh) or key terms were used in the English search, namely "Dry Eye Syndromes" OR "Dry Eye Syndrome", "Dry Eye Disease" OR "Dry Eye Diseases", "Dry Eye" OR "Dry Eyes", "Evaporative Dry Eye Disease" OR "Evaporative Dry Eye Syndrome", "Evaporative Dry Eye" OR "Dry Eye, Evaporative" OR "Evaporative Dry Eyes". OR "diquafosol" OR "diquafosol tetrasodium" OR "DQS", "INS-365" OR "INS365" OR "INS 365", "diquafosol ophthalmic solution" OR "diquafosol sodium eye drop" OR "Diquafosol sodium" OR "diquafosol ophthalmic solution" OR "Diquafosol sodium ophthalmic solution". OR "randomized controlled trial" OR "randomized" OR "placebo" OR "RCT" OR "Random".

Literature screening and data extraction

Two researchers (PC and SLL) read the literature, extracted required data and cross-checked it. In case of disagreement, they had internal discussions or consulted third-party evaluators (LJ or FJ) to assist in judgment. Firstly, a comprehensive search of databases was done. This was followed by checking pieces of literature imported into NoteExpress software to establish the corresponding database. In the light of inclusion and exclusion criteria, NoteExpress was applied to quickly browse

literature titles and abstracts to eliminate unrelated literature, and subsequently carefully read the full text, to decide whether the literature would be included in the study. Data extraction should include the first author and publication time, study type, intervention drug, control group drug, time of the therapy, disease type, and sample size and outcome indicators.

Risk of bias assessment

Bias assessment of the included literature was made based on the RCT original study's risk of bias assessment criteria provided by the Cochrane collaboration, including high risk, low risk and unclear judgment. The evaluation items include random allocation methods, allocation concealment, blind method, incompleteness of outcome data, selectively reporting study results and other sources of bias.

Statistical analysis

The STATA software was used for statistical analysis. The odds ratio (OR) showed binary categorical variables and Ordinal data indicators. While the continuous variable selected standardized mean difference (SMD) as representation, at the same time 95 % Confidence Interval (CI) was calculated, and a forest plot was made. The heterogeneity was quantified by I^2. When there was $p > 0.1$ and $I^2 < 0.05$, a fixed-effect model was conducted. Otherwise, a random effect model was put into use. $P < 0.05$ showed statistical difference.

RESULTS

Literature search and screening results

By searching the following databases, like CNKI, VIP, WANFANG, CBM, DUXIU, PubMed, Embase, Cochrane, Web of Science, Ovid MEDLINE, Scopus, and ProQues, 477 related documents were acquired. The corresponding database was established by NoteExpress software, and after careful and comprehensive screening, a total of 13 documents were included (Figure 1).

Basic information about the included studies

A total of 13 studies were brought into analysis after screening with relevant criteria [18-30]. A total of 1243 patients with dry eye syndrome were included, and all of them were randomized controlled trials. Nine (9) studies received DQS combined with sodium hyaluronate eye drops treatment, in which the shortest treatment time was 2 weeks and the longest treatment time was 3 months. Finally, 6 studies were surgery-related dry eye disease, and the details are shown in Table 1.

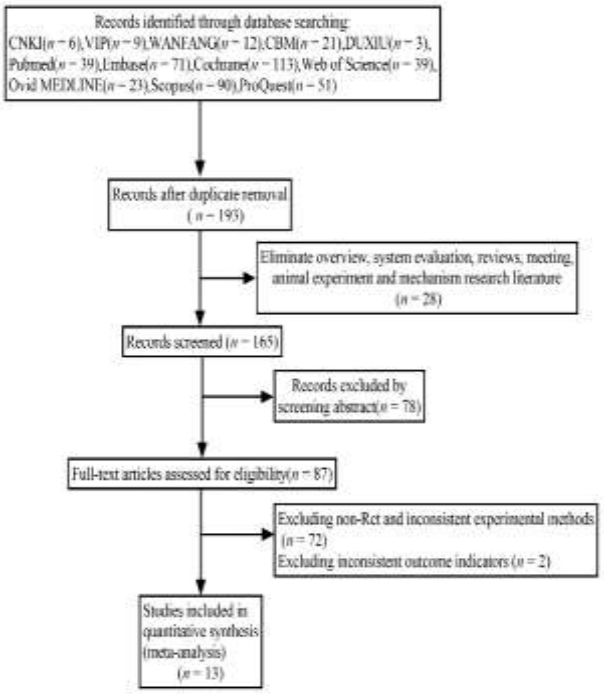

Figure 1: Flowchart of the literature search

Quality evaluation of included pieces of literature

The quality of each study was assessed according to the risk of bias provided by the Cochrane Collaboration and the modified Jadad scale (total score from 1 - 3 for low quality, 4 - 7 for high quality). The specific evaluation results are as follows: In the randomized allocation method, nine studies explicitly mentioned "random number table method", one study mentioned "randomized controlled study", one study mentioned "randomization method", and the remaining two studies only mentioned "randomization". Three studies explicitly indicated non-blind methods, and all studies did not specify whether outcome assessments were blinded. Only one study indicated that the allocation scheme was hidden and the remaining studies were not clear. All study results had complete data without selective reporting outcome indicators. All information can be seen in Figure 2 A and B and Table 2.

Clinical efficacy

A total of 7 studies reported the clinical efficacy of combining DQS in the treatment of dry eye disease compared with control group. Among them, 3 studies divided clinical efficacy into four grades: Cure, Excellent, Effective and Ineffective,

and 4 studies divided the clinical efficacy into three grades: Excellent, Effective and Ineffective.

The three studies that divided clinical efficacy into the four grades of cure, excellence, effective and ineffective were tested for heterogeneity, I^2 = 0 % < 50 %, and p = 0.962 > 0.1, suggesting that the heterogeneity among the literature selected for this study was not statistically significant, so fixed effects could be selected for meta-analysis. To ensure accuracy and stability, sensitivity analysis was conducted. The sensitivity analysis of the three articles showed that none of them had caused great interference to the results, as shown in Figure 3 A, the results of this study were relatively stable. The pooled OR value of the three studies was 5.474, and 95 % confidence interval was 1.632 - 18.357, Z = 2.75, p < 0.05 suggested that the efficacy of combined DQS treatment for dry eye disease was significantly better than control group, as shown in Figure 3 B. The funnel plot diagram showed whether any publication bias existed in this study. A symmetrical funnel plot meant no publication bias. The funnel plot diagram of this study is shown in Figure 3 C. Based on Begg's test, p = 1.000 > 0.05 indicated that the 3 articles selected for this study had no publication bias.

Determination of clinical efficacy

Clinical efficacy was divided into 3 grades in four studies: excellence, effective and ineffective. Then they were tested for heterogeneity, with I^2 = 0 % < 50 % and p = 0.792 > 0.1, suggesting that there was no heterogeneity among the literature selected for this study, hence the use of fixed. To ensure accuracy and stability, a sensitivity analysis was carried out. It showed that none of them had caused great interference to the results, as shown in Figure 4 A. The results of this study were relatively stable. The pooled OR values of the four studies were 6.755, and 95 % confidence interval was 2.800 - 16.292, Z = 4.25, p < 0.05, suggesting that the efficacy of combining DQS in the treatment for dry eye disease was significantly better than control group, as shown in the Figure 4B. The funnel plot diagram showed whether any publication bias existed in this study. Symmetrical funnel plot meant no publication bias. The funnel plot diagram of this study is shown in Figure 4 C. Based on Begg's test, p = 0.734 > 0.05 indicated that the 4 articles selected for this study had no publication bias.

Tear film break-up time

A total of 8 studies reported the tear film break-up time, where the intervention group drug was the same drug combined with DQS. These were heterogeneous studies (p = 0, I^2 = 87.72 %), so a random effect was chosen. The meta-analysis showed that the tear film break-up time of the intervention group was 0.98 longer than that of control group, which was a significant effect, and the degree of prolongation was statistically significant (t = 4.21, p < 0.05). This suggested that a combination with DQS could prolong the tear film break-up time (Figure 5 A).

Subgroup analysis of surgery-related dry eye disease and dry eye disease

The heterogeneity between the two groups was extremely strong. The dry eye disease group had heterogeneity with an effect size of 0.92 (Z = 6.59, p < 0.05), reaching a significant effect. The surgery-related dry eye disease group had heterogeneity with an effect size of 1.17 (Z = 10.50, p < 0.05), thus reaching a significant effect (Figure 5 B). Therefore, combining DQS treatment could prolong the break-up time of the tear film.

Tear secretion test

A total of 11 studies reported the tear secretion test. Heterogeneity existed between the studies (p = 0, I^2 = 92.29), so random effects were chosen. Meta-analysis showed that the amount of tear secretion in the DQS treatment group was more than in control group, which was a significant effect, and the increase was statistically significant (t = 4.38, p < 0.05). It indicated that the including diquafosol tetrasodium in the treatment could increase the amount of tear secretion in patients with dry eye syndrome (Figure 6 A). Subgroup analysis that showed different drugs combined with DQS that divided the 11 articles into two groups are shown in Figure 6 B. One group had DQS combined with sodium hyaluronate eye drops, and the other group received DQS combined with other drugs. Based on the subgroup analysis, the heterogeneity between the two groups was extremely strong. The group that received the combination of diquafosol tetrasodium with sodium hyaluronate eye drops had heterogeneity with effect size 1.15 (Z = 12.06, p < 0.05), reaching a significant effect. Other groups that received diquafosol tetrasodium combined with other drugs had heterogeneity with effect size 0.59 (Z = 6.93, p < 0.05), reaching a medium effect. Therefore, DQS combination with other treatments increased tear secretion, while DQS combined with sodium hyaluronate eye drops had better efficacy.

Table 1: Baseline characteristics of included studies

Parameter	Group	OSDI, Sit, TMH, BUT	Tear volume, BUT, FSS, RBS, subjective symptoms and adverse events	clinical effect, BUT, Sit, FL	clinical effect, BUT, SIt, FL, adverse event	clinical effect, BUT, SIt, FL	clinical effect, adverse event	BUT, SIt, FL, DSQL, adverse events
Mean age, year	Control	58.67±8.87	62.6±12.8	46.02±5.83	40.15±10.13	63.16±8.73	45.83±4.62	42.7±3.7
	Intervention	59.03±8.92	62.6±12.8	44.95±5.16	40.05±10.33	62.85±8.54	45.75±4.71	42.3±4.0
Male/ female, n	Control	42/78	5/27	24/25	20/20	unclear	22/18	12/21
	Intervention	61/99	5/27	23/26	18/22	unclear	23/17	26/14
Patients, n		280	32	98	80	54	80	73
Specific type of DES		Meibomian gland dysfunction related dry eye	DES	DES	Diabetes-related dry eye	Dry eye syndrome after cataract surgery	DES	DES
Regimen duration (weeks)		4	4	2	4	4	2	2
Comparator (% HA)		Yangxue Runmu Granules+0.3% HA	0.1	0.1 Tacrolimus	20% Deproteinized Calf Blood Extract Eye Gel	0.3	0.1	0.1
Intervention		Yangxue Runmu Granules+3%DQS	3% DQS+0.1% HA	3% DQS+0.1% Tacrolimus	3% DQS+20% Deproteinized Calf Blood Extract Eye Gel	3%DQS+0.3% HA	3%DQS+0.1%HA	3%DQS+0.1 %HA
Study design		RCT	RCT	RCT	RCT	RCT	RCT	RCT
Author; Year		Liu et al 2022 **Error! Reference source not found.**	Kamiya *et al* 2012 **Error! Reference source not found.**	Gao *et al* 2022 **Error! Reference source not found.**	Zhang *et al* 2022 **Error! Reference source not found.**	Liu *et al* 2020 **Error! Reference source not found.**	Wu *et al* 2020 **Error! Reference source not found.**	Ma *et al* 2021 **Error! Reference source not found.**

Table 2: Baseline characteristics of included studies *(continued)*

Parameter	Group	SPEED, BUT, SIT, CFS	clinical effect, BUT, SIt, FL, adverse events	adverse events, FL, BUT, STI, SPEED, Visual function quantification table	vision, BUT, TMH, Schirmer Ⅱ	adverse events, BUT, STI, contrast sensitivity, NEI VFQ-25	SIt, BUT
Mean age (year)	Control	71. 42±7. 09	63.5±5.8	67.51±4.35	20.00 (5.00)	45.5±5.1	23.42±4.73
	Intervention	70. 54±6. 19	62.4±6.3	67.32±4.16	21.00 (4.00)	46.2±3.0	24.38±6.47
Male/female (n)	Control	18/22	26/24	42/38	15/6	27/23	unclear
	Intervention	16/24	28/22	43/37	14/8	25/25	unclear
Patients (n)		80	100	160	43	100	63
Specific type of DES		Dry eye syndrome after cataract surgery	Dry eye syndrome after cataract surgery	Dry eye syndrome after cataract surgery	Dry eye after SMILE surgery	DES	Dry eyes after FS-LASIK surgery
Regimen duration (month)		1	1	1	1	1	3
Comparator (%HA)		0.1	Pranoprofen	0.3	0.1	0.1	0.1
Intervention		3%DQS+0.1%HA	3%DQS+Pranoprofen	3%DQS+0.3%HA	3%DQS+0.1%HA	3%DQS+0.1%HA	3%DQS+0.1% HA
Study design		RCT	RCT	RCT	RCT	RCT	RCT
Author; Year		Liu *et al* 2022 **Error! Reference source not found.**	Zhang *et al* 2020 **Error! Reference source not found.**	Mei *et al* 2021 **Error! Reference source not found.**	Zhang *et al* 2023 **Error! Reference source not found.**	Huang *et al* 2022 **Error! Reference source not found.**	Zhou *et al* 2022 **Error! Reference source not found.**

Note: *CT, Randomized controlled trial; DQS, Diquafosol; HA, Hyaluronic acid; DES, Dry eye syndrome; BUT, break-up time; FL fluorescein staining scores; OSDI, Ocular surface disease index; SIt, Schirmer I test; TMH, tear meniscus height; DSQL, Quality of life; SPEED, Standard dry eye symptom assessment*

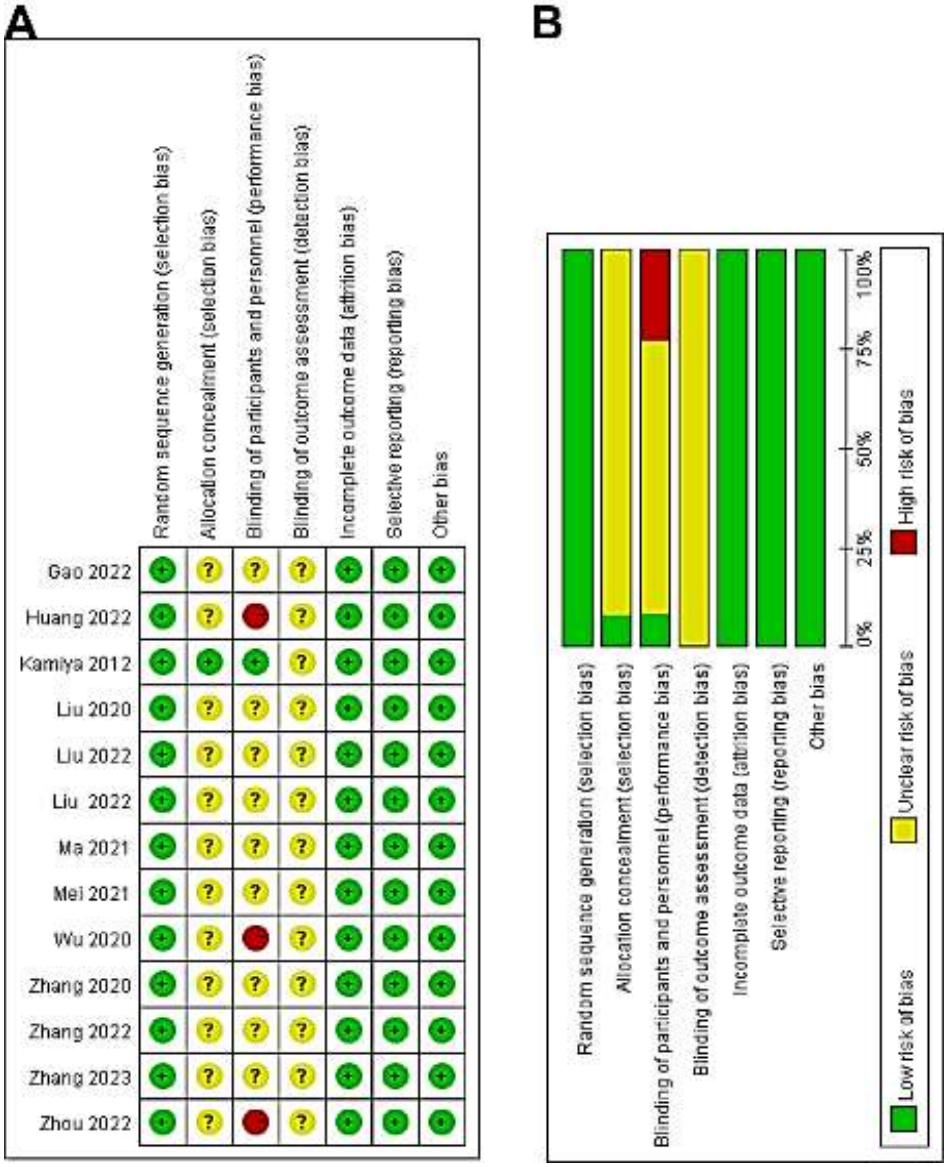

Figure 2: Methodological quality assessment. (A) Schematic diagram of methodological quality assessment of the literature in this study; (B) The proportion of methodological quality evaluation items in this literature. ***Note*:** + indicates that this standard was met, and - indicates that this standard was not met

Table 3: Quality assessment of included studies based on Jadad Scale for included studies

Authors; year	Randomized	Allocation concealment	Blinding	withdrawals and dropouts	Total
Gao 2022	2	1	0	1	4
Huang 2022	2	1	0	1	4
Kamiya 2012	1	2	0	1	4
Liu 2020	1	1	0	1	3
Liu 2022	2	1	0	1	4
Liu 2022	2	1	0	1	4
Ma 2021	2	1	0	1	4
Mei 2021	2	1	0	1	4
Wu 2020	2	1	0	1	4
Zhang 2020	1	1	0	1	3
Zhang 2022	2	1	0	1	4
Zhang 2023	2	1	0	1	4
Zhou 2022	1	1	0	1	3

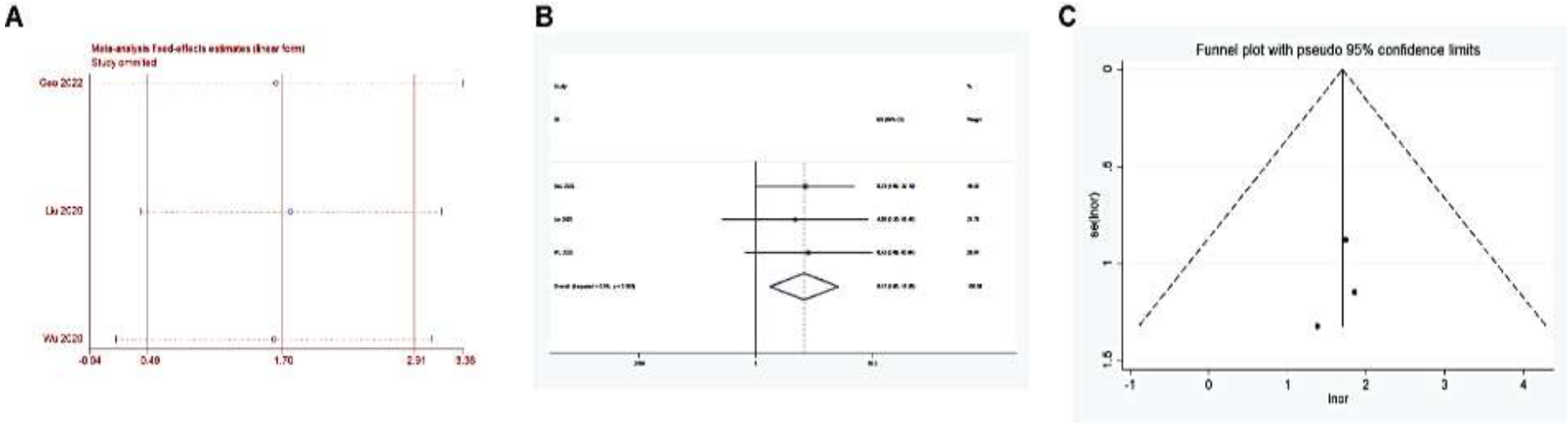

Figure 3: Clinical efficacy assessment. A: Sensitivity analysis; B: Forest plot for Clinical effect; C: Funnel plots for Clinical effect

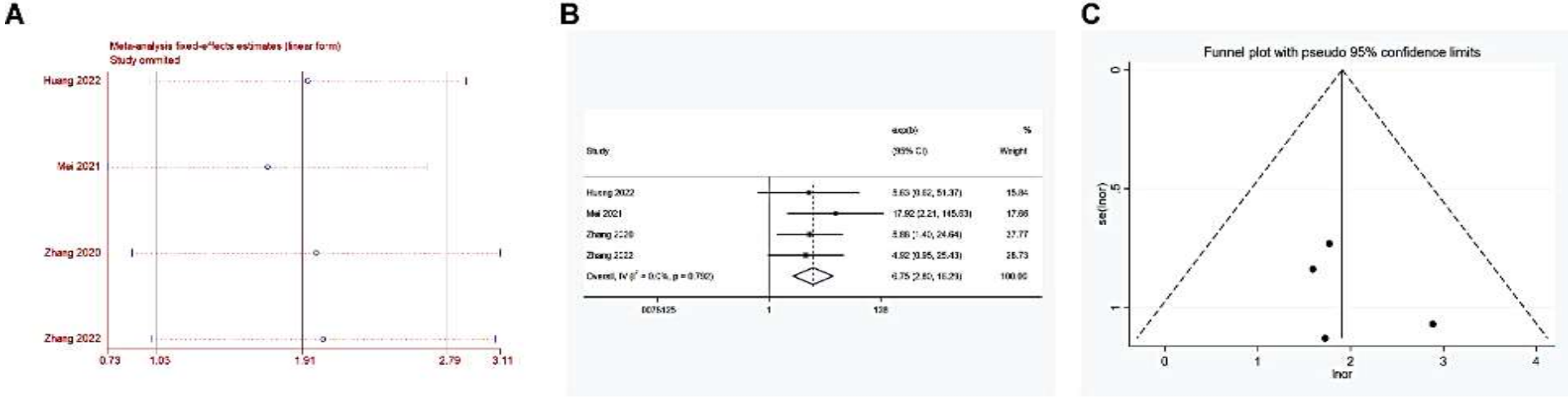

Figure 4: Sensitivity analysis. A: sensitivity analysis; B: Forest plot for Clinical effect; C: Funnel plots for Clinical effect

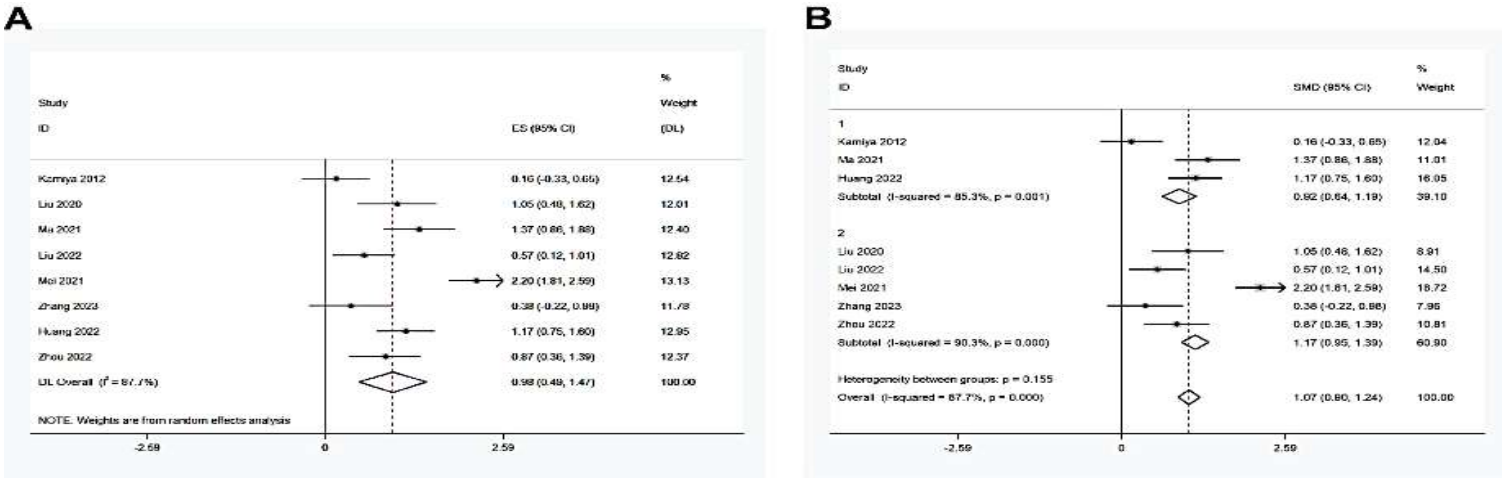

Figure 5: Analysis for BUT. A: Forest plot for BUT; B: Forest plot of subgroup analysis for BUT. ***Note:*** 1 stands for dry eye disease and 2 stands for surgery-related dry eye disease

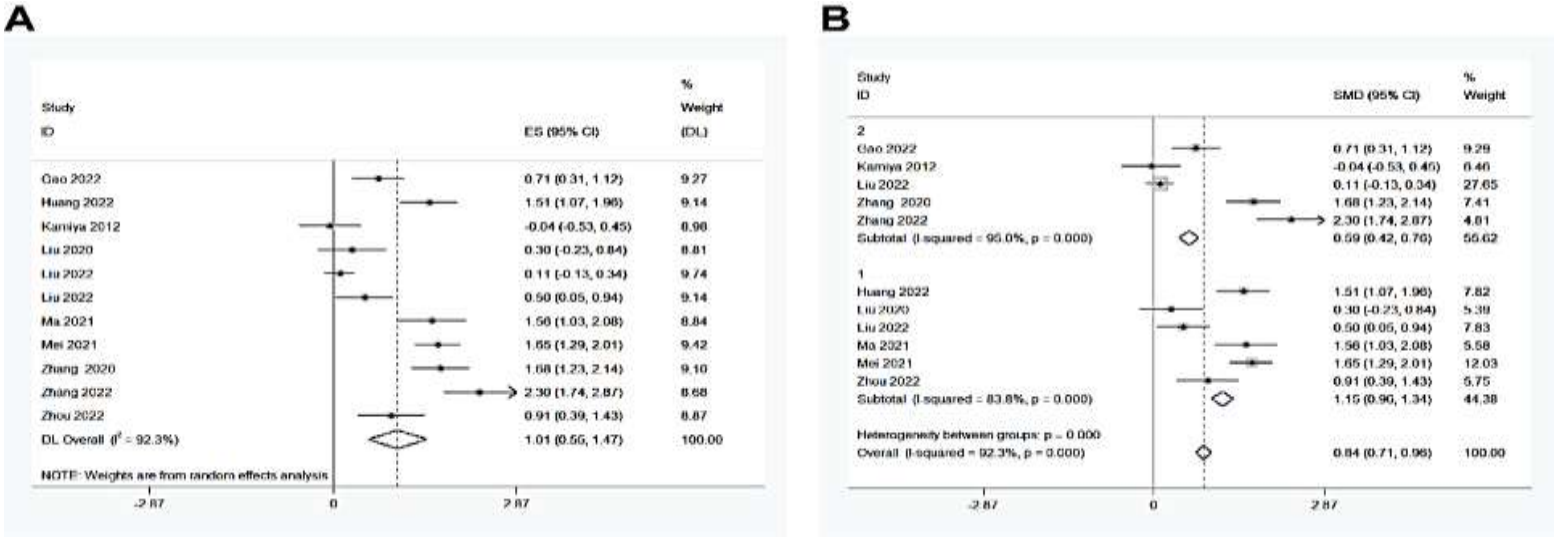

Figure 6: Analysis for Sit. A: Forest plot for Sit; B: Forest plot of subgroup analysis for SIt (1 represents diquafosol tetrasodium combined with sodium hyaluronate eye drops, 2 represents diquafosol tetrasodium combined with other drugs)

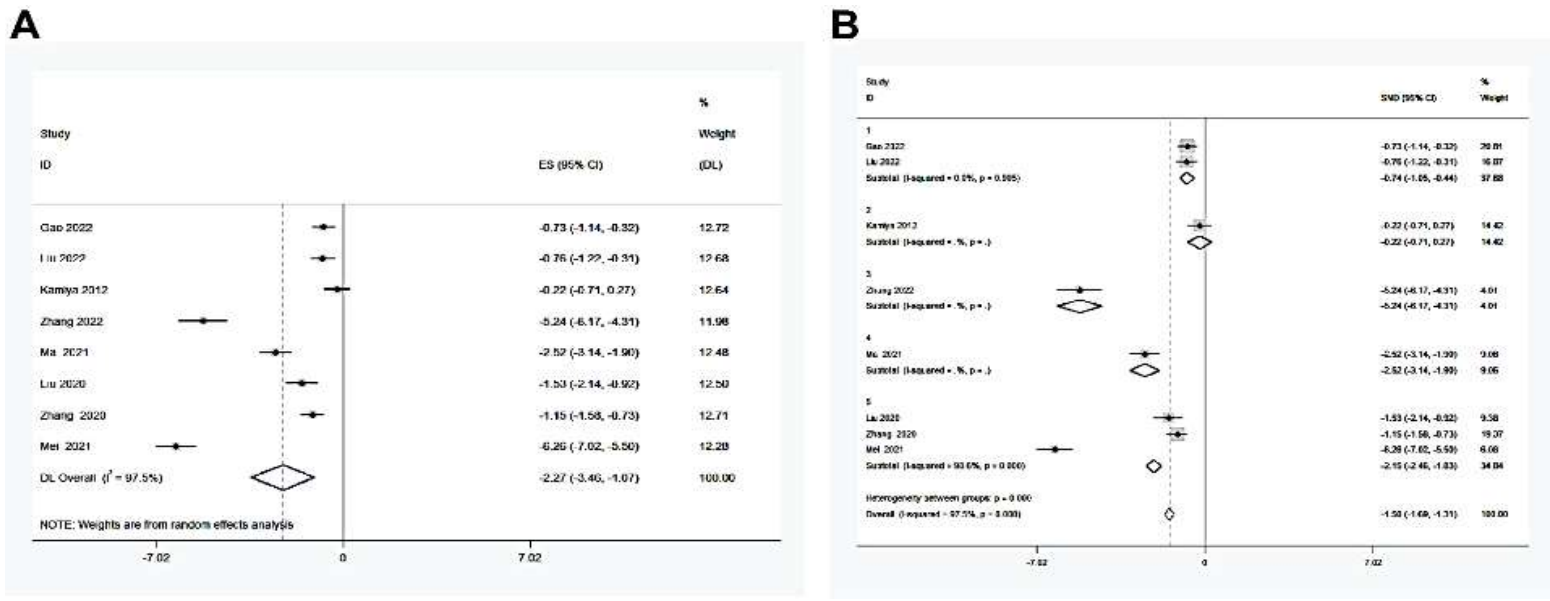

Figure 7: Analysis for FL. A: Forest plot for FL; B: Forest plot of subgroup analysis for FL

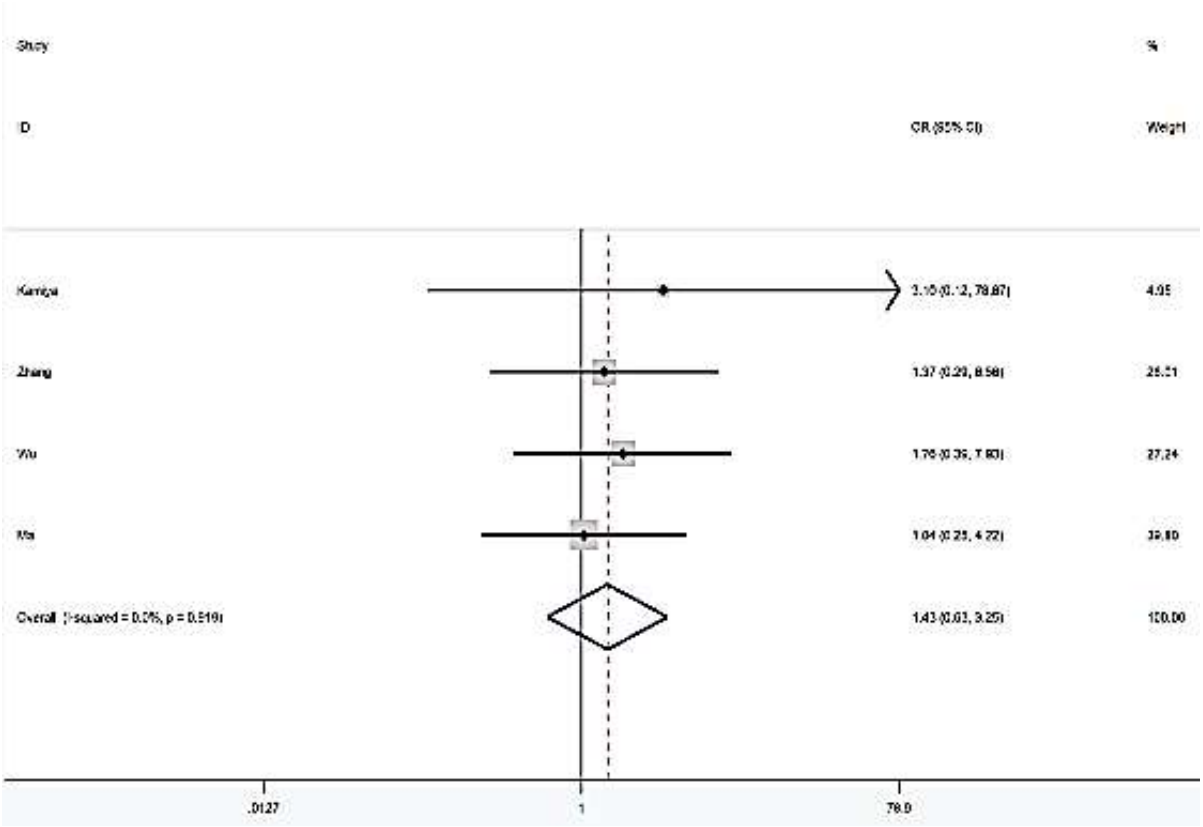

Figure 8: Forest plot for adverse reactions

Corneal fluorescein staining score

A total of 8 studies were reported corneal fluorescein staining. Heterogeneous existed among studies (p = 0, I^2 = 97.47), so random effects were chosen. The meta-analysis suggested that the corneal fluorescein staining score in DQS combination group was 2.27 lower than that in control group, which is significant (t = -2.88, p < 0.05). It suggested that DQS combination treatment reduce corneal fluorescein staining and promote corneal epithelial repair in patients with dry eye disease (Figure 7 A). Subgroup analysis of 8 articles show that different evaluation methods of corneal fluorescent staining were divided into 5 groups (1 meant "0 - 12" points, 2 meant "0 - 9" points, 3 meant "0 - 3" points, 4 meant "the number of people who get better was the criterion", 5 meant "the scoring method wasn't indicated"). It showed extremely strong heterogeneity among the five groups, reaching high heterogeneity (Figure 7 B). Consideration of different evaluation criteria was one of the main reasons for heterogeneity.

Adverse effects

Four studies reported the adverse effects of combining DQS and control groups in the treatment of dry eye disease. Homogeneity existed among studies (p = 0.919, I^2 = 0 %), so the fixed effect model was used. The results indicated that the combined treatment group and control group showed no significant difference in adverse effects (OR = 1.429, 95 % CI (0.628, 3.255), Z = 0.85, p = 0.395 > 0.05), indicating no difference in the safety of the two treatment modalities (Figure 8).

DISCUSSION

Dry eye disease is a kind of chronic ocular surface disease with a high incidence rate. It is caused by a variety of factors with many manifestations, such as instability of the tear film, or the imbalance of the microenvironment of the ocular surface, which has some adverse effects on the patient's visual status and quality of life. Finding an appropriate treatment to reduce patient symptoms and signs is critical. Exogenous artificial tear, like sodium hyaluronate and methylcellulose improves the tear deficiency symptoms to some extent, promote corneal epithelial repair and reduce discomfort caused by exposed nerve endings. However, the efficacy is limited.

The 3 % DQS is a brand-new artificial tear. It activates the Ca^{2+} channels, promotes the secretion of mucins, water fluids and lipids, enhances the repair ability of corneal epithelial

cell hyperplasia and inhibits inflammation. At present, 3 % DQS is the local secretagogue that promotes mucin secretion [31]. DQS simultaneously improves the composition of the tear film, comprehensively enhances the tear film stability and reduces eye discomfort and corneal epithelial damage [13]. By inhibiting the expression of inflammatory mediators such as IL-1β, IL-6, TNF-α and matrix metalloproteinase 2 [32], and inhibiting the NF-κB pathway, 3 % DQS alleviates the inflammatory response induced by hyperosmotic factors, increases the surface tension of the tear film and strengthens the tear membrane homeostasis [33]. Therefore, a meta-analysis of the clinical efficacy of combining diquafosol tetrasodium in the treatment of dry eyes is significant, but a similar statistical analysis has not been conducted before.

The included 13 RCTs indicated that there was better clinical efficacy by combining with DQS treatment for dry eye disease. Compared with control group, a combination with DQS was better in prolonging tear film break-up time, increasing tear secretion and reducing corneal fluorescent staining effect. Most importantly, there was no significant difference in adverse reactions and safety between the combination of DQS and control group in the treatment of dry eye disease, The sensitivity and bias testing of clinical efficacy showed that no article interfered with the results of the meta-analysis of clinical efficacy, and there was good stability and no publication bias.

Limitations of this study

This study had some limitations, such as the need for an improvement in the accuracy of meta-analysis. Also, only RCT study of the combination with DQS in treatment of dry eye disease was included. Heterogeneity was another limitation of this paper. Most of the studies included in this paper are from China. There are also differences in dry eye disease types, as well as different types of treatment methods in control group, intervention time, and differences in evaluation methods, which are all factors that can lead to heterogeneity. Since dry eye disease is induced by multiple factors, it is necessary to increase the samples of DQS combination for the treatment of dry eye disease in the future. Therefore, its effectiveness and safety still need to be further evaluated.

CONCLUSION

The current evidence suggests that for dry eye disease treatment, using combined DQS has better efficacy in prolonging the tear film break-up time, increasing tear secretion, reducing corneal fluorescent staining and improving clinical efficacy. However, on account of the limited quantity and quality of the included studies, further studies including larger sample sizes, multicenter, and high-quality randomized controlled clinical trials should be carried out.

DECLARATIONS

Acknowledgements

None.

Funding

None provided.

Ethical approval

This study was approved by the Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (approval no. 2022KL-017).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, Na KS, Schaumberg D, Uchino M, Vehof J, et al TFOS DEWS II Epidemiology Report. Ocul Surf 2017; 15(3): 334-365.
2. Matossian C, McDonald M, Donaldson KE, Nichols KK, MacIver S, Gupta PK. Dry Eye Disease: Consideration for Women's Health. J Womens Health 2019; 28(4): 502-514.
3. Huang X, Wang D, Lin D, Zhou Z. Efficacy of diquafosol sodium combined with M22 optimized pulsed light in the treatment of dry eye due to meibomian gland dysfunction. Trop J Pharm Res 2023; 22(10): 2163-2169 doi: 10.4314/tjpr.v22i10.18
4. Yazdani M, Elgstoen K, Rootwelt H, Shahdadfar A, Utheim OA, Utheim TP. Tear metabolomics in dry eye disease: a review. Int J Mol Sci 2019; 20(15).
5. Wu X, Chen X, Ma Y, Lin X, Yu X, He S, Luo C, Xu W. Analysis of tear inflammatory molecules and clinical correlations in evaporative dry eye disease caused by meibomian gland dysfunction. Int Ophthalmol 2020; 40(11): 3049-3058.
6. Fjaervoll K, Fjaervoll H, Magno M, Noland ST, Dartt DA, Vehof J, Utheim TP. Review on the possible pathophysiological mechanisms underlying visual display terminal-associated dry eye disease. Acta Ophthalmol 2022; 100(8): 861-877.
7. Sekhon AS, He B, Iovieno A, Yeung SN. Pathophysiology of corneal endothelial cell loss in dry eye disease and other inflammatory ocular disorders. Ocul Immunol Inflamm 2023; 31(1): 21-31.
8. Yi S, Lujia C, Jie Z. Diagnostic evaluation and treatment specification of dry Eye-2021 Expert Consensus Interpretation. J Recent Adv Ophthal 2022; 42 (10): 757-762.
9. Sheppard J, Shen LB, Periman LM. Dry eye disease: identification and therapeutic strategies for primary care clinicians and clinical specialists. Ann Med 2023; 55(1): 241-252.
10. Jin XM, Shen N. Application of diquafosol on tear film dys-function-related corneal and conjunctival epithelial damage. J Chin J Geriatr 2020; 39(9): 1104-1107.
11. Kim S, Shin J, Lee JE. A randomized, prospective study of the effects of 3% diquafosol on ocular surface following cataract surgery. Sci Rep-Uk 2021; 11(1): 9124.
12. Keating GM. Diquafosol ophthalmic solution 3 %: a review of its use in dry eye. Drugs 2015; 75(8): 911-922.
13. Wang Y, Huang YQ, Yang YN. Effect of sodium eye drops on ocular surface condition and visual quality in patients with moderate to severe dry eyes. Chin J Optom Ophthalmol Vis Sci, 2022, 23(5): 329-335.
14. Hori Y, Oka K, Inai M. Efficacy and safety of the long-acting diquafosol ophthalmic solution DE-089C in patients with dry eye: a randomized, double-masked, placebo-controlled phase 3 study. Adv Ther 2022; 39(8): 3654-3667.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj-Brit Med J 2021; 372: n71.
16. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. Bmj-Brit Med J 2021; 372: n160.
17. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch V. Cochrane handbook for systematic reviews of interventions version 6.2. The Cochrane Collaboration. 2021
18. Zibin L, Rui Z, Neng Li, Jian L. 3 % of diquafosol sodium eye drops for the treatment of meibomian gland dysfunction-related dry eye disease. Int Ophthalmol 2022; 22(08): 1271-1276.
19. Kamiya K, Nakanishi M, Ishii R, Kobashi H, Igarashi A, Sato N, Shimizu K. Clinical evaluation of the additive effect of diquafosol tetrasodium on sodium hyaluronate monotherapy in patients with dry eye syndrome: a prospective, randomized, multicenter study. Eye 2012; 26(10): 1363-1368.
20. Chenming G, Rui Z, Luning H. Analysis of the effect of diquafosol sodium combined with tacrolimus eye drops in patients with dry eye disease. China Prescript Drug 2022; 20(11): 78-80.
21. Hui Z. Clinical efficacy of diquafosol sodium eye drops combined with deproteinized calf blood extracts eye gel for the treatment of diabetes-related dry eye disease. Contemp Med 2022; 28(17): 112-114.
22. Yang L, Jianguo Y, Shixin Q, Yanli L. Study on the efficacy of diquafosol sodium combined with sodium hyaluronate eye drops in the treatment of dry eyes after cataract surgery. China Prescript Drug 2020; 18(07): 103-105.
23. Xuesong W. Clinical effect and safety analysis of diquafosol sodium combined with sodium hyaluronate eye drops in the treatment of dry eye. China Pract Med 2020; 15(07): 13-15.
24. Yuanyuan M. Clinical effect and safety of diquafosol sodium and sodium hyaluronate eye drops in patients with dry eye. China J Pharmaceut Econ 2021; 16(10): 119-121 + 125.
25. Miao L, Yu J, Liu L. Effect of different medication on senile patients with dry eye disease after phacoemulsification combined with intraocular lens implantation. Chin J Gerontol 2022; 42(17): 4235-4238.
26. Rui Z, Jing Z. Efficacy of diquafosol sodium combined with pranoprofen in treating dry eye after cataract surgery. Chronic Pathematol J 2020; 21(04): 568-570.
27. Hongyun M, Jixu Z, Youyi S. Study on the application value of diquafosol sodium and sodium hyaluronate in the treatment of dry eyes after cataract surgery. J World Latest Medical Inform 2021; 21(94): 433-434.
28. Jing Z, Jie H, Yahui D, Xinghua Y, Yulin L. Comparison of the efficacy of diquafosol sodium and sodium hyaluronate eye drops in dry eyes after SMILE. Chin J

Ocular Trauma Occupational Eye Dis 2023; 45(1): 28-34.

29. *Di H, Shuqi S, Zhenzhen W, Xiaojuan L, Pengfei Z. Effect of diquafosol sodium eye drops on visual quality and related quality of life in patients with dry eyes. Med Innovation China 2022; 19(29): 115-118.*
30. *Jin Z, Li L, Yuping S, Peng Z, Jun X, Yawei L, Silin B. Study of the clinical effect of diquafosol sodium and sodium hyaluronate in dry eyes after FS-LASIK. Chin J Modern Drug Appli 2022; 16(15): 137-140.*
31. *Wang YL. Mechanism of action and clinical application of eye drops. Chi J Exp Ophthalmol 2020; 38(12): 10871090.*
32. *Kim YH, Yang IJ, Nguyen L, Gum SI, Yu S, Lee GJ, Kim BA, Jung JC, Park YJ. Effect of diquafosol on hyperosmotic stress-induced tumor necrosis factor-alpha and interleukin-6 expression in human corneal epithelial cells. Korean J Ophthalmol 2020; 34(1): 1-10.*
33. *Yokoi N, Sonomura Y, Kato H, Komuro A, Kinoshita S. Three percent diquafosol ophthalmic solution as an additional therapy to existing artificial tears with steroids for dry-eye patients with Sjogren's syndrome. Eye 2015; 29(9): 1204-1212.*