THE ROLE OF HYALURONIC ACID EYE DROPS IN MANAGING DRY EYE SYNDROME: PSYCHOLOGICAL AND FUNCTIONAL PERSPECTIVES: A SYSTEMATIC REVIEW

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Abstract

Background: Dry eye syndrome (DES) is a prevalent ocular condition characterized by insufficient tear production or excessive tear evaporation, leading to discomfort, visual disturbances, and ocular surface damage. Hyaluronic acid (HA) eye drops are widely used due to their hydrating and lubricating properties, yet their efficacy compared to non-HA treatments, such as saline and artificial tears (ATs), remains debated. This study systematically reviews the effectiveness of HA eye drops in improving DES symptoms and clinical outcomes.

Methods: A systematic literature search was conducted across multiple databases for randomized controlled trials (RCTs) comparing HA-based eye drops with non-HA alternatives. Objective measures included Schemer's test (SH test), tear breakup time (TBUT), and corneal fluorescein staining, while subjective outcomes were assessed using the Ocular Surface Disease Index (OSDI).

Results: A total of 17 RCTs were included. Pooled analysis showed that HA significantly increased tear production compared to non-HA eye drops (SMD 0.18; 95% CI 0.03, 0.33). Subgroup analysis revealed that HA was superior to saline in improving SH test (SMD 0.27; 95% CI 0.05, 0.49) and TBUT (SMD 0.28; 95% CI 0.03, 0.52).

Conclusion: HA eye drops demonstrated statistically significant improvements in tear production and tear film stability compared to saline but were not superior to ATs. While HA offers potential benefits in DES management, the clinical relevance of these findings remains uncertain. Further large-scale RCTs are required to determine the long-term efficacy of HA-based treatments.

Keywords: Dry eye syndrome, hyaluronic acid, eye drops, clinical outcomes, tear production.

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Introduction

Dry eye syndrome (DES) occurs due to inadequate tear production or excessive tear evaporation, resulting in discomfort, visual impairment, and irritation of the ocular surface [1]. This condition is also associated with increased tear film osmolality and ocular surface inflammation. The prevalence of DES is estimated to range between 5% and 30% among individuals over the age of 50 [2].

Although DES is a common condition in adults [3,4], a standardized method for its diagnosis and treatment assessment has not yet been established. Symptom evaluation often relies on self-reported questionnaires such as the ocular surface disease index (OSDI). Additionally, clinicians conduct various diagnostic tests, including the Schirmer (SH) test, tear breakup time (TBUT), corneal and conjunctival staining, tear meniscus height measurement, tear osmolality, and tear lysozyme analysis [5].

The management of DES depends on symptom severity, with available treatments including tear replacement therapy and punctal plugs, both aimed at restoring the natural homeostasis of the tear film and ocular surface. In recent years, pharmacological agents have been introduced to stimulate tear production [6]. Artificial tears (ATs), formulated with different lubricants such as hyaluronic acid (HA), polyacrylic acid, carboxymethyl cellulose (CMC), dextran, HP-guar, hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, and polyethylene glycol, are commonly used to alleviate ocular discomfort [6]. However, these formulations lack the biologically active components found in natural tears [7,8], leading to the addition of supplementary agents to enhance lubrication and extend retention time on the ocular surface.

HA, also known as sodium hyaluronate, is a glycosaminoglycan biopolymer composed of repeating disaccharide units of N-acetyl-glucosamine and glucuronate [9]. Since the early 1990s, topical HA has been utilized to promote water and mucin secretion on the ocular surface [10]. Various studies in both human and animal models have demonstrated that different concentrations of HA eye drops improve tear film stability, ocular surface health, and dry eye symptoms [11,12,13,14,15]. However, some studies suggest that AT formulations other than HA-based drops may be equally or more effective in improving DES symptoms and reducing ocular inflammation [16,17,18,19,20]. While HA eye drops appear to produce significant improvements in both subjective and objective DES outcomes, their standalone efficacy remains a subject of debate.

Several systematic reviews and meta-analyses have compared the effectiveness of HA-based and non-HA-based eye drops for DES treatment, compiling data from multiple studies [21,22,23]. However, no significant differences were observed in objective measures such as TBUT and remission rates [22,23]. Another study reported minor differences in pre- and post-treatment SH test values (0.238 mm) and TBUT (0.566 s), suggesting that while these variations were statistically significant, their clinical relevance might be questionable [21]. Given these findings, further research is needed to establish more definitive evidence on the therapeutic efficacy of HA eye drops for DES management.

This study aims to compare the effectiveness of HA-only eye drops with non-HA-based alternatives using widely recognized objective and subjective assessment methods. Non-HA-based eye drops were classified into saline and artificial tears, as some studies have used saline alone in DES treatment without additional lubricants. Objective measures included SH test results, TBUT, and corneal fluorescein staining scores, while the subjective outcome was assessed using the OSDI.

Materials and Methods

A comprehensive search was conducted across multiple databases, including PubMed, Cochrane Central Register of Controlled Trials, EMBASE, and several regional repositories. The search encompassed all studies published until September 2024. The keywords used included terms related to dry eye disease, such as ("dry eye" or "Keratoconjunctivitis sicca" or "Sjogren's syndrome" or "xerophthalmia"), along with those associated with hyaluronic acid, including ("hyaluronic acid" or "hyaluronan"). No language or source restrictions were applied.

The eligibility criteria for study selection were as follows: (1) Study design: Only randomized controlled trials (RCTs) were included; (2) Study population: Individuals diagnosed with dry eye disease (DES), with no limitations on age, sex, or ethnicity; (3) Intervention: Use of topical eye drops containing hyaluronic acid (HA) at various concentrations; (4) Control: Comparison with non-HA-based eye drops, including artificial tears (ATs) and saline solutions; (5) Outcomes: At least one of the following measures had to be reported-Schemer's test (SH test), tear breakup time (TBUT), corneal fluorescein staining score (Oxford grading scale, 0–5), and ocular surface disease index (OSDI); and (6) Follow-up period: A minimum duration of 7 days from treatment initiation.

Studies were excluded if they met any of the following criteria: (1) Non-RCT designs, including observational studies, self-controlled trials, and reviews; (2)

Abstract-only publications or conference proceedings; (3) Participants with a history of ocular surgery or cataract procedures; (4) Use of other therapeutic eye drops (e.g., glaucoma medications) or contact lenses; (5) Initial follow-up conducted after more than 5 weeks; and (6) Articles not published in English or another specified language.

Key data points were extracted, including study author, publication year, participant demographics, disease severity, randomization process, blinding methods, follow-up period, percentage of HA in the intervention, and the type of control eye drop used (Table 1). In crossover trials, only the first treatment phase data were considered to avoid potential biases.

To maintain consistency, data from studies reporting outcomes within a timeframe of 1 to 5 weeks after treatment initiation were included. If a study investigated multiple non-HA-based eye drops, each dataset was analyzed separately. When results were provided for both eyes individually, only the right eye data were included to ensure analytical accuracy.

Statistical Analysis

Data was collected and analyzed, the quantitative assessment involved analyzing the mean changes and standard deviations for SH test scores, TBUT, corneal staining scores, and OSDI from baseline to follow-up.

Results

The initial search yielded a total of 1850 studies, from which 1,679 were identified as duplicates and subsequently excluded. After screening the remaining titles and abstracts, 1,140 articles did not meet the eligibility criteria and were removed. Full-text evaluations were conducted on 91 studies, leading to the final selection of 17 studies that reported findings on at least one of the following assessments: SH test, TBUT, corneal staining score, and OSDI [11,12, 16,18,19,20,25,26,27,28,29,30,31,32,33,34,35].

The 17 selected studies were published over a span of three decades, from 1988 to 2018. Most were conducted in Europe [11,12,16,18,19,25,26,27,28,29, 30,31,34], while others were carried out in Asia [20,33], the United States [35], and Canada [32] (Table 1). Among these, 12 followed a parallel study design, while five utilized a crossover design. All studies implemented randomization, with 15 specifying single or double masking, while one was openly labelled, and another did not clarify whether masking was applied. The participants encompassed individuals diagnosed with dry eye syndrome (DES) at varying severities, ranging from mild to severe. Seven studies did not specify severity levels. Follow-up durations varied between 14 and 90 days. A total of 627 individuals received HA-based eye drops, whereas 712 were given non-HA-based eye drops. One study recorded data based on the number of eyes rather than the number of participants [16]. The average age of participants was predominantly between 50 and 60 years, with two exceptions—one study included a 38-year-old participant, while another had a participant aged 72. The majority of the sample population consisted of women. In terms of HA concentration, six studies administered 0.1%, whereas 11 used concentrations ranging from 0.15% to 0.4%. The most frequent ingredient in non-HA-based eye drops was methylcellulose (n = 6), with other studies utilizing emulsions, polyvinyl alcohol, or carbomer. Four studies employed saline as a comparator.

nine studies provided SH test results (n = 10) [11,12,16,19,26,29,31,32,35]. The HA eye drop group included 362 participants, while the non-HA group had 348.

Further subgroup analysis indicated a significant improvement in SH test scores for the HA group compared to the saline group

A total of 15 studies contributed data for TBUT outcomes (n = 21) [11,12,16,18, 19,25,26,27,28,29,30,32,33,34,35]. The HA group consisted of 707 participants, while 693 were assigned to the non-HA group. No significant difference was noted in TBUT changes between the groups

Subgroup analysis showed that HA-based treatment led to a significant improvement in tear film stability compared to saline. No major difference was found between the HA and ATs groups

Data on corneal fluorescein staining scores were available from four studies (n = 7) [19,27,29,34]. A total of 286 cases were assigned to the HA group, while 272 were in the ATs group. The data extracted pertained only to ATs, preventing subgroup analysis. Both treatment groups exhibited similar improvements (Table 1).

HA: Hyaluronic acid; N: Number; M: Men; W: Women; Conc.: Concentration; RCT: Randomized controlled trial; KCS: Keratoconjunctivitis sicca; CMC: Carboxymethylcellulose; CE: Cathoic emulsion; TSP: Tamarind seed

Table 1. Baseline characteristics of included studies.

First Author	Study Design	Masking	Patients	Follow Up Duration (Days)	Sample Size (N)		Mean Age (Years)	Sex Ratio (M:W)	HA Conc. (%)	Type of Non-HA Eye Drops
					HA	Non-HA				
Groβ [28]	RCT (Parallel)	Single	Dry eye disease (Moderate)	84	41	39	55.8	24:56	0.1	0.5% CMC
Essa [27]	RCT (Crossover)	Single	Dry eye disease	28	50	50	60.8	35:15	0.15, 0.4	Pospholipid liposome
										0.25% CMC
Pinto-Fraga [11]	RCT (Crossover)	Double	Dry eye patients (Mild)	30	16	16	58.0	8:8	0.2	0.9% Saline
Lopez-de la Rosa [26]	RCT (Crossover)	Double	Dry eye disease (Moderate to severe)	30	16	16	57.5	4:12	0.3	0.9% Saline
Lambiase [19]	RCT (Parallel)	Double	Dry eye patients	14	20	15	56.9	3:36	0.18	Lubricin
Robert [25]	RCT (Parallel)	Single (Investigator)	Dry eye patients (Moderate to severe)	90	41	44	62.6	16:69	0.18	Hypotonic CE
Kinoshita [20]	RCT (Parallel)	Quadruple	Dry eye patients	28	95	93	55.6	25:163	0.1	2% Rebamipide
Baudouin [29]	RCT (Parallel)	Single (Investigator)	Dry eye patients	35	29	37	56.8	8:69	0.18	0.5% CMC
Baeyens [12]	RCT (Parallel)	Double	Dry eye patients (Moderate)	84	100	96	59.3	41:245	0.18	Saline
						91				0.3% Carbomer
Lee [33]	RCT (Parallel)	Single (Observer)	Dry eye patients (Mild to moderate)	56	32	33	38	6:59	0.1	0.5% CMC
Sanchez [16]	RCT (Parallel)	Single (Observer)	Dry eye syndrome or Sjogren's syndrome	30	15 *	14 *	71.8	All female	0.15	0.5% Carmellose
NCT00938704 [34]	RCT (Parallel)	Double	Dry eye patients	14	37	33	51.5 †	19:51	0.18	0.5% CMC
Rolando [18]	RCT (Parallel)	Open label	Dry eye syndrome	90	9	11	60.3	10:20	0.2	0.5% TSP
						10				1% TSP
Brignole [30]	RCT (Parallel)	Single (Observer)	Dry eye syndrome (Moderate)	56	10	11	63	1:20	0.18	1% CMC
Condon [31]	RCT (Crossover)	Double	Dry eye syndrome (Severe)	28	34	36	61	12:58	0.1	0.9% Saline
Nelson [35]	RCT (Parallel)	Double	Dry eye syndrome (Moderately severe)	56	20	15	58.55	4:31	0.1	1.4% PVA
Laflamme [32]	RCT (Crossover)	No comment	Dry eye patients (Severe)	56	12	12	58	Not reported	0.1	1.4% PVA

polysaccharide; PVA: Polyvinyl Alcohol. * number of eyes; † median age.

Discussion

Hyaluronic acid (HA) eye drops have become increasingly utilized in managing various ocular surface conditions due to their hydrating and lubricating properties. However, prior research has not consistently demonstrated a clear advantage of HA over other treatments for dry eye syndrome (DES) [21,22,23]. This study aimed to evaluate the effects of HA eye drops on DES in comparison to non-HA alternatives, such as saline and artificial tears (ATs). Both objective assessments (e.g., Schemer's test, tear breakup time (TBUT), and corneal staining using the Oxford scale) and subjective evaluations (e.g., the Ocular Surface Disease Index (OSDI)) were employed.

results indicated that the HA group exhibited significantly greater tear production, as measured by the Schemer's test, compared to the non-HA group. However, TBUT and corneal fluorescein staining scores were comparable between the HA and non-HA groups. Additionally, while HA appeared to improve OSDI scores relative to non-HA treatments, statistical significance was not observed.

In subgroup analysis, HA treatment significantly enhanced tear production (Schemer's test) and tear film stability (TBUT) compared to normal saline. Furthermore, HA significantly reduced OSDI scores compared to saline.

The Schemer's test is a widely used clinical method for evaluating tear production [36]. However, limitations such as measurement variability and inconsistent reproducibility have been reported [37]. The results of this study revealed that HA significantly increased Schemer's test scores compared to non-HA treatments, although the effect size (0.18 mm) was relatively small, which may limit its clinical impact on patient symptoms. Individual trials included in the analysis generally reported that both HA and non-HA treatments were beneficial for DES management. The observed minor differences between HA and non-HA treatments may be attributed to variations in study conditions. A previous meta-analysis reported a similar improvement in Schemer's test scores (0.238 mm) after HA use compared to non-HA treatments [21]. Notably, two studies included in that analysis were excluded from the current study due to methodological differences-one involved HA-based polyethylene glycol [38], while the other lacked standard deviation data [39]. Nevertheless, the overall findings reinforce the beneficial role of HA in enhancing tear production compared to non-HA alternatives.

Similar to Schemer's test results, TBUT scores significantly improved after HA treatment compared to saline, whereas no notable differences were observed between HA and ATs. However, findings for ATs demonstrated high heterogeneity. TBUT measures tear film stability by assessing the interval between a complete blink and the initial disruption of the tear film [36,40]. This method is commonly used in clinical settings due to its ease of application. A prior meta-analysis suggested that HA resulted in marginal TBUT improvements compared to non-HA preparations, but the effect was not statistically significant [21,23].

Among prior studies, only one reported superior efficacy of a non-HA preparation over HA in terms of TBUT [16]. The study by Sanchez et al. (2010) [16] was identified as a potential source of heterogeneity in earlier research, as it reported significantly better TBUT improvements with ATs compared to HA. The authors suggested that age differences between study groups may have influenced treatment efficacy. When this study was excluded, heterogeneity decreased, though standardized mean differences between HA and ATs remained largely unchanged.

Corneal fluorescein staining scores were similar between HA and ATs. Fluorescein, rose Bengal, and lissamine green are commonly used dyes for assessing ocular surface disorders. Various grading scales exist for evaluating staining severity, with this study utilizing the Oxford Scheme (scale 0–4). According to the analysis, heterogeneity was low. While corneal staining is an informative marker for severe DES, its correlation with symptoms in mild to moderate cases is weak [41]. This suggests that staining results may not fully reflect patient-reported symptom severity.

Regarding subjective measures, HA provided symptom relief comparable to non-HA treatments, though statistical significance was not reached. The OSDI is frequently employed in clinical research to assess DES severity, incorporating symptom frequency, environmental factors, and vision-related quality of life [36]. Although self-reported, OSDI is recognized for its reliability and reproducibility compared to other objective indicators [42]. Therefore, subjective assessments such as OSDI may be particularly relevant when evaluating treatment outcomes for DES.

Many randomized controlled trials (RCTs) incorporated blinding or masking techniques to reduce bias, yet maintaining blinding across studies was challenging due to variations in instillation frequency, chemical composition, and ocular sensation following HA or non-HA administration. To enhance data uniformity, outcomes were extracted between one and five weeks' post-treatment, in alignment with prior studies [21].

Conclusion

The findings suggest that HA eye drops may contribute to improved dry eye symptoms and clinical outcomes compared to non-HA-based solutions. By performing subgroup analyses, heterogeneity was minimized, strengthening the reliability of these findings. These results offer valuable insights for clinical decision-making. Further large-scale RCTs are warranted to establish the definitive effectiveness of HA relative to non-HA eye drops for managing DES.

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