JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

https://doi.org/10.61919/0j3dy188

Original Article

Comparative Analysis of Honey-Based and Hyaluronic Acid Eye Drops on Tear Film Stability in Post-Menopausal Dry Eye Disease

Syeda Wafa Batool Naqvi[1], Irum Riaz[2], Haram Jawed[1], Nimra Muzaffar[1], Muhammad Sohaib Azhar[1], Zaryab Khan[3]

[1] Student, The Superior University, Lahore, Pakistan
[2] Lecturer, The Superior University, Lahore, Pakistan
[3] Lecturer, The Superior University Lahore, Sargodha Campus, Sargodha, Pakistan

***Corresponding author: Syeda Wafa Batool Naqvi, s.wafabatool@gmail.com**

"Cite this Article" Received: 24 March 2026; **Accepted**: 06 June 2026; **Published**: 20 June 2026

Author Contributions: SWBN and IR contributed to concept and design; SWBN, HJ, NM, and MSA contributed to data collection; IR and ZK contributed to supervision and analysis; SWBN, IR, HJ, NM, MSA, and ZK contributed to drafting, critical revision, and final approval of the manuscript. **Ethical Approval**: Superior University, Lahore, Pakistan. **Informed Consent**: Written informed consent was obtained from all participants; **Conflict of Interest**: The authors declare no conflict of interest. **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: N/A.

ABSTRACT

Background: Postmenopausal women are vulnerable to dry eye disease because hormonal changes may alter lacrimal function, meibomian gland activity, ocular surface homeostasis, and tear-film stability. Honey-based and hyaluronic acid-based eye drops may improve dry eye parameters through different biological mechanisms, but direct comparative evidence in postmenopausal women remains limited. Objective: To compare the effects of honey-based and hyaluronic acid-based eye drops on tear-film stability and tear secretion among postmenopausal women with dry eye disease. Methods: This quasi-experimental pre–post comparative study included 100 postmenopausal women with clinically diagnosed dry eye disease. Participants were divided into two equal groups: 50 received honey-based eye drops and 50 received hyaluronic acid-based eye drops, administered once daily for four weeks. Tear break-up time and Schirmer test wet length were measured at baseline and after treatment. Normality was assessed using the Shapiro–Wilk test. Within-group and between-group comparisons were performed using Wilcoxon signed-rank and Mann–Whitney U tests, respectively. Results: Both groups showed significant improvement in tear break-up time and Schirmer test values after four weeks. TBUT increased from 5.86 ± 1.49 to 9.60 ± 1.50 seconds in the hyaluronic acid group and from 5.78 ± 1.63 to 9.02 ± 1.56 seconds in the honey-based group. Schirmer test values increased from 7.22 ± 1.51 to 11.40 ± 1.73 mm and from 6.72 ± 1.23 to 10.16 ± 1.70 mm, respectively. Post-treatment outcomes favored hyaluronic acid for TBUT and Schirmer test. Conclusion: Both eye drop formulations improved objective dry eye parameters, but hyaluronic acid-based eye drops showed greater post-treatment improvement in tear-film stability and tear secretion. Keywords: Postmenopausal Women; Dry Eye Disease; Hyaluronic Acid; Honey; Tear Break-Up Time; Schirmer Test

INTRODUCTION

Natural menopause is defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity and is clinically recognized after 12 consecutive months of amenorrhea in the absence of another pathological or physiological cause (1). The postmenopausal period is accompanied by substantial endocrine changes, including reductions in estrogen and androgen activity, which may influence ocular surface homeostasis, lacrimal gland function, meibomian gland physiology, and tear-film composition. These hormonal alterations are clinically relevant because postmenopausal women commonly experience symptoms and signs of dry eye disease, often before advanced ocular surface damage becomes apparent (2). Meibomian gland dysfunction and reduced tear stability have also been

identified as important contributors to dry eye in this population, highlighting the multifactorial nature of postmenopausal ocular surface disease (3).

Dry eye disease is a common and clinically burdensome disorder characterized by tear-film instability, ocular discomfort, burning, irritation, redness, fluctuating vision, and light sensitivity. Beyond ocular symptoms, dry eye disease can impair reading, screen use, driving, occupational performance, and overall quality of life, making it an important public health concern among middle-aged and older women (4). The burden appears particularly high after menopause, with previous population-based evidence showing a greater prevalence of dry eye among women than men after the age of 50 years, while studies in perimenopausal and postmenopausal women have reported substantial dry eye symptom burden (5). Despite this frequency, dry eye disease in postmenopausal women may remain undertreated, and management often begins with patient education, environmental modification, behavioral changes, and ocular lubricants aimed at improving tear-film stability and ocular surface protection.

Topical lubricants remain a central component of dry eye management, but their effectiveness depends on the biological and physical properties of the formulation. Honey-based ophthalmic preparations have gained attention because honey contains bioactive compounds with antioxidant, antimicrobial, anti-inflammatory, and epithelial-supportive properties. These effects may help improve ocular surface comfort and tear-film stability when honey is used in appropriately formulated topical ocular preparations. Evidence from studies of honey-based interventions suggests potential benefit in dry eye-related parameters, particularly through reduction of ocular surface inflammation and support of epithelial recovery (6). However, the mechanism of honey differs from conventional lubricating polymers because its effect is more likely related to ocular surface modulation than prolonged tear-film residence.

Hyaluronic acid, also known as sodium hyaluronate in ophthalmic preparations, is a naturally occurring glycosaminoglycan with strong water-binding, viscoelastic, and mucoadhesive properties. These characteristics allow hyaluronic acid eye drops to increase tear-film hydration, prolong ocular surface retention, reduce mechanical friction during blinking, and support epithelial healing. Topical hyaluronic acid has been widely used in dry eye disease and has shown beneficial effects on ocular surface health, tear-film stability, and dry eye-related clinical parameters across different patient populations (7). Because postmenopausal dry eye disease is strongly associated with tear-film instability and reduced ocular surface protection, hyaluronic acid may offer particular benefit in this group.

Although honey-based and hyaluronic acid-based eye drops have both been studied as therapeutic options for dry eye disease, direct comparative evidence in postmenopausal women remains limited. This gap is clinically important because honey-based preparations may represent a natural or alternative treatment option, while hyaluronic acid is an established ocular lubricant with strong tear-retention properties. A direct comparison of these approaches can help clarify whether both treatments improve objective dry eye parameters and whether one produces greater improvement in tear-film stability and tear secretion. Therefore, this study aimed to compare the effects of honey-based and hyaluronic acid-based eye drops on tear break-up time and Schirmer test values among postmenopausal women with dry eye disease. The research question was whether hyaluronic acid-based eye drops produce greater improvement in tear-film stability and tear secretion than honey-based eye drops after four weeks of treatment in postmenopausal women with dry eye disease.

MATERIALS AND METHODS

This study was designed as a two-arm quasi-experimental pre–post comparative study conducted at Superior University Lahore over a six-month period. The study evaluated the effects of honey-based and hyaluronic acid-based eye drops on tear-film stability and tear secretion among postmenopausal women diagnosed with dry eye disease. A quasi-experimental design was used because the study compared two

active topical interventions in naturally occurring clinical participants without describing a randomized allocation process. The target population comprised postmenopausal women with clinically confirmed dry eye disease, and the main outcomes were tear break-up time and Schirmer test wet length measured before and after four weeks of intervention.

A total sample of 100 postmenopausal women was included, with 50 participants assigned to the honey-based eye drop group and 50 participants assigned to the hyaluronic acid-based eye drop group. Participants were selected using non-probability convenience sampling. Eligible participants were women aged 45 years or older who had attained menopause, defined as absence of menstruation for more than 12 months, and who were clinically diagnosed with dry eye disease after ocular assessment using tear break-up time and Schirmer test. Women were excluded if they wore contact lenses, had a history of intraocular surgery or ocular trauma, had active ocular infection, had used tear replacement therapy, topical ocular medication, or dietary supplements affecting the tear film within the preceding six months, or had systemic conditions affecting tear production, including Sjögren's syndrome.

Recruitment was conducted among eligible postmenopausal women after assessment of menstrual history, ocular complaints, and relevant systemic history. Each participant underwent a comprehensive ocular evaluation, including slit-lamp examination and objective dry eye assessment. Baseline demographic and clinical information, including age, duration since menopause, ocular complaints, and relevant medical history, was recorded before intervention. Tear-film stability was assessed using tear break-up time, measured in seconds, while tear secretion was assessed using Schirmer test wet length, measured in millimeters. These assessments were performed at baseline and repeated after four weeks of treatment to evaluate within-group and between-group changes in dry eye parameters.

Participants in the honey-based eye drop group received one drop of honey-based eye drops in each affected eye once daily for four weeks. Participants in the hyaluronic acid-based eye drop group received one drop of hyaluronic acid-based eye drops in each affected eye once daily for four weeks. All participants were instructed to administer the assigned drops at the same time each day and to avoid using other topical ocular therapies during the study period. The four-week follow-up assessment included repeat tear break-up time and Schirmer test measurements using the same outcome definitions applied at baseline. The primary outcome was change in tear break-up time from baseline to four weeks, and the secondary outcome was change in Schirmer test wet length from baseline to four weeks. The sample size was calculated for comparison between two groups using a two-group mean difference formula, with 80% power, 10% level of significance, an assumed mean of 5 in one group, an assumed mean of 4.5 in the comparison group, and a standard deviation of 1. Based on these assumptions, 100 participants were included, with 50 participants in each treatment group. The calculation was based on the formula $n = 2\sigma^2(Z1-\alpha + Z1-\beta)^2 / (\mu1 - \mu2)^2$, where σ represented the assumed standard deviation, $\mu1$ and $\mu2$ represented the expected group means, and Z values represented the selected significance level and study power.

Data were entered and analyzed using IBM SPSS Statistics version 22. The Shapiro–Wilk test was used to assess normality of continuous outcome variables within each treatment group. Because tear break-up time and Schirmer test values did not satisfy the assumption of normal distribution, non-parametric statistical tests were applied. Within-group pre- and post-treatment comparisons were performed using the Wilcoxon signed-rank test, while post-treatment between-group comparisons were performed using the Mann–Whitney U test. Continuous variables were summarized as mean ± standard deviation in accordance with the available manuscript data, and statistical significance was set at $p < 0.05$. The analysis focused on participant-level comparison of pre-treatment and post-treatment tear break-up time and Schirmer test outcomes in the two intervention groups.

Measures to reduce bias included applying the same baseline and follow-up outcome measures to both groups, using objective clinical tests for tear-film stability and tear secretion, maintaining the same four-week treatment duration across both interventions, and instructing participants to avoid additional

topical ocular therapies during the study period. Data integrity was supported through standardized recording of demographic, clinical, and outcome variables before entry into SPSS and by using predefined statistical tests based on distributional assessment. Ethical approval was obtained from the relevant institutional ethics committee before commencement of the study, and participants were enrolled after informed consent.

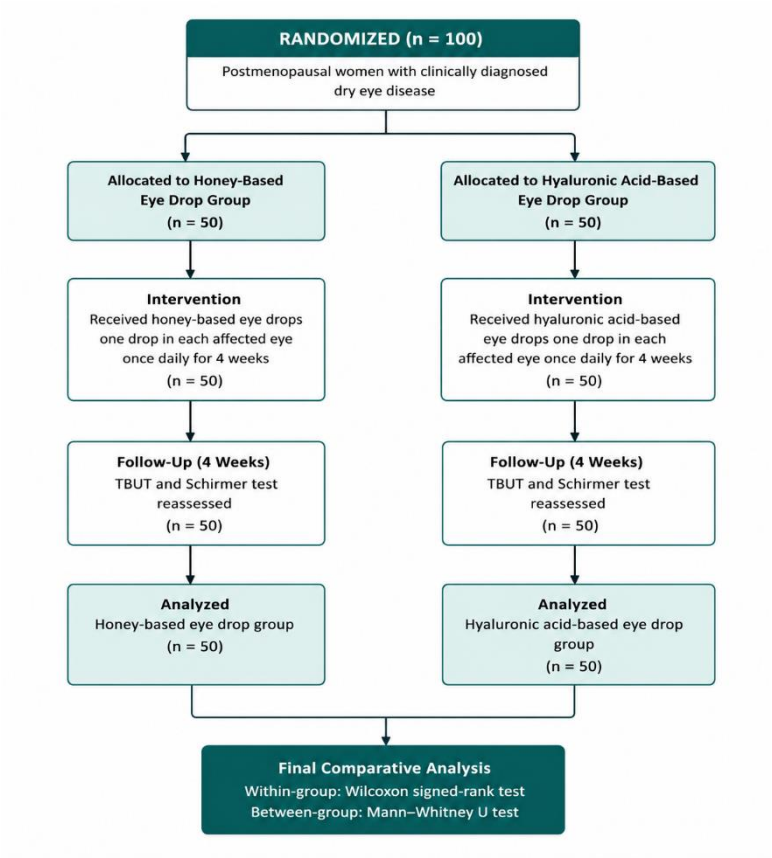

Figure 1 CONSORT Flowchart

RESULTS

A total of 100 postmenopausal women with dry eye disease were included in the analysis, with 50 participants in the hyaluronic acid-based eye drop group and 50 participants in the honey-based eye drop group. The mean age of the study population was 55.22 ± 5.08 years, with an age range of 47 to 67 years. Normality testing using the Shapiro–Wilk test showed non-normal distribution of tear break-up time and Schirmer test values in both intervention groups, supporting the use of non-parametric tests for within-group and between-group comparisons.

Table 1. Available Baseline Characteristics and Pre-Treatment Outcome Values

Variable	Hyaluronic Acid-Based Eye Drops	Honey-Based Eye Drops	Overall
Participants, n	50	50	100
Age, years, Mean ± SD	—	—	55.22 ± 5.08
Age range, years	—	—	47–67
Pre-treatment TBUT, seconds, Mean ± SD	5.86 ± 1.49	5.78 ± 1.63	—
Pre-treatment Schirmer test, mm, Mean ± SD	7.22 ± 1.51	6.72 ± 1.23	—

TBUT: tear break-up time; SD: standard deviation.

At baseline, both groups had reduced tear-film stability and tear secretion values consistent with dry eye disease. Pre-treatment TBUT was similar between the hyaluronic acid-based and honey-based groups, with mean values of 5.86 ± 1.49 seconds and 5.78 ± 1.63 seconds, respectively. Baseline Schirmer test values were 7.22 ± 1.51 mm in the hyaluronic acid-based group and 6.72 ± 1.23 mm in the honey-based

group. Group-wise age distribution, menopause duration, dry eye severity category, ocular comorbidities, and baseline symptom scores were not available in the supplied dataset.

Table 2. Within-Group Pre–Post Comparison of Tear Film and Tear Secretion Outcomes

Outcome	Pre-Treatment Mean ± SD	Post-Treatment Mean ± SD	Mean Change	Percentage Change	p-value
TBUT, seconds	5.86 ± 1.49	9.60 ± 1.50	3.74	63.8	<0.001
TBUT, seconds	5.78 ± 1.63	9.02 ± 1.56	3.24	56.1	<0.001
Schirmer test, mm	7.22 ± 1.51	11.40 ± 1.73	4.18	57.9	<0.001
Schirmer test, mm	6.72 ± 1.23	10.16 ± 1.70	3.44	51.2	<0.001

Within-group p-values were obtained using the Wilcoxon signed-rank test. Percentage change was calculated from the reported mean values. TBUT: tear break-up time; SD: standard deviation.

Both interventions were associated with statistically significant improvement in tear-film stability and tear secretion after four weeks of treatment. In the hyaluronic acid-based group, mean TBUT increased from 5.86 ± 1.49 seconds to 9.60 ± 1.50 seconds, corresponding to a mean change of 3.74 seconds and a 63.8% increase from baseline. In the honey-based group, mean TBUT increased from 5.78 ± 1.63 seconds to 9.02 ± 1.56 seconds, corresponding to a mean change of 3.24 seconds and a 56.1% increase. Schirmer test values increased from 7.22 ± 1.51 mm to 11.40 ± 1.73 mm in the hyaluronic acid-based group and from 6.72 ± 1.23 mm to 10.16 ± 1.70 mm in the honey-based group. The mean increase in Schirmer test wet length was 4.18 mm in the hyaluronic acid-based group and 3.44 mm in the honey-based group.

Table 3. Between-Group Comparison of Post-Treatment Outcomes

Outcome	Group	n	Post-Treatment Mean ± SD	Mean Rank	Mann–Whitney U	p-value
TBUT, seconds	Hyaluronic acid-based eye drops	50	9.60 ± 1.50	56.68	941.00	0.029
TBUT, seconds	Honey-based eye drops	50	9.02 ± 1.56	44.32	—	—
Schirmer test, mm	Hyaluronic acid-based eye drops	50	11.40 ± 1.73	60.87	731.50	<0.001
Schirmer test, mm	Honey-based eye drops	50	10.16 ± 1.70	40.13	—	—

Between-group p-values were obtained using the Mann–Whitney U test. TBUT: tear break-up time; SD: standard deviation.

Post-treatment between-group comparison showed higher tear-film stability and tear secretion values in the hyaluronic acid-based group than in the honey-based group. The hyaluronic acid-based group had a higher post-treatment TBUT mean rank than the honey-based group, with mean ranks of 56.68 and 44.32, respectively, and this difference was statistically significant using the Mann–Whitney U test. Similarly, post-treatment Schirmer test mean rank was higher in the hyaluronic acid-based group than in the honey-based group, with mean ranks of 60.87 and 40.13, respectively. These findings indicate greater post-treatment tear-film stability and tear secretion in the hyaluronic acid-based group, although the analysis was based on post-treatment comparison rather than baseline-adjusted change-score modelling.

Table 4. Derived Between-Group Post-Treatment Mean Differences and Effect Sizes

Outcome	Hyaluronic Acid-Based Eye Drops Mean ± SD	Honey-Based Eye Drops Mean ± SD	Mean Difference	95% CI	Cohen's d
TBUT, seconds	9.60 ± 1.50	9.02 ± 1.56	0.58	-0.03 to 1.19	0.38
Schirmer test, mm	11.40 ± 1.73	10.16 ± 1.70	1.24	0.56 to 1.92	0.72

Mean difference was calculated as hyaluronic acid-based group minus honey-based group. Confidence intervals and Cohen's d were derived from the reported post-treatment means, standard deviations, and group sizes. CI: confidence interval; SD: standard deviation; TBUT: tear break-up time.

The derived post-treatment mean difference for TBUT was 0.58 seconds in favor of the hyaluronic acid-based group, with a 95% CI ranging from -0.03 to 1.19 seconds and a Cohen's d of 0.38. For Schirmer test wet length, the derived post-treatment mean difference was 1.24 mm in favor of the hyaluronic acid-based group, with a 95% CI ranging from 0.56 to 1.92 mm and a Cohen's d of 0.72. The effect estimate for Schirmer test showed a clearer separation between groups than the estimate for TBUT, suggesting that the between-group difference was more pronounced for tear secretion than for tear-film break-up time.

Comparison of mean change values showed improvement in both groups, with numerically larger gains in the hyaluronic acid-based group. The between-group difference in mean change was 0.50 seconds for TBUT and 0.74 mm for Schirmer test, both favoring the hyaluronic acid-based group. However, inferential testing of change-score differences could not be performed from the supplied aggregate data because standard deviations of change scores and participant-level paired observations were not available. Reviewer-style statistical note: The supplied manuscript reported non-normal outcome distributions but presented outcome values as mean ± standard deviation. For stronger statistical alignment with the Wilcoxon signed-rank and Mann–Whitney U tests, the final manuscript should also report median and interquartile range for TBUT and Schirmer test values at baseline and follow-up. A baseline characteristics table should be completed with group-wise age, menopause duration, dry eye severity, ocular history, and relevant systemic variables. If participant-level data are available, the preferred comparative analysis would include change-score comparison or baseline-adjusted modelling to estimate the treatment effect more robustly.

Table 5. Derived Mean Change Comparison from Baseline to Four Weeks

Outcome	Hyaluronic Acid-Based Eye Drops Mean Change	Honey-Based Eye Drops Mean Change	Difference in Mean Change
TBUT, seconds	3.74	3.24	0.50
Schirmer test, mm	4.18	3.44	0.74

Mean change was calculated from the reported pre-treatment and post-treatment mean values. Confidence intervals and p-values for between-group change were not calculated because standard deviations of change scores or individual-level paired data were not available. TBUT: tear break-up time.

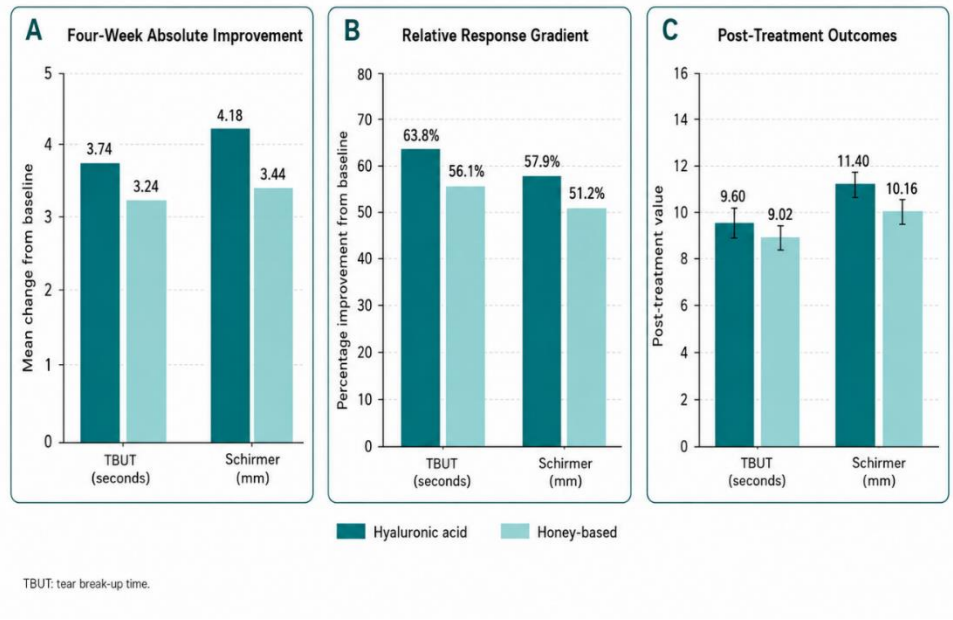

Figure 1. Comparative Tear-Film Response After Hyaluronic Acid and Honey-Based Eye Drops

The panelled figure demonstrates that both interventions produced measurable improvement in tear-film stability and tear secretion after four weeks, with consistently greater gains in the hyaluronic acid-based group. TBUT increased by 3.74 seconds in the hyaluronic acid group compared with 3.24 seconds in the honey-based group, corresponding to relative improvements of 63.8% and 56.1%, respectively. Schirmer test wet length increased by 4.18 mm in the hyaluronic acid group and 3.44 mm in the honey-based group, corresponding to relative improvements of 57.9% and 51.2%, respectively. The derived post-treatment between-group effect favored hyaluronic acid for both outcomes, with a mean difference of 0.58 seconds for TBUT and 1.24 mm for Schirmer test. The 95% confidence interval for TBUT crossed zero (-0.03 to 1.19), whereas the Schirmer test interval remained above zero (0.56 to 1.92), indicating a clearer post-treatment separation between groups for tear secretion than for tear-film break-up time.

DISCUSSION

The present study compared the effects of honey-based and hyaluronic acid-based eye drops on tear-film stability and tear secretion among postmenopausal women with dry eye disease. Both interventions produced statistically significant improvement in tear break-up time and Schirmer test values after four weeks, indicating that each treatment was associated with measurable improvement in objective dry eye parameters. However, the hyaluronic acid-based group demonstrated higher post-treatment values than the honey-based group for both TBUT and Schirmer test. The derived mean improvement was 3.74 seconds for TBUT and 4.18 mm for Schirmer test in the hyaluronic acid-based group, compared with 3.24 seconds and 3.44 mm, respectively, in the honey-based group. These findings suggest that while both formulations may provide therapeutic benefit, hyaluronic acid-based eye drops were associated with comparatively greater improvement in tear-film stability and tear secretion in this postmenopausal population.

The low baseline TBUT values observed in both groups are consistent with the pathophysiology of postmenopausal dry eye disease, in which hormonal changes may affect lacrimal gland function, meibomian gland activity, tear-film composition, and ocular surface homeostasis. Previous evidence has shown that postmenopausal women commonly present with dry eye symptoms and clinical signs, and that tear-film instability may occur as part of age-related and hormone-related ocular surface dysfunction (8). In the current study, baseline TBUT values were 5.86 ± 1.49 seconds in the hyaluronic acid group and 5.78 ± 1.63 seconds in the honey-based group, reflecting reduced tear-film stability before treatment. The subsequent increase in TBUT in both groups indicates that topical ocular therapy can improve tear-film behavior over a short intervention period, although the magnitude of response differed between the two formulations.

The improvement observed with honey-based eye drops is biologically plausible because honey contains compounds with antioxidant, antimicrobial, anti-inflammatory, and epithelial-supportive properties. In this study, TBUT improved from 5.78 ± 1.63 seconds to 9.02 ± 1.56 seconds in the honey-based group, while Schirmer test wet length increased from 6.72 ± 1.23 mm to 10.16 ± 1.70 mm. These findings are consistent with previous work evaluating honey-based ocular preparations, where formulated honey eye drops were associated with improvement in tear-film properties among individuals with dry eye disease (9). A systematic review of manuka honey for dry eye also reported that honey-based preparations may improve dry eye-related clinical parameters, although tolerability, formulation type, and patient selection remain important considerations when interpreting these effects (10). The present findings therefore support honey-based eye drops as a potentially useful natural or adjunctive option, provided that the preparation is sterile, ophthalmologically appropriate, and clinically monitored The hyaluronic acid-based group showed a larger numerical and statistical response than the honey-based group. TBUT increased from 5.86 ± 1.49 seconds to 9.60 ± 1.50 seconds, while Schirmer test values increased from 7.22 ± 1.51 mm to 11.40 ± 1.73 mm. This pattern is consistent with the known pharmacological and biophysical properties of hyaluronic acid, which has strong water-binding, viscoelastic, and mucoadhesive effects on the ocular surface. Previous clinical evidence has shown that hyaluronic acid-containing preparations can improve tear-film stability and ocular surface parameters in dry eye disease, including in postmenopausal or older female populations (11). Similarly, sodium hyaluronate therapy has been associated with improved tear-film stability in dry eye states, supporting the clinical relevance of the improvements observed in the present study (12). These effects may be explained by enhanced lubrication, prolonged ocular surface residence time, reduced blink-related friction, and support of epithelial recovery.

The between-group analysis further supports a stronger post-treatment response in the hyaluronic acid-based group. Mean rank values for post-treatment TBUT and Schirmer test were higher in the hyaluronic acid group than in the honey-based group, with statistically significant between-group differences. The derived post-treatment mean difference was 0.58 seconds for TBUT and 1.24 mm for Schirmer test in

favor of hyaluronic acid. The 95% confidence interval for the TBUT difference crossed zero, indicating that the magnitude of between-group separation for tear-film break-up time should be interpreted cautiously. In contrast, the Schirmer test confidence interval remained above zero, suggesting a clearer separation between treatments for tear secretion. This interpretation is compatible with recent evidence showing that lubricant eye drops may differ in ocular retention time and surface residence, which can influence clinical performance (13). Experimental evidence also supports the role of high-molecular-weight hyaluronic acid in mucoadhesion on ocular surface models, offering a plausible explanation for its comparatively stronger effect on tear-film support (14).

Although the findings favor hyaluronic acid-based eye drops, they should be interpreted within the design and reporting limitations of the study. The quasi-experimental design limits causal inference, particularly because the allocation method was not described as randomized and no masking procedure was reported. Baseline values were broadly similar for TBUT but differed numerically for Schirmer test; therefore, a baseline-adjusted comparison or formal change-score analysis would strengthen the estimate of between-group treatment effect. The manuscript reported non-normal outcome distributions but presented results mainly as mean ± standard deviation, whereas median and interquartile range would provide better alignment with the Wilcoxon signed-rank and Mann–Whitney U tests. In addition, the short four-week follow-up prevents assessment of long-term efficacy, recurrence, adherence, and safety. The absence of symptom-score data also means that improvement can be concluded only for objective tear-film and tear-secretion measures, not for subjective symptom relief or quality of life. Future studies should include randomized allocation, masked outcome assessment, validated symptom scales, adverse-event monitoring, longer follow-up, and baseline-adjusted statistical modelling. Overall, this study contributes clinically relevant comparative evidence on two topical approaches for postmenopausal dry eye disease. Both honey-based and hyaluronic acid-based eye drops improved TBUT and Schirmer test values after four weeks, but hyaluronic acid-based eye drops produced higher post-treatment outcomes and larger mean improvements. These findings support the continued use of hyaluronic acid as an effective ocular lubricant for tear-film instability, while also suggesting that honey-based eye drops may have a role as a natural alternative or adjunct in selected patients. However, stronger controlled trials with detailed formulation reporting and patient-centered outcomes are needed before firm comparative recommendations can be made.

CONCLUSION

Honey-based and hyaluronic acid-based eye drops were both associated with significant improvement in tear break-up time and Schirmer test values among postmenopausal women with dry eye disease after four weeks of treatment. The hyaluronic acid-based group showed greater improvement in tear-film stability and tear secretion than the honey-based group, with higher post-treatment TBUT and Schirmer test values. These findings suggest that hyaluronic acid-based eye drops may provide stronger objective improvement in postmenopausal dry eye disease, while honey-based eye drops may remain a potentially useful natural alternative when appropriately formulated for ocular use. Because the study was quasi-experimental and did not include long-term follow-up, symptom-score assessment, or baseline-adjusted modelling, further randomized and controlled studies are recommended to confirm comparative efficacy, safety, tolerability, and patient-centered benefit.

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