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Clinical impact of varying the molecular weight of hyaluronic acid in artificial tears – A randomised controlled crossover trial

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ABSTRACT

Purpose: To assess the impact of molecular weight of hyaluronic acid, of the same concentration, in artificial tears.

Methods: A size exclusion high-performance liquid chromatography system with ultraviolet detection was used to measure hyaluronic acid content and establish a relative molecular weight, based on standardised hyaluronic acid samples. The rheology of HydraMed®, Evolve® and Hylo-Forte® eye drops, which all report containing 0.2 % hyaluronic acid as the principal constituent, was assessed at shear rates of relevance to blink conditions in-vitro, using a research rheometer fitted with a 60 mm aluminium flat plate measuring system at 31 °C.

Twenty-five participants (aged 23.6 ± 9.2 years) meeting the TFOS DEWS II criteria for a diagnosis of dry eye disease were randomised to receive one double-masked application of each drop, on separate days. Dry eye symptom severity, non-invasive breakup time, tear meniscus height and ocular redness were assessed at baseline and 5, 15, 30, 45, 60 and 90 min after application.

Results: Rheology demonstrated Hylo-Forte (2.5 M Da, 0.16 % hyaluronic acid) had a more non-linear (non-Newtonian) relationship between viscosity and sheer force ($r^2 = 0.295$) compared to HydraMed (0.8 M Da, 0.26 % hyaluronic acid; $r^2 = 0.485$) and Evolve (1.3 M Da, 0.24 % hyaluronic acid; $r^2 = 0.521$). Dry eye symptoms rapidly reduced and tear stability improved with drop instillation and the effect slowly declined with time ($p < 0.001$), with all drops following a similar profile ($p > 0.05$). Hylo-Forte demonstrated the greatest reduction in dry eye symptoms and sustained improvement in tear stability. Tear meniscus height increased with drop instillation and then declined with time ($F = 18.643$, $p < 0.001$), with Evolve having a reduced initial effect compared to HydraMed and Hylo-Forte ($F = 4.045$, $p < 0.001$). Average bulbar redness was low (0.63 ± 0.44 Efron grade) and did not change with drop application ($F = 1.721$, $p = 0.120$).

Conclusions: Artificial tear formulation impacts its rheology, leading to differences in clinical effectiveness, even from a single application. Higher molecular weight hyaluronic acid in Hylo-Forte demonstrated more non-Newtonian behaviour, which is more aligned with the rheology of the natural tear film.

1. Introduction

Dry eye disease (DED) is a common condition characterised by unpleasant symptoms of discomfort and visual disturbance and is one of the most frequent causes of visits to eyecare practitioners [1]. The second Dry Eye Workshop of the Tear Film and Ocular Surface Society (TFOS DEWS II) Definition and Classification Report defined DED as follows: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [2]. TFOS DEWS II also advocated a standardised system for the diagnosis of DED based on validated symptoms questionnaires and key clinical signs [3], as well as an evidence-based staged management algorithm to guide practitioners [4].

Estimates of the prevalence of DED vary considerably, due to the differing diagnostic criteria adopted by each research study and the study population examined, but generally range from 5-50 % when diagnosis involves symptoms and/or signs and can be up to 75 %; when only signs are assessed to 'diagnose' dry eye [5]. The high prevalence of DED results in considerable burden, both human and economic, due to

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loss of productivity and healthcare costs to individuals and health systems [6–8]. It has also been reported that the quality of life impact of severe cases equates to chronic systemic conditions such as angina [9].

Dry eye disease is broadly divided into evaporative (EDE) and aqueous deficient (ADDE) subclasses, with some sufferers having a combination of both, but EDE pre-dominates [2]. Regardless of the subtype and aetiology, artificial tears are typically included in first-line management options, being easily accessible in a wide range of formulations, and having a low risk-profile [4]. Most artificial tear preparations have been found to be effective in reducing the symptoms and signs of DED, however there have been few high quality randomised controlled trials comparing them with each other [4,10]. Although drops designed for specific layers of the tear film appear to be equally effective [11,12], research indicates that the optimal drop for a person can be anticipated based on their initial diagnosis. Drops with phospholipids are more beneficial for individuals with evaporative dry eye [13,14] whereas osmoprotectants are advantageous for those with elevated tear film osmolarity [14].

Artificial tears are generally aqueous or lipid-based. Aqueous-based drops often contain viscosity enhancing agents, such as carbomer 940 (polyacrylic acid), carboxymethyl cellulose, dextran, hyaluronic acid, HP-guar, hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone and polyethylene glycol, which lubricate and increase their retention time on the ocular surface [4]. Hyaluronic acid is a naturally occurring glycosaminoglycan, which is found in and around body cells and tissues, for example in synovial fluid, and vitreous and aqueous humour [15]. Its use in ophthalmology was pioneered by Andre Balazs in the late 1960s [16], with Polack and McNiece [17] being the first to report its use in dry eye. It has also demonstrated efficacy in promoting corneal wound healing [18,19].

Hyaluronic acid is water soluble and is capable of binding large quantities of water, compared to its own weight, but its physical properties vary depending upon its molecular weight [20]. There is variability in the definition of high molecular weight hyaluronic acid in the literature with one paper suggesting in biology this is typically approximately 2,000 kDa [21], whereas another suggests anything > 500 kDa has a different biological function [22]. There is evidence from animal models to suggest that higher molecular weight hyaluronic acid (HMWHA) is superior in the treatment of DED compared to its low molecular weight counterpart [23]. Furthermore, HMWHA has been found in in-vitro models to be protective against corneal epithelial cell apoptosis due to benzalkonium chloride toxicity, ultraviolet light radiation and chemical burns [24–26], as well as being anti-inflammatory and having a role in reducing pain sensation in a rat model [23,27].

It is important that artificial tear drops behave in a similar way to natural tears. One aspect of this is rheology, which refers to the way fluids and soft solids flow. The viscosity of human tears decreases during each blink cycle, in order to protect the ocular surface from damage due to fluid turbulence [28]. Similarly, HMWHA has been shown to exhibit non-Newtonian shear-thinning properties [29], making it suitable for use in artificial tears [30]. Non-Newtonian behaviour results in lower viscosity when a force is applied (such as during blinks, potentially reducing friction) and higher viscosity at rest (such as between blinks, potentially increasing tear stability and comfort duration).

While some previous clinical trials have compared the efficacy of different artificial tear products [31], little is known about the impact of the rheology of these formulations, to inform practitioner management decisions [13,14,31]. The chain length of hyaluronic acid determines its physical as well as its physiological properties [20]. Hence, the purpose of this trial was to assess whether volume-matched drops – with hyaluronic acid as their main viscosity agent – containing the same concentration but different molecular weight hyaluronic acid (and hence displaying different rheological properties) [32], would vary in terms of ocular surface symptoms and signs.

2. Methods

2.1. Interventions

The study compared the effects of three commercially available hyaluronic acid-containing artificial tear drops on dry eye symptoms, the tear film and ocular surface. They were selected as having hyaluronic acid as their main viscosity agent, having the same reported concentration (0.2 %), but of different molecular weights: HydraMed® (Farmigea, Manchester, UK) contains sodium hyaluronate (molecular weight 950 kDa)[33], tamarind seed polysaccharide, mannitol, sodium citrate and citric acid monohydrate; Evolve® (Medicom, Fareham, UK) contains sodium hyaluronate, sodium chloride, boric acid and borax; and Hylo-Forte® (Scope Ophthalmics Ltd, West Sussex, UK) contains sodium hyaluronate (molecular weight 1748 kDa)[32], citric acid anhydrous, sodium citrate and sorbitol.

2.2. Molecular weight and concentration

A size exclusion high-performance liquid chromatography system with ultraviolet detection was used to measure hyaluronic acid content and to establish a relative molecular weight based on standardised hyaluronic acid samples. The products and specific lot codes for the studied products are given in Table 1.

Three lots of hyaluronic acid were used as comparison materials based on the molecular weights provided by the vendor (Table 2).

Samples were analysed on an Agilent 1100 HPLC (Degasser: G1322A; Quaternary Pump: G1311A; Autosampler: G1313A; Column Heater: G1316A; Variable Wavelength Detector: G1314A). The high-performance liquid chromatography consisted of two Advanced Bio SEC 300 Å 4.6 × 300 mm columns (Agilent Technologies, Santa Clara, CA, USA) and one Zorbax GF-250 4.6 × 250 mm column (Agilent Technologies) [34]. The separation conditions were: flow rate: 0.300 mL/min; mobile phase: isocratic, 50 mM sodium phosphate, pH 7.4; injection volume; 60 μL; column temperature: 40 °C; detector wavelength: 205 nm; run time: 45 min. Samples were prepared by diluting 0.5 mL of each product with 0.5 mL of a diluent containing 0.1 M sodium phosphate at pH 7.4, with 200 mM EDTA. Standards were prepared by weighing ~ 50 mg of hyaluronic acid into a 20 mL flask and dissolving in water prior to filling the flasks to volume. Each hyaluronic acid standard was injected twice. The retention time and peak area of each was determined.

2.3. In-Vitro rheology measures

To characterise the rheological performance of the three selected artificial tears, solution in-vitro rheology testing was performed by the Centre for Industrial Rheology (Warnford, Hampshire, UK) using a research rheometer (DHR2, TA Instruments, New Castle, Delaware, USA) fitted with a 60 mm aluminium flat plate measuring system at 31 °C. A solvent trap cover was employed to minimise drying of the sample at the exposed edges. Shear rate profiling across a wide range of shear rates encompassing zero-shear viscosity plateau behaviour, of relevance to residence time on the eye, and very high shear rates, of relevance to blink conditions, was performed three times [29,30]. Following a 30 s

Table 1
Hyaluronic acid-containing products analysed.

Product	Manufacturer	Lot Number(s)	Exp Date
Hylo-Forte	Ursapharm	3088812	10/2026
		307964	07/2026
HydraMed	Farmigea	0050324	03/2027
		0500224	02/2027
Evolve HA	Medicom Healthcare Ltd	RE0223	08/2026

Table 2
Hyaluronic acid samples used for reference.

Hyaluronic Acid Lot Code	Intrinsic Viscosity Range (m^3/kg)	Intrinsic Viscosity Measured (m^3/kg)
H3897	1–1.5	1.21
H4157	1.5–2.0	1.78
H4362	3–3.3	3.12

equilibration time at 31 °C the samples were exposed to a shear rate sweep, 1.0 s^{-1} to a nominal 50000 s^{-1}, logarithmically scaled, 5 points per decade of shear rate, shear applied for 30 s at each rate with viscosity calculated over the final 10 s of each step. In addition, normal stress measurement (when an elastic fluid is sheared a stress is generated normal (i.e. perpendicular) to the direction of shear) was measured on a research rheometer through a force transducer fitted in the rheometer "head". The magnitude of this force is strongly associated with film-forming ability, a pre-requisite for thick-film lubrication. A good film-former typically generates a high normal stress compared to a poor one at a given shear rate. Following a 60 s equilibration time, the samples (maintained at 31 °C) were exposed to a linear measurement sweep.

2.4. Participants

This prospective, double-masked, randomised crossover trial was conducted in adherence with the tenets of the Declaration of Helsinki and received favourable ethical clearance from Aston University Research Ethics Committee (ID: 1831). Visits were completed at a clinical academic site in the UK. Participants were required to be 18 years or older, with manifest symptoms and signs of dry eye disease according to the TFOS DEWS II diagnostic criteria (Ocular Surface Disease Index (OSDI) score $\geq$ 13 or 5-Item Dry Eye Questionnaire (DEQ-5) $\geq$ 6, with at least one positive indicator of homeostatic imbalance based on non-invasive tear film breakup time, tear osmolarity and/or ocular surface staining) [3]. In addition, participants were required: not to wear contact lenses during the study (none were habitual contact lens wearers); to report no history of major ocular conditions and to report no ophthalmic surgery in the previous three months or during the treatment period. Habitual therapeutic measures to treat dry eye were allowed during the study period, however, no changes to any treatment courses or routines (such as warm compresses) were permitted during the study. Eligible participants were enrolled for baseline screening after providing written informed consent to participate. A total of 25 eligible participants (80 % females; mean ± SD age, 23.6 ± 9.2 years, range 19 to 65 years) were recruited (based on sample size guidance)[3] and completed all three visits on separate days, but at the same time of day.

2.5. Measurements

Participants received one topical application of each drop in both eyes in a randomised order. Randomisation was achieved via a pre-determined Latin square system so that each sequence of drops occurred an equal number of times. An unmasked investigator removed the product labels, which were replaced with customised labels to obscure the contents and achieve double masking. Participants were instructed to avoid eye drop instillation, and any other treatments such as warm compresses or lid hygiene on the day of testing. Prior to the start of the trial, each drop was weighed. It was determined that two drops of Hylo-Forte would be required for one application, to roughly match the larger drop size of the two other drops (Hylo-Forte average 0.017 g / drop; HydraMed 0.044 g / drop; Evolve 0.040 g / drop). All participants were assessed at the same site, by the same masked investigator (DS), in the same facility, with a room temperature of approximately 21 °C and relative humidity of around 30 %. Ocular measurements were conducted on the right eye only of each participant, though drops were applied to both eyes. Clinical tests were conducted in accordance with the recommendations of the TFOS DEWS II Diagnostic Methodology subcommittee [3]. To reduce the impact on tear film physiology, the tests were ordered from least to most invasive at each study visit (conjunctival hyperaemia, TMH, non-invasive tear film breakup time). Symptoms were assessed at each time point before ocular signs, using a visual analogue scale "severity of dry eye symptoms" question, scaled from 0 (very mild) to 100 (very severe). All tear film and ocular surface measurements were assessed using the Keratograph 5M (Oculus Optikgeräte, Wetzlar, Germany) in the following order. Conjunctival hyperaemia was evaluated by automated objective evaluation of high magnification digital imaging (nasal and temporal regions averaged), benchmarked against the JENVIS grading scale, ranging from 0 to 4 [35]. The lower tear meniscus height was assessed by capturing a high magnification digital image and applying pre-calibrated digital callipers taking an average of three readings; one each from the lower lid margin beneath the nasal and temporal limbus edge and centrally. Non-invasive tear film breakup time was measured using automated detection of first breakup, while the participant maintained fixation and was requested to refrain from blinking. Two breakup time readings were averaged in each case (due to the limited time between measurements and to minimise the impact of the forced stare on subsequent ocular symptoms and tear assessments). Outcome measures were evaluated at baseline at each visit, and then repeated after 5, 15, 30, 45, 60 and 90 min after drop instillation. Participants remained in the temperature-controlled clinic throughout the assessments and were not permitted to conduct any demanding tasks such as viewing their smartphone.

2.6. Statistical analysis

The minimum required sample size was calculated to be 13 with a two-tailed repeated measures analysis of variance (ANOVA), to detect clinical significance with 95 % power, at a significance level of 0.05 (G*Power v3.1; Franz Faul, Universität Kiel, Germany). This was increased to 25, in order to make it more comparable with similar studies [36,37] and to increase the robustness of the statistical tests.

Data analysis was conducted using SPSS (v29; IBM, New York, USA). As the measures were all continuous and not restricted by a ceiling or floor effect, repeated measures ANOVA was applied with artificial tear and time as within-participant variables. This reduced the number of statistical tests and hence the chance of a type I error. T-tests post-hoc testing was applied to compare each artificial tear's effect compared to baseline at a particular time point, only when a significant difference with time had been detected by the ANOVA.

3. Results

3.1. Molecular weight and concentration

The estimated molecular weight of the hyaluronic acid in each of the products is presented in Table 3 alongside the measured hyaluronic acid concentration.

3.2. In-Vitro rheology

Hylo-Forte showed a less linear (more non-Newtonian) relationship

Table 3
Hyaluronic acid estimated molecular weight and concentration for each of the tested products.

Product	Measured MW (Da)
HyloForte	2.5 M
HydraMed	0.8 M
Evolve HA	1.3 M

between viscosity and sheer force ($r^2 = 0.295$) compared to HydraMed ($r^2 = 0.485$) and Evolve ($r^2 = 0.521$; Fig. 1).

3.3. Clinical testing

Dry eye symptoms improved rapidly with drop instillation and then slowly declined with time ($F = 12.460$, $p < 0.001$), with all drops following a similar profile ($F = 0.814$, $p = 0.636$; Fig. 2). While there was no significant difference between a single application of the drops ($F = 0.048$, $p = 0.953$), the HMWHA (Hylo-Forte) drop was the only one above baseline at the $p < 0.001$ level after 90 min.

Non-invasive breakup time improved rapidly following drop instillation and then slowly declined with time ($F = 7.182$, $p < 0.001$), with all drops following a similar profile ($F = 1.472$, $p = 0.134$; Fig. 3). HydraMed was unable to maintain the initially improved tear stability ($F = 4.198$, $p = 0.021$) and Hylo-Forte was the only artificial tear to retain tear stability significantly above baseline at 30 min post instillation ($p < 0.05$).

Tear meniscus height increased rapidly following drop instillation and then declined slowly with time ($F = 18.643$, $p < 0.001$) reaching a plateau after 30 min, with Evolve having a reduced initial effect compared to HydraMed and Hylo-Forte (interaction $F = 4.045$, $p < 0.001$, Fig. 4). Overall, there was no statistically significant difference between the artificial tears ($F = 1.875$, $p = 0.164$).

Average bulbar redness was not significantly affected over time ($F = 1.721$, $p = 0.120$) with any of the artificial tears ($F = 1.249$, $p = 0.296$; Fig. 5). However, the average redness grade at baseline was just 0.63 ± 0.44.

4. Discussion

The purpose of this trial was to assess whether volume-matched drops containing the same reported concentration (0.2 %) of hyaluronic acid, but with different molecular weights, and hence rheological properties, vary in terms of their short-term impact on patient symptoms, tear measures or ocular redness. Previous studies have compared drops containing different concentrations of hyaluronic acid [37,38]. Conversely, the premise of this study was to evaluate the effects of molecular weight and hence rheology of hyaluronic acid, in formulations of the same concentration. The hyaluronic acid molecular weights have been reported as 950 kDa for HydraMed [33] and 1748 kDa for Hylo-Forte [32], differing by 1.8 times. Measurement against hyaluronic acid-containing standards gave a similar order of molecular weights for HydraMed (800 kDa) and Hylo-Forte (2500 kDa although the actual values differed), with Evolve being more mid-range, at 1300 kDa. Evolve, like Hylo-Forte, has 0.2 % hyaluronic acid as the only active component, hence any difference in in-vitro rheology can be reasonably attributed to the molecular weight of the hyaluronic acid. HydraMed contains tamarind seed polysaccharide, which can exhibit non-Newtonian sheer thinning behaviour [39], but other stated constituents such as sodium chloride [40] have low viscosity at room temperature, so are unlikely to contribute to artificial tear rheology. Despite this potential non-hyaluronic acid-based advantage, HydraMed still did not perform as well as the higher molecular weight artificial tear.

The drop volume was roughly matched, to remove this as a confounding factor, although in clinical practice most of the drop volume is wasted due to the limited storage capacity of the ocular surface and surrounding anatomy [41] so a smaller drop will increase the time until the product is used up, but should not affect efficacy. The molecular weight of hyaluronic acid should be taken into account when comparing different products as this was shown to significantly affect their in-vitro

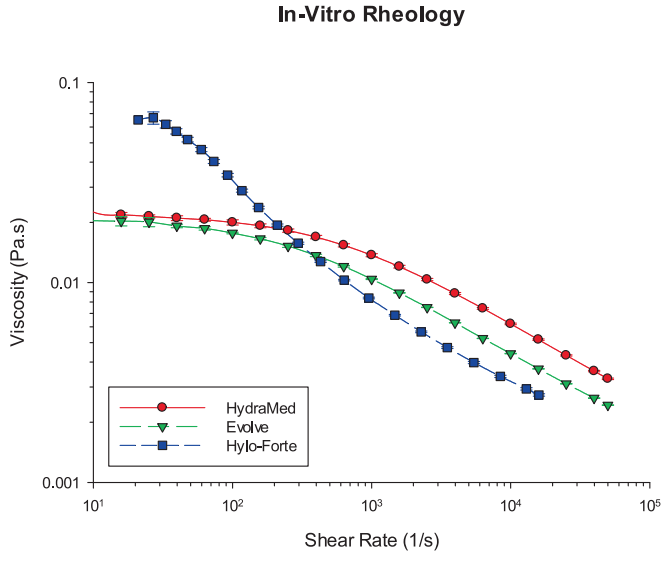

Fig. 1. In-Vitro Rheology of each of the artificial tears tested three times. Error bars = ±1 S.D.

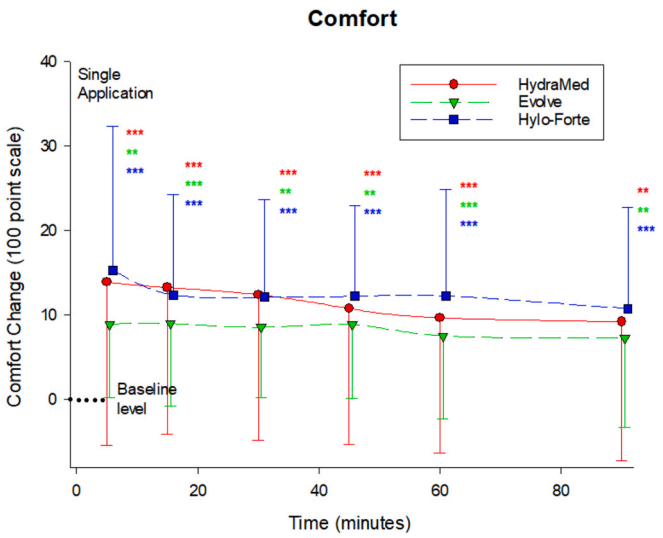

Fig. 2. Dry eye symptoms change compared to baseline over time with 0.2 % hyaluronic acid-based artificial tears of different molecular weights. N = 25. Error bars = ±1 S.D. *** $p < 0.001$ and ** $p < 0.01$ versus baseline.

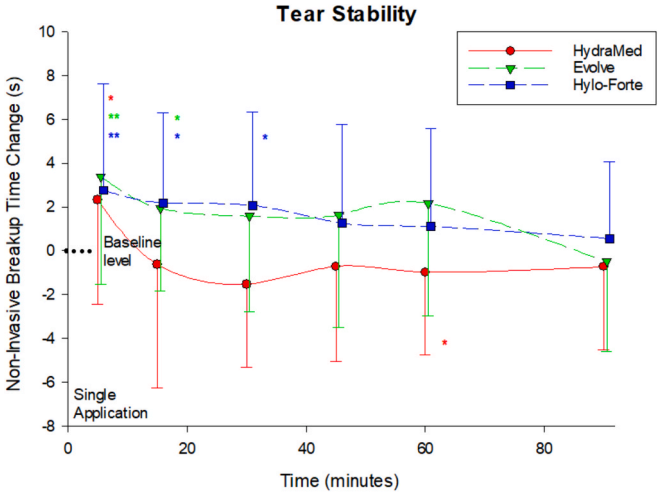

Fig. 3. Non-invasive tear breakup time change compared to baseline over time with 0.2 % hyaluronic acid-based artificial tears of different molecular weights. N = 25. Error bars = ±1 S.D. ** $p < 0.01$ and * $p < 0.05$ versus baseline.

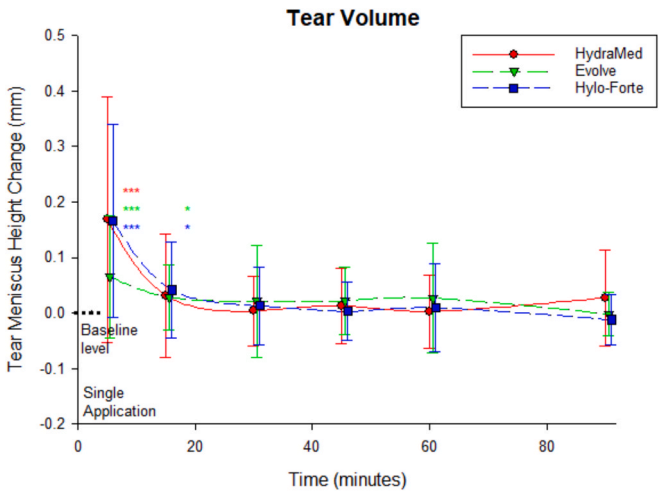

Fig. 4. Tear meniscus height change compared to baseline over time with 0.2 % hyaluronic acid-based artificial tears of different molecular weights. N = 25. Error bars = ±1 S.D. *** $p < 0.001$ and * $p < 0.05$ versus baseline.

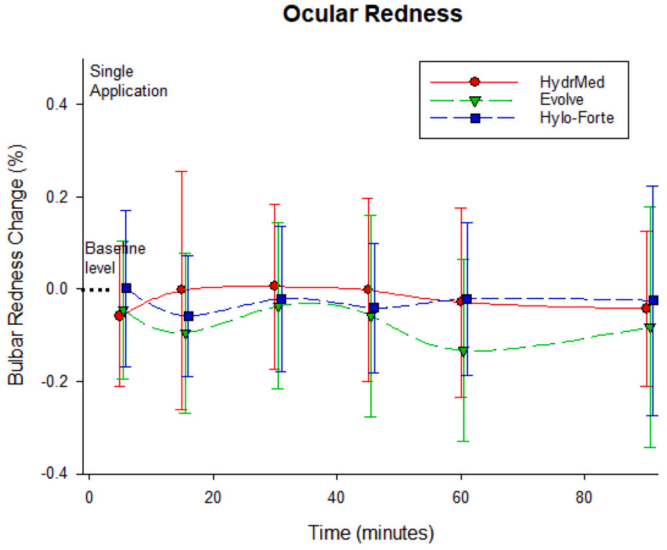

Fig. 5. Ocular redness change compared to baseline over time with 0.2 % hyaluronic acid-based artificial tears of different molecular weights. N = 25. Error bars = ±1 S.D.

rheology – as had been shown previously with different hyaluronic acid formulations [32] – and hence the viscosity in between (ideally high) and during (ideally low) a blink (Fig. 1). Moreover, results of clinical trials of similarly formulated artificial tears may not be directly comparable without knowing the molecular weight of hyaluronic acid concerned [20].

With regard to the primary outcome measure of dry eye symptom severity (VAS), the results demonstrated that whilst all of the study drops reduced symptoms, only the HMWHA drop (Hylo-Forte) had a statistically significant benefit at the > 0.001 alpha level after 90 min. Secondary outcome measures were tear breakup time, tear volume, and ocular redness. All three drops improved tear stability (tear breakup time), however the HMWHA was the only drop to maintain tear stability significantly above baseline after 30 min ($p < 0.05$). HydraMed performed worst in this metric. For tear volume, there was no significant difference between the drops; for a short-term assessment this could have been affected by a range of aspects such as ocular irritation and the drop size dispensed, so a longer-term dispensing study would be needed to assess the true effect on tear volume at times longer after drop instillation. Likewise, there was no significant difference for ocular redness, but as mentioned previously, this was low at baseline in the study population.

As with other trials of artificial tears, all the study drops produced improvements in the symptoms and signs of dry eye, with differences between product formulations on a single application being relatively small. This adds to the weight of evidence showing that artificial tears are beneficial for the majority of patients with DED. Participants were assessed at baseline and six times within 90 min after the treatment, and this repeated testing could have disrupted the tear film, impacting the ocular surface. Despite this, symptoms of dry eye were still reduced, and tear stability was improved over this complete time-period, following artificial tear instillation. As is common in dry eye, signs and symptoms were not closely associated [42,43]. For example, in this study, HydraMed performed considerably worse in terms of tear stability, however it performed relatively well in terms of subjective dry eye symptom reduction.

In the present study, participants received each drop only once; however, even after just this single instillation, some significant differences were observed. The sample size was modest, and most participants were young females, however this may have made the results more comparable than had the study population been more heterogenous. Future trials expanding upon this research would be useful, with a larger sample size and repeated instillations of each drop over weeks or months, followed by a washout period and repeat measurements with other drops. Ideally this would take the form of a large, high-quality, level-1, randomised controlled trial.

In conclusion, this study enhances our current understanding of how molecular weight, and the resulting rheological differences, affect at least the short-term clinical performance of artificial tear preparations. This is important, because it fills a knowledge gap and has practical applications in helping to inform prescribing decisions, which is beneficial to eye care providers, medical and other prescribers, and not least their patients. Higher molecular weight hyaluronic acid has rheological properties similar to the natural tear film [44] and this study demonstrates how this positively impacts its short-term clinical effectiveness compared to its low molecular weight counterparts.

Declaration of Competing 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.

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