



Immediate effects of artificial tears with and without preservatives containing hyaluronic acid and carboxymethyl cellulose

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ABSTRACT

Background: Currently, hyaluronic acid (HA) and carboxymethyl cellulose sodium (CMC) are common polymers incorporated in artificial tears (ATs). The aim of the present study was to evaluate the immediate effect of preservative- and preservative-free HA- and CMC-containing ATs on tear-film parameters and determine patient preference after AT instillation.

Methods: In this prospective, double-blind, randomized, comparative study, we assessed fluorescein tear break-up time (TBUT), bulbar redness, and tear ferning pattern (TFP) up to 60 min after the instillation of ATs with and without preservatives containing HA and CMC in the recruited participants. To test patient preference, each patient was administered with the Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire (OOD4SQ; scale of 0–5) before and 60 min after the instillation of ATs. The selection of 14 descriptive words based the 11-point Ora Calibra™ Drop Comfort Scale (ODCS; scale of 0–10) was administered immediately after instillation of each AT to test the drop comfort score.

Results: We enrolled 200 eyes of 200 patients, including 163 (81.5%) women and 37 (18.5%) men, with a mean (standard deviation) age of 28.38 (5.42) years. Immediately or 5, 15, or 60 min after the instillation, the mean TBUT did not differ by presence of preservatives, HA, or CMC (all $P > 0.05$). However, it was significantly higher 5-min post-instillation compared to baseline and significantly lower 15- and 60-min post-instillation (all $P < 0.05$). The mean grade of bulbar redness immediately or 3, 5, 15, or 60 min after instillation did not differ by presence of preservatives for HA or CMC containing ATs (all $P < 0.05$). It did not differ significantly 3-, 5-, 15-, or 60-min post-instillation compared to baseline (all $P > 0.05$). The mean drop comfort scale after the instillation of ATs did not differ significantly by presence of preservatives, HA, or CMC (all $P < 0.05$). Positive descriptive words were selected by a higher proportion of participants in both groups. According to OOD4SQ, the overall discomfort and mean dryness scores improved significantly after instillation of HA-containing ATs (both $P < 0.05$), while the mean burning sensation, grittiness, and stinging scores remained unchanged (all $P > 0.05$). The overall discomfort and mean scores for each ocular symptom ($P < 0.05$), except for stinging ($P > 0.05$), improved significantly after instillation of CMC-containing ATs. The TFP did not change significantly from baseline to 60 min after the instillation of any AT ($P > 0.05$).

Conclusions: Both ATs with and without preservatives containing HA and CMC produced positive short-term objective and subjective effects. However, TBUT, TFP, bulbar redness, and patient feedback were comparable for both HA- and CMC-containing ATs. Further trials with longer observation periods or the recruitment of patients with different severities of dry eye could provide more robust and clinically applicable conclusions.

KEYWORDS

artificial tear, hyaluronate sodium, carboxymethyl cellulose, tear, patient preferences, questionnaire

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INTRODUCTION

The tear film consists of three layers, each contributing to the lubrication and integrity of the ocular surface [1]. The outermost layer, composed of lipid, is secreted by the meibomian gland and prevents tears from evaporating [2], indirectly providing tear stability [3]. The middle layer, an aqueous layer secreted by the lacrimal gland, provides ocular lubrication and oxygen to the ocular surface. The innermost layer, a mucin layer secreted by goblet cells, promotes tear adherence to the ocular surface and indirectly moistens the ocular surface [4, 5].

Dry eye disease is a multifactorial disease of the ocular surface characterized by the loss of tear-film homeostasis accompanied by ocular symptoms. Its etiologies include tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities [6, 7]. Artificial tears (ATs) can provide immediate relief to patients with dry eye disease [8, 9]. However, ATs are commonly contaminated because of contact with the tip of a bottle [10]. Preservatives incorporated in AT formulations act as antimicrobial agents that reduce the risk of microbial infections from bottle-tip contamination [11] and are safe to use [10]. However, preservative-free ATs have been developed to overcome the disadvantage of allergic reactions triggered by preservatives on the ocular surface [12].

Currently, hyaluronic acid (HA) and carboxymethyl cellulose sodium (CMC) are common polymers incorporated in ATs [13]. HA has mucus-adhesive and hygroscopic properties and improves eye lubrication and hydration; thus, it is suitable for use in ATs [14]. In addition, it has advantages of strong biocompatibility, viscoelastic properties, and anti-inflammatory properties, conducive to corneal wound healing [8, 14]. CMC-containing ATs improve tear quality and alleviate patient symptoms [15, 16].

The aim of the present study was to evaluate the immediate effect of preservative- and preservative-free HA- and CMC-containing ATs on tear-film parameters and determine patient preference after AT instillation.

METHODS

In this prospective, double-blind, randomized, comparative study, we recruited volunteers through convenience sampling from January to September 2021. The study protocol was approved by the International Islamic University Malaysia (IIUM) Research Ethics Committee (IIUM/504/14/11/2/ IREC 2019-KAHS (U)). Participants provided informed consent before data collection. All standard optometry procedures were performed at the IIUM Optometry Clinic, Kulliyah, Allied Health Sciences, Kuantan, Pahang, Malaysia.

Inclusion criteria were good ocular and general health, age between 20 and 40 years [17-19], without known sensitivity or intolerance to any product used in this study, no use of contact lens [1], a fluorescein tear break-up time (TBUT) > 5 s [20-22], ocular surface disease index (OSDI) score < 13 [23], and Schirmer test I > 10 mm of wetting/5 min [20]. Exclusion criteria were a history of ocular trauma; evidence of active ocular infection in either eye; significant underlying ocular pathology affecting the ocular surface, such as the pterygium [19, 20]; current treatment with drugs affecting tear production; and pregnancy, lactation, or lack of menstruation in female participants [1, 24, 25].

Initially, detailed optometric and ophthalmic examinations were performed for all participants, as outlined before [26, 27]. Subsequently, 200 of the 233 participants who fulfilled the inclusion criteria were included in analyses (Figure 1). Bulbar redness and TBUT were evaluated using a digital high-definition slit-lamp biomicroscope (HD-SLB; Model SL 990, SLB Mega Digital Vision HR, Costruzione Strumenti Oftalmici, Italy) at primary gaze and under standard illumination and magnification [28]. Bulbar redness was graded using the Efron grading scale [29]. Fluorescein TBUT was recorded using HD-SLB built-in imaging software. Three TBUT measurements were acquired, and the mean value was recorded for data analyses [30].

For the tear ferning pattern (TFP), the temperature and humidity of the examination room were kept constant at 20°C–24°C and 40%–50%, respectively [31]. Some tear was collected using a capillary tube (Hematocrit Capillaries, Hirschmann Laboratories GmbH & Co., Germany) from the inferior palpebral conjunctival fold and allowed to dry on glass microscope slides (HmbG Model, 227101 × Ground Edges, 45° corners - Orioner High-tech Sdn. Bhd, Kuala Lumpur, Malaysia). The slide was left to dry before being observed under a digital monocular light microscope (T-17541C Digital CoreScope, Ken-A-Vision Manufacturing, Co., Inc., Missouri, USA) to evaluate the TFP grade using Rolando's Classification [32, 33].

To test patient preference, each patient was administered with the Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire (OOD4SQ; scale of 0–5) before and 60 min after the instillation of ATs. OOD4SQ requires each patient to grade ocular discomfort, burning, drying, grittiness, and stinging on a scale of 0–5, where 0 indicates “no discomfort” and 5 indicates “the worst discomfort” [34-36].

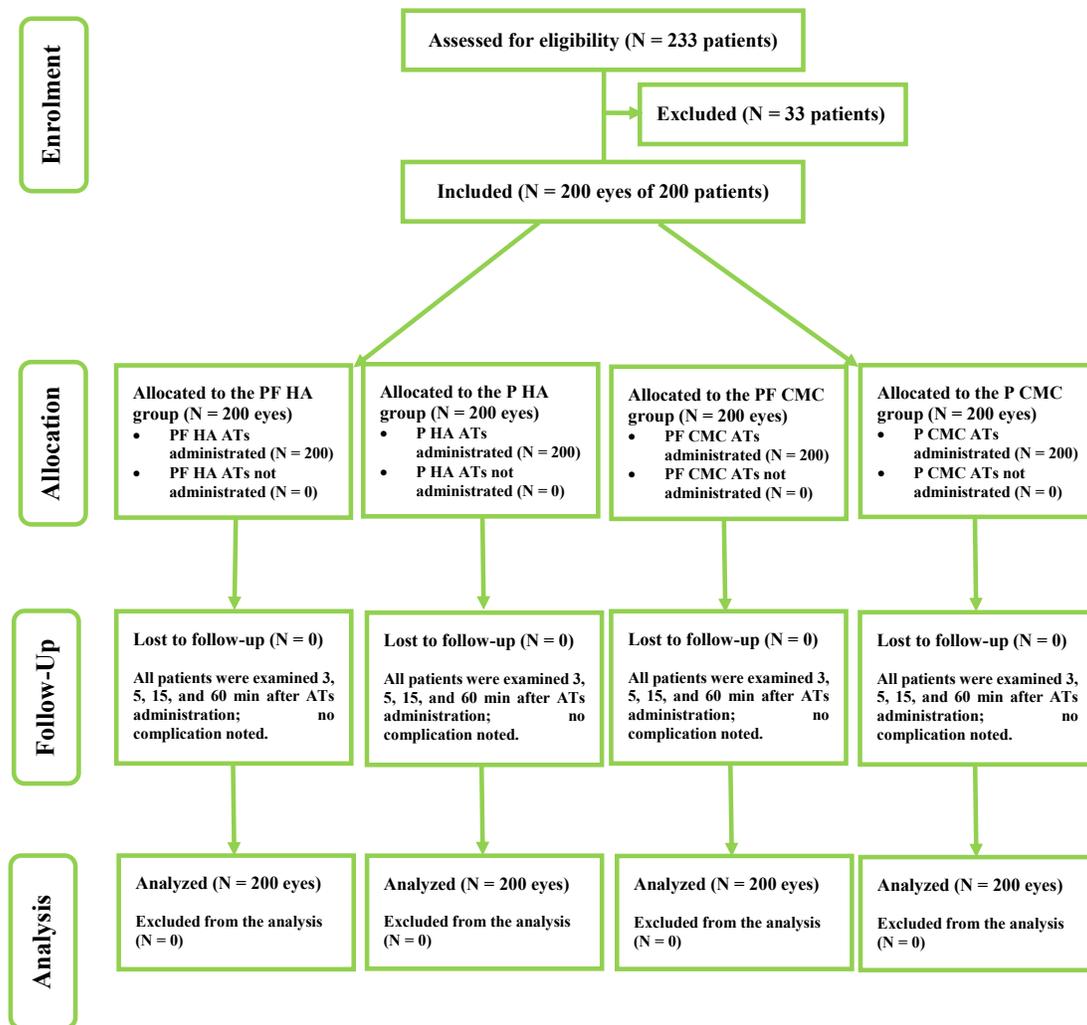


Figure 1. CONSORT flow diagram of the study process. Abbreviations: N, numbers; PF, preservative-free; HA, hyaluronic acid containing ATs; ATs, artificial tears; P, preservative; CMC, carboxymethyl cellulose sodium containing ATs; min, minutes.

We used four ATs, including two preservative-free ATs, i.e., the Systane® hydration unit dose (Alcon Laboratories Inc., Fort Worth, TX, USA), and Optive® unit dose (Allergan, Inc., Irvine, CA, USA), and two ATs with preservatives, i.e., Systane® hydration (Alcon Laboratories Inc., Fort Worth, TX, USA), and Optive® (Allergan, Inc., Irvine, CA, USA). Optive® unit-dose and Optive® ATs contain CMC [37]. Systane® hydration unit-dose and Systane® hydration ATs contain HA [38]. The double-masked randomization approach was used. The participants were blinded to the type of AT instilled. Unrelated personnel blinded to the AT type prepared the AT in off-label bottles “A,” “B,” “C,” and “D.” The sequence of which eye received which AT first, during which run, was also randomized using research randomizer software (Research Randomizer, version 4.0) [39]. The washout period between complete assessments for each AT was at least 24 h [1]. Overall, the study constituted four runs, in which only one eye from each patient was treated with ATs (200 eyes from 200 patients in each treatment group). The patients were subjected to a 24-h washout period, after which the next AT was administered to assess the study objectives. A total of four runs of the AT treatment were conducted for each patient (Figure 1).

Before AT instillation, a fixed volume of 60 µL (approximately equivalent to one drop) was standardized using a micropipette for each AT. Immediately after instillation, the participants were required to grade the comfort rate for the right or left eye on the 11-point Ora Calibra™ Drop Comfort Scale (ODCS; scale of 0–10) and instructed to choose three out of 14 descriptive words to describe the comfort after instillation of ATs; these descriptors were comfortable, cool, refreshing, smooth, soothing, thick, filmy, sticky, burning, itchy, fuzzy, stinging, irritating, and gritty. The selection of 14 descriptive word-based ODCS was provided in the form of a sheet to each patient during the assessment [36].

Three minutes after the instillation of each AT, bulbar redness was evaluated using HD-SLB. Measurements of TBUT and bulbar redness were repeated after AT instillation at 5, 15, and 60 min. TFP was evaluated only at baseline and 60 min after the instillation of ATs. Patients were required to complete the OCOD4SQ within an observation period of 60 min. The same steps were repeated for each study.

All collected data were analyzed using the Statistical Package for Social Science Software (version 25, Statistical Package for Social Sciences; SPSS Inc., IBM Corp., Armonk, NY, USA). Each patient was instructed to select descriptors outlined in the ODCS to assist them in describing their comfort regarding the instillation of ATs, and the frequency (percentage) of the reported descriptors was presented. Normality testing was performed based on skewness and kurtosis tests. The repeated-measures analysis of variance or *t*-test was used to compare the outcomes. The significance level was set at *P*-value < 0.05.

RESULTS

Overall, we enrolled 200 eyes of 200 patients, including 163 (81.5%) women and 37 (18.5%) men, with a mean age (standard deviation [SD]) of 28.38 (5.42) years. The mean (SD) TBUT, OSDI scores, and Schirmer test I scores were 5.33 (0.2) s, 11.32 (0.42), and 12.43 (1.12) mm, respectively.

At baseline (immediately after instillation) and 5, 15, and 60 min after instillation, the mean TBUT did not differ significantly by presence of preservatives, HA, or CMC (all *P* > 0.05; Table 1). However, from baseline, the mean TBUT increased significantly for all ATs 5 min post-instillation and decreased significantly 15 and 60 min post-instillation (all *P* < 0.05) (Table 1).

The mean grade of bulbar redness at baseline (immediately after instillation) was comparable to that at 3-, 5-, 15-, and 60-min post-instillation of ATs (all *P* > 0.05; Tables 2 and 3). Further, it did not differ significantly by presence of preservatives, HA, or CMC (all *P* > 0.05; Tables 2 and 3).

The mean drop comfort scale based on the ODCS after the instillation of ATs did not differ significantly by presence of preservatives, HA, or CMC (all *P* > 0.05; Table 4). However, both preservative-free ATs showed slightly lower mean drop comfort scores. Lower drop comfort scores signified better comfort and fewer symptoms (Table 4).

As the previous analysis of the drop comfort score revealed no significant difference (Table 4), the three descriptive words were evaluated in two groups: HA and CMC. For three descriptive words, a specific descriptor was assigned to describe patient feedback. Each participant was required to select the descriptor that represented their feelings after AT instillation. A larger percentage of participants in both groups selected positive descriptive

Table 1. Comparing tear breakup time between ATs with and without preservatives containing HA and CMC in the 60-min observation period

Time point	Preservative ATs, Mean ± SD		Preservative-free ATs, Mean ± SD		P-value
	HA	CMC	HA	CMC	
Baseline	4.30 ± 1.50	4.13 ± 1.50	4.13 ± 1.40	4.23 ± 1.20	<i>P</i> ₂ = 0.568
	<i>P</i> ₄ = 0.103		<i>P</i> ₄ = 0.140		<i>P</i> ₃ = 0.492
5 min	5.27 ± 1.20	5.00 ± 1.30	5.17 ± 1.1	5.07 ± 1.10	<i>P</i> ₂ = 0.476
	<i>P</i>₁ < 0.001	<i>P</i>₁ < 0.001	<i>P</i>₁ < 0.001	<i>P</i>₁ < 0.001	<i>P</i> ₃ = 0.693
	<i>P</i> ₄ = 0.080		<i>P</i> ₄ = 0.170		
15 min	5.07 ± 1.40	4.83 ± 1.30	4.93 ± 1.10	4.83 ± 1.20	<i>P</i> ₂ = 0.501
	<i>P</i>₁ < 0.001	<i>P</i>₁ < 0.001	<i>P</i>₁ < 0.001	<i>P</i>₁ < 0.001	<i>P</i> ₃ = 0.855
	<i>P</i> ₄ = 0.090		<i>P</i> ₄ = 0.210		
60 min	4.80 ± 1.30	4.60 ± 1.50	4.70 ± 1.20	4.70 ± 1.40	<i>P</i> ₂ = 1.000
	<i>P</i>₁ = 0.003	<i>P</i>₁ = 0.006	<i>P</i>₁ < 0.001	<i>P</i>₁ = 0.003	<i>P</i> ₃ = 0.942
	<i>P</i> ₄ = 0.078		<i>P</i> ₄ = 0.440		

Abbreviations: HA, hyaluronic acid containing ATs; CMC, carboxymethyl cellulose sodium containing ATs; ATs, artificial tears; min, minutes; SD, standard deviation; TBUT, fluorescein tear break-up time. Note: *P*-values < 0.05 are shown in bold; *P*-value is from the repeated-measures analysis of variance; *P*₁, *P*-value is for the comparison between baseline and 5-, 15-, and 60-min TBUTs for ATs with and without preservatives containing HA or CMC; *P*₂, *P*-value is for the comparison of ATs with and without preservatives containing HA among specific time point; *P*₃, *P*-value is for the comparison between ATs with and without preservatives containing CMC at specific time points; *P*₄, *P*-value is for the comparison between ATs with preservatives containing HA and CMC or ATs without preservatives containing HA and CMC at specific time points.

Table 2. Comparing bulbar redness between ATs with and without preservatives containing HA in the 60-min observation period

Time point	Preservative HA, Mean ± SD	Preservative-free HA, Mean ± SD	P-value
Baseline	1.00 ± 0.37	0.97 ± 0.32	$P_2 = 0.573$
3 min	1.03 ± 0.41	1.03 ± 0.41	$P_2 = 0.326$
	$P_1 = 0.326$	$P_1 = 0.161$	
5 min	1.03 ± 0.41	1.00 ± 0.37	$P_2 = 0.573$
	$P_1 = 0.326$	$P_1 = 0.326$	
15 min	1.00 ± 0.37	0.97 ± 0.32	$P_2 = 0.326$
	$P_1 = 0.680$	$P_1 = 0.580$	
60 min	1.00 ± 0.37	1.00 ± 0.33	$P_2 = 0.326$
	$P_1 = 0.680$	$P_1 = 0.326$	

Abbreviations: HA, hyaluronic acid containing ATs; ATs, artificial tears; min, minutes; SD, standard deviation. Note: P -value is from a paired t -test or independent t -test; P_1 , P -value is from the comparison between baseline and 3, 5, 15, and 60 min; P_2 , P -value is from the comparison between ATs with and without preservatives containing HA at specific time points.

Table 3. Comparison of bulbar redness between ATs with and without preservatives containing CMC in the 60-min observation period

Time point	Preservative CMC, Mean ± SD	Preservative-free CMC, Mean ± SD	P-value
Baseline	1.03 ± 0.41	0.97 ± 0.32	$P_2 = 0.580$
3 min	1.10 ± 0.48	1.03 ± 0.41	$P_2 = 1.000$
	$P_1 = 0.161$	$P_1 = 0.161$	
5 min	1.07 ± 0.45	1.07 ± 0.45	$P_2 = 0.161$
	$P_1 = 0.573$	$P_1 = 0.830$	
15 min	1.03 ± 0.41	0.97 ± 0.32	$P_2 = 0.580$
	$P_1 = 1.000$	$P_1 = 0.580$	
60 min	1.03 ± 0.41	0.97 ± 0.32	$P_2 = 0.326$
	$P_1 = 1.000$	$P_1 = 0.580$	

Abbreviations: CMC, carboxymethyl cellulose sodium containing ATs; ATs, artificial tears; min, minutes; SD, standard deviation. Note: P -value is from a paired t -test or independent t -test; P_1 , P -value is from the comparison between baseline and 3, 5, 15, and 60 min; P_2 , P -value is from the comparison between ATs with and without preservatives containing CMC at specific time points.

Table 4. Comparison of drop comfort score of ATs with and without preservatives containing HA and CMC

Type of ATs		Mean ± SD	P-value	
Preservative	HA	2.13 ± 1.61	$P_1 = 0.274$	$P_3 = 0.134$
	CMC	1.97 ± 1.73		
Preservative-free	HA	1.77 ± 1.50	$P_2 = 0.512$	$P_4 = 0.183$
	CMC	1.87 ± 1.36		

Abbreviations: HA, hyaluronic acid containing ATs; CMC, carboxymethyl cellulose sodium containing ATs; ATs, artificial tears; SD, standard deviation. Note: P_1 , P -value is for the comparison of ATs with preservatives containing HA and CMC; P_2 , P -value is for the comparison of ATs without preservatives containing HA and CMC; P_3 , P -value is for the comparison of ATs with and without preservatives containing HA; P_4 , P -value is for the comparison of ATs with and without preservatives containing CMC.

words. Most patients chose “cool” (75.0% for HA-containing ATs versus 63.0% for CMC-containing ATs), “comfortable” (60.0% for HA-containing ATs versus 56.5% for CMC-containing ATs), and “refreshing” (both HA- and CMC-containing ATs at 50.0%). However, no patients reported burning, itching, irritation, or grittiness with HA-containing ATs or itchiness or stinging with CMC-containing ATs. Overall, the trends were similar for both ATs, regardless of whether or not they were preservative-free (Table 5).

Table 6 compares the mean ocular symptoms derived from the OOD4SQ before and after AT instillation. For HA-containing ATs, the overall discomfort and mean dryness scores improved significantly after instillation (both $P < 0.05$), but the mean burning, grittiness, and stinging scores remained unchanged (all $P > 0.05$;

Table 5. Responses to the Ora Calibra™ Drop Comfort Scale after instillation of HA- and CMC-containing ATs

Type of Symptom	Descriptor	Type of ATs	
		HA, n (%)	CMC, n (%)
Positive symptoms	Comfortable	120 (60.0)	113 (56.5)
	Cool	150 (75.0)	126 (63.0)
	Refreshing	100 (50.0)	100 (50.0)
	Smooth	25 (12.5)	27 (13.5)
	Soothing	60 (30.0)	67 (33.5)
	Thick	87 (43.5)	80 (40.0)
	Filmy	10 (5.0)	7 (3.5)
Negative symptoms	Sticky	54 (27.0)	40 (20.0)
	Burning	0 (0.0)	14 (7.0)
	Itchy	0 (0.0)	0 (0.0)
	Fuzzy	20 (10.0)	14 (7.0)
	Stinging	14 (7.0)	0 (0.0)
	Irritating	0 (0.0)	7 (3.5)
	Gritty	0 (0.0)	7 (3.5)

Abbreviations: HA, hyaluronic acid containing ATs; CMC, carboxymethyl cellulose sodium containing ATs; ATs, artificial tears; n, number of participants; %, percentage. Note: The percentages presented in the table for HA- or CM-containing ATs are calculated for 200 participants.

Table 6. Comparing Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire mean scale before and after instillation of HA- and CMC-containing ATs

Type of ATs	Symptom	Pre-instillation, Mean ± SD	Post-instillation, Mean ± SD	P-value
HA	Overall discomfort	0.70 ± 0.92	0.27 ± 0.64	0.001
	Burning	0.03 ± 0.18	0.02 ± 0.05	0.326
	Dryness	0.77 ± 0.86	0.33 ± 0.66	< 0.001
	Grittiness	0.17 ± 0.59	0.10 ± 0.55	0.161
	Stinging	0.10 ± 0.46	0.10 ± 0.31	0.161
CMC	Overall discomfort	0.77 ± 1.04	0.20 ± 0.61	0.001
	Burning	0.17 ± 0.38	0.13 ± 0.14	0.023
	Dryness	0.73 ± 0.94	0.50 ± 0.73	0.017
	Grittiness	0.40 ± 0.81	0.17 ± 0.65	0.032
	Stinging	0.10 ± 0.40	0.07 ± 0.25	0.326

Abbreviations: HA, hyaluronic acid containing ATs; CMC, carboxymethyl cellulose sodium containing ATs; ATs, artificial tears; SD, standard deviation. Note: P-value, P-value from the comparison between pre- and post-instillation values; Pre- or post-instillation overall discomfort did not differ significantly between HA- and CMC-containing ATs ($P = 0.126$).

Table 6). For CMC-containing ATs, the overall discomfort and mean scores for each ocular symptom improved significantly (all $P < 0.05$), except for stinging symptoms ($P > 0.05$; Table 6).

The TFP analysis revealed a type-II pattern at the baseline assessment in all participants, with a mean (SD) of TFP of 1.43 (0.3). The mean (SD) at 60 min of TFP in ATs without preservatives containing HA, with preservatives containing HA, without preservatives containing CMC, and with preservatives containing CMC were 1.41 (0.23), 1.48 (0.15), 1.45 (0.33), and 1.44 (0.27), respectively. At 60 min, the TFP did not significantly change between baseline and 60 min in preservative- and preservative-free HA- or CMC-containing ATs ($P > 0.05$). No drug-related adverse events were reported by participants at the end of each run or trial.

DISCUSSION

We evaluated the immediate effects of preservative- and preservative-free HA- and CMC-containing ATs on tear film parameters and subjective assessments. We noted a short-term improvement in TBUT in the four AT

groups, with a subsequent return to almost the baseline value. However, immediately or at 5, 15, and 60 min after instillation, the mean TBUT did not differ significantly by presence of preservatives, HA, or CMC. Despite the lack of significance, HA-containing ATs revealed greater improvement in mean changes in TBUT compared to their CMC counterparts. This could be attributed to the longer residence time of HA-containing ATs on the ocular surface [40] or the greater water retention capacity of HA [41]. The possibility of each justification should be verified in future trials.

A recent study [42] has commented that HA plays an important role in water retention and serves as a reservoir for water molecules that lubricate the ocular surface. The authors also commented that HA improved tear film quality. A previous study [43] reported that the HA polymer, composed of glycosaminoglycan or mucopolysaccharide, plays an important role in providing a longer retention period, resulting in significantly higher improvements in TBUT, even at lower (0.1% HA versus 0.5% CMC) and different concentrations [44, 45]. In contrast, several studies have reported the comparable efficacy of HA- and CMC-containing ATs [46-48]. Some studies have reported contradictory findings, with CMC being more effective than HA [15, 16]. These findings could be attributed to different patient selection criteria employed in each study.

Evaluation of bulbar redness revealed comparable findings between HA- and CMC-containing ATs. This could be because of several reasons. First, the effects were too subtle and reduction of inflammation might not be prominent, as most recruited participants had a baseline Efron grade of 1; therefore, the improvement after instilling both ATs might not be clinically detectable. Davitt et al. [49] reported that HA- and CMC-containing ATs significantly reduced both corneal and bulbar staining in a more severe dry eye group, indicating that the improvement could be related to the severity of dry eye [49]. Second, the observed insignificant difference could be because of the short observation period in the present study. Tavazzi et al. observed an improvement in ocular redness and eye comfort in contact lens wearers 2 weeks after the use of HA-containing preservative-free ATs [50]. However, further studies are required to verify this hypothesis.

TFP did not change significantly from baseline to 60 min after the instillation of any AT. This can be attributed to several factors. First, the initial tear ferning grade for all participants was grade II, which indicated good tear film quality [32]. Second, TFP might be less strongly correlated with TBUT, as an improvement in TBUT does not necessarily improve TFP [51]. In contrast, several studies have commented that TFP and TBUT are in agreement with each other [32, 52, 53]. This controversy could result from differences in the target groups employed in each study, such as smokers [54], those taking supplements [18, 52], or those having diabetes mellitus [55]. Further studies, including different groups of participants with underlying diseases or habits, are required to reach more robust and applicable conclusions.

We found no significant difference in comfort rates between HA- and CMC-containing ATs, consistent with a recent study [56]. Both HA- and CMC-containing ATs showed lower drop comfort scores, which signified that both ATs were equally comfortable [18, 57]. However, GroB et al. [45] found significantly higher comfort in the HA group throughout the study involving patients treated for moderate keratitis or keratoconjunctivitis related to dry eye. Stinging and itching revealed significantly more favorable results with 0.1% HA [45]. We found that 50% of the participants chose comfortable, cool, and refreshing as their three descriptive words [1]. Although both HA- and CMC-containing ATs showed an improvement in overall discomfort, the improvement was not clinically significant because the changes were subtle. Most participants responded with positive descriptive words concerning the drop comfort using the ODCS questionnaire [36]. A previous study [49] found significant improvement in overall discomfort; however, it had a different duration, i.e., 6 weeks, which is longer than the period in the present study.

This double-masked, prospective, comparative study objectively and subjectively investigated the immediate effects of four ATs. However, this study has a few limitations. First, all participants were either healthy or had mild dry eye. Therefore, any improvement revealed in this study may be too subtle for clinical detection. Therefore, we suggest a wider scope for patient selection be done to gain a better understanding of this matter in the future. Second, the duration set for the present study reflected the immediate or short-term effects of both types of ATs; therefore, the improvement was valid only for short-term effects. A longer follow-up duration would be useful for evaluating the long-term effects of their usage. Third, we used only two types of ATs with preservative- and preservative-free subtypes; therefore, the effects were limited based on the respective formulations of HA- or CMC-containing ATs used in this study. In future studies, several types of ATs could be administered to each subgroup of participants to evaluate their short- or long-term effectiveness and perform comparisons.

CONCLUSIONS

Both ATs with and without preservatives containing HA and CMC produced positive short-term objective and subjective effects. However, TBUT, TFP, bulbar redness, and patient feedback were comparable for both HA- and CMC-containing ATs. Further trials with longer observation periods or the recruitment of patients with different severities of dry eye could provide more robust and clinically applicable conclusions.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the IIUM Research Ethics Committee (IIUM/504/14/11/2/ IREC 2019-KAHS (U)). Participants provided informed consent before data collection.

Conflict of interests: None.

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