Original Article

Contralateral eye comparison of the efficacy and safety of two artificial tear formulations for corneal subbasal nerve fiber regeneration after photorefractive keratectomy

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ABSTRACT

Background: Currently, artificial tears (ATs) are the first-line agents for managing dry eye disease (DED). This study compared the efficacy and safety of two different AT formulations, Systane® Hydration (SH) and Systane® Ultra (SU), on symptoms of DED and regeneration of the subbasal corneal nerve fiber length (CNFL) in photorefractive keratectomy (PRK)-treated eyes.

Methods: This prospective contralateral comparative study recruited myopic eyes scheduled for PRK, and either SH or SU were administered for up to 3 months postoperatively. All participants underwent a standard comprehensive preoperative ophthalmological examination, *in vivo* confocal microscopy to evaluate the subbasal CNFL, and completed Ocular Surface Disease Index (OSDI) questionnaire for assessing dry eye symptoms. Image analysis software was used to calculate the subbasal CNFL (μm/mm^2). Assessments were repeated at the 1- and 3-month follow-up visits. Pre- and postoperative subbasal CNFL and OSDI scores were compared to determine inter- and intra-group differences.

Results: Fifty eyes of 25 participants were included in this study. The mean (standard deviation) age of the participants was 22.7 (3.8) years. The OSDI scores for both groups increased significantly at 1 month (both $P < 0.05$), followed by a decrease at 3 months to values comparable to the preoperative scores (both $P > 0.05$). Although OSDI scores were comparable at baseline and at the 1-month postoperative visit (both $P > 0.05$), the SU-treated eyes had a significantly better OSDI score at the 3-month visit ($P < 0.05$), despite being clinically insignificant. Preoperative subbasal CNFL differed significantly between the groups ($P = 0.001$), yet the mean values at both postoperative visits were comparable (both $P > 0.05$). In both groups, subbasal CNFL was significantly reduced at 1 month, followed by a significant increase at the 3-month postoperative visit compared to baseline (all $P < 0.05$). No treatment-related complications were observed at the end of the study period.

Conclusions: No significant difference was found between the preoperative and 3-month postoperative OSDI scores in the SH- or SU-treated eyes. Subbasal CNFL regeneration indicated a positive effect of both ATs, with a longer mean CNFL noted in the SH-treated eyes at the final visit. This suggests that SH may be a better option for improving corneal reinnervation after PRK. These observations must be verified in further trials with longer follow-up periods and larger sample sizes.

KEYWORDS

artificial tears, photorefractive keratectomies, dry eye syndrome, corneas, neural tissue regenerations, questionnaire

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INTRODUCTION

Photorefractive keratectomy (PRK) is a type of refractive surgery that uses excimer laser photoablation for removal of the corneal epithelial basement membrane and anterior stroma to correct myopia, hyperopia, or astigmatism [1, 2]. Although the safety and efficacy of PRK have been proven in many studies [3, 4], postoperative dry eye remains inevitable and is one of the most common complications of PRK [5].

Dry eye symptoms are usually subjectively evaluated using standardized questionnaires such as the Ocular Surface Disease Index (OSDI) [6]. PRK-induced dry eye is specifically attributed to photoablation of the nerve plexus, where large numbers of corneal afferent sensory nerve fibers are transversely cut [7]. Reduction of the subbasal nerve plexus density to approximately 60% at 12 months after PRK has been previously reported [8]. Corneal nerve damage leads to temporarily decreased corneal sensitivity, ocular surface inflammation, reduced tear production due to declining afferent input to the lacrimal functional unit, depletion of conjunctival goblet cells, and a decline in blink frequency [8-10].

Currently, artificial tears (ATs) are the first-line agents for managing dry eye disease (DED) because they enhance tear stability, reduce tear loss due to evaporation, and reduce ocular surface inflammation [11]. Previous work [12] reported that ATs containing sodium hyaluronate significantly improved ocular surface impairment associated with DED. Therefore, sodium hyaluronate may have a role in healing corneal wounds. However, few studies have addressed the efficacy of ATs in the regeneration of the subbasal nerve plexus and the reduction of dry eye symptoms post-PRK [13, 14]. Thus, we evaluated dry eye symptoms and changes in the subbasal corneal nerve fiber length (CNFL) in myopic eyes treated with PRK with the intervention of two different AT formulations, Systane® Hydration (SH; Alcon Laboratories, Inc., Fort Worth, TX, USA) and Systane® Ultra (SU; Alcon Laboratories) in the short-term postoperative period.

METHODS

In this prospective, randomized, double-blind, contralateral comparative study, we recruited myopic eyes scheduled for PRK between January 2020 and December 2020 at the International Islamic University Malaysia (IIUM) Eye Specialist Clinic (IESC), Kuantan, Pahang, Malaysia. Prior to commencement of the study, ethical approval was obtained from the IIUM Research Ethics Committee and the study conformed to the tenets of the Declaration of Helsinki. Participants were provided with adequate information regarding the methods and risks of all procedures conducted in the study. All participants voluntarily participated in the study and provided written informed consent. Data were collected from the IIUM Optometry Clinic, Kuliyyah of Allied Health Sciences, IIUM, IESC, and Kuliyyah of Medicine, Kuantan, Pahang, Malaysia.

We included healthy male and female participants aged 19 to 25 years with a preoperative refractive error between - 3.00 diopters (D) and - 6.00 D, a maximum cylindrical error of - 1.25 diopter cylinder (DC), and maximum pupil size of 6.5 mm under scotopic conditions. The exclusion criteria included abnormal tear film parameters, previously diagnosed ocular surface disorders such as DED and meibomian gland dysfunction [15, 16], abnormal corneal irregularity-related conditions such as pterygium [17, 18], history of ocular trauma such as penetrating injury, and systemic diseases. Participants who wore soft contact lenses within 2 weeks of the measurements, or within 4 weeks for rigid gas-permeable contact lenses, were excluded [19-21]. Participants undergoing hormone therapy and women who were menstruating, lactating, or pregnant were excluded.

Each participant underwent complete optometric and ophthalmological examinations. The right and left myopic eyes were examined separately. Manifest and cycloplegic refraction using tropicamide 1% (Mydriacyl™; Alcon Laboratories) was conducted by an optometrist [22]. The best-corrected distance visual acuity was measured using a Snellen chart (auto chart projector CP 670; Nidek Co., Ltd., Gamagori, Japan). Intraocular pressure was measured using an applanation tonometer (KAT T-type; Keeler, UK). The anterior and posterior segments were examined using digital slit-lamp biomicroscopy (Model SL 9900; CSO, Italy).

Postoperatively, each included eye was randomly assigned to receive either the SH or SU formulation of ATs using double-blind randomization via Research Randomizer software (Research Randomizer, Version 4.0) [23]. Equal numbers of eyes were allocated to the SH and SU groups. Both AT formulations were prepared off-label by an ophthalmic nurse who was blinded to the study. An equal numbers of drops was used with each formulation. Both ATs were produced by the same manufacturer using the preservative polidronium chloride 0.001%, along with similar inactive ingredients and lubricants; however, they varied in concentrations of polyethylene glycol 400, propylene glycol, and hydroxypropyl guar [24, 25]. This was done to ensure that the ingredients were relatively similar, thus reducing bias.

PRK was performed by a consultant ophthalmologist (K.M.K.) at IESC who was blinded to the group

allocations. The ocular surfaces of both eyes were sterilized using a 5% povidone–iodine ophthalmic solution (Betadine® 5%; Sigma Pharmaceuticals, Inc., IA, USA), followed by one drop of proparacaine 0.5% (Alcaine®; Alcon Laboratories). A Lieberman-type lid speculum (Katena Products, Inc., Parsippany, NJ, USA) was used to isolate the eyelashes from the operating field. All participants were treated using the PRK protocol described elsewhere [26]. After photoablation, the corneal bed was irrigated using a balanced salt solution, and soft contact lenses (Air Optix® Night & Day® Aqua; Alcon Laboratories) were placed on both eyes. Before removal of the lid speculum, one drop of moxifloxacin 0.5% (Vigamox®; Alcon Laboratories) and fluorometholone acetate 0.1% (Flarex®; Alcon Laboratories) were instilled on the eye. Positioning of the contact lens was verified using postoperative slit-lamp biomicroscopy.

Postoperatively, all participants were prescribed moxifloxacin 0.5% 4 times daily for 1 week and prednisolone acetate 1% (Alcon Laboratories) every 2 h for the first 24 h, followed by 4 times daily for 1 week. Postoperative ATs were prescribed based on the group allocation at the beginning of the study, with a frequency of one drop 4 times daily. The frequency of subsequent visits was determined by the nature of the postoperative complications and any treatment required. At a minimum, participants were scheduled for postoperative follow-up at 1 day, 1 week, 1 month, and 3 months. Three months was the defined endpoint for this study; however, further standard follow-up visits were continued at 6 and 12 months postoperatively.

The Heidelberg Retinal Tomograph with Rostock Cornea Module (HRT3 RCM; Heidelberg Engineering, Germany) [27] at the Sultan Ahmad Shah Medical Center at IIUM was used to conduct *in vivo* confocal microscopy on the participants preoperatively and at the 1-month and 3-month postoperative visits. This was performed by an operator who was blinded to the AT groups. The main parameter measured was subbasal CNFL expressed as micrometers per square millimeter (μm/mm^2) [28, 29]. A sterile Tomocap™ (Heidelberg Engineering) was placed to cover the microscope lens, while one drop of GenTeal® Gel (carbomer 0.22%, hypromellose 0.3%; Alcon Laboratories) was applied to the front surface of the microscope lens. One drop of the topical anesthetic proparacaine 0.5% was then instilled into the eye. Images of the central cornea were captured as the machine probe touched the corneal surface. The subbasal nerve plexus located at around 40–60 μm depth of the central cornea [30] was the area of interest, where consecutive images were captured. The two best-focused images of high contrast, distinguished from the background and without motion or pressure-induced artifacts in the JPEG format, were chosen for analysis. Manual tracing of the subbasal nerves was performed using the NeuronJ plug-in of ImageJ image analysis software (Wayne Rasband, National Institutes of Health, Bethesda, MD, USA) [30, 31].

All participants completed the OSDI questionnaire for each eye preoperatively and at 1 and 3 months postoperatively to subjectively report the impact of dry eye symptoms. The OSDI consists of 12 items or questions in three subscale domains: vision-related function, ocular symptoms, and environmental triggers. Schiffman et al. [32] calculated the total OSDI score ranging from 0 to 100 as follows: OSDI = (total score of all questions × 100) / (total number of questions × 4). The final score is classified into four severities of dry eye [33]: normal (0–12), mild (13–22), moderate (23–32), and severe (33–100). The cutoff OSDI score used in this study was < 13, as suggested in a previous study [34]. Figure 1 presents the CONSORT flow diagram for this study.

The collected data were analyzed using IBM SPSS Statistics for Windows, a predictive analytics software package (version 26.0; IBM Corp., Armonk, NY, USA). Normality testing was based on skewness and kurtosis ratios, with ± 2.50 considered as normally distributed [35]. Data with normal distribution are expressed as means and standard deviations (SD). Repeated measures analysis of variance was employed to compare the preoperative mean values of subbasal CNFL regeneration and OSDI scores with values measured at 1 and 3 months postoperatively. Post-hoc tests using the Bonferroni correction were performed, if applicable. The independent *t*-test and paired *t-test* were used to determine the inter- and intra-group differences at each visit, respectively. A *P*-value < 0.05 was set as the significance level.

RESULTS

Fifty eyes of 25 participants were included in the study. All data were normally distributed. The mean (SD) age of the participants was 22.7 (3.8) years (range: 19–25). The OSDI scores showed a significant increment between the preoperative and 1-month postoperative visits (both $P < 0.05$), followed by a decrease at 3 months to values comparable to the preoperative scores (both $P > 0.05$). SH treatment yielded the mean OSDI score closer to the baseline levels compared to those of SU treatment. Despite comparable OSDI scores at baseline and 1 month postoperatively (both $P > 0.05$) between the study groups, at 3 months postoperatively, SH-treated eyes had a significantly higher score than those treated with SU ($P < 0.05$), despite being clinically insignificant. (Table 1). Figure 2 illustrates the trends in OSDI scores throughout the study period.

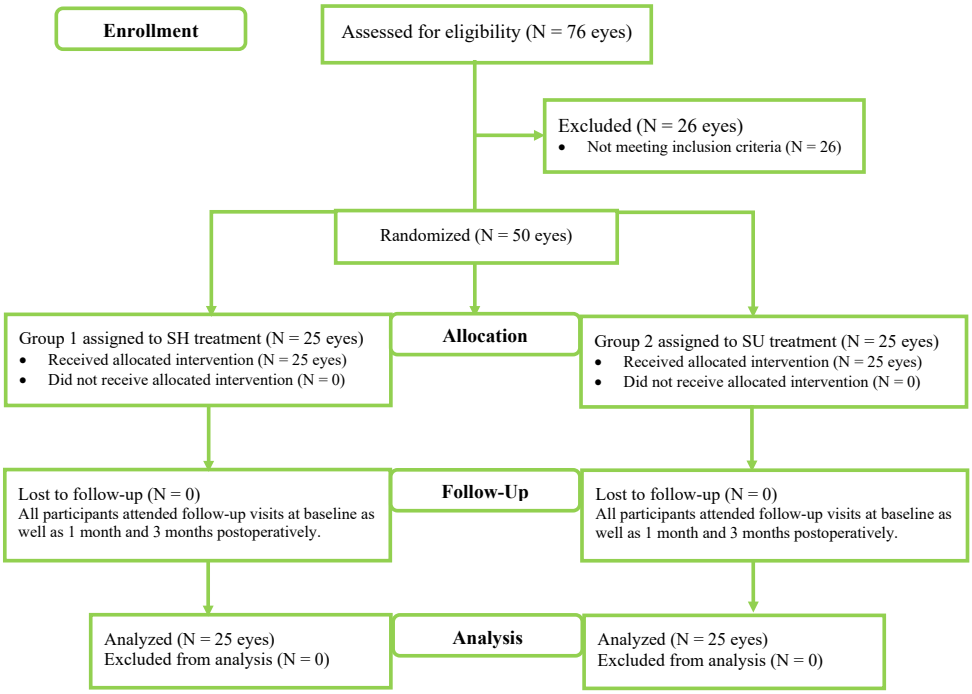

Figure 1. Patient allocation into Group 1 or Group 2. Abbreviations: N, number of eyes; SH, Systane® Hydration ATs; SU, Systane® Ultra ATs; PRK, photorefractive keratectomy; ATs, artificial tears. Note: Group 1 was administered Systane® Hydration (Alcon Laboratories, Inc., Fort Worth, TX, USA); Group 2 was administered Systane® Ultra (Alcon Laboratories).

Table 1. Baseline and postoperative OSDI scores and subbasal CNFLs in the study groups

Time Point	Variable	Group 1	Group 2	Intergroup *P*-value
Baseline, Mean ± SD	**OSDI (score)**	13.3 ± 1.4	12.8 ± 2.3	0.321
	Subbasal CNFL (μm/mm²)	8350.3 ± 1379.8	10147.4 ± 1152.9	**0.009**
1-month post-op, Mean ± SD	**OSDI (score)**	15.9 ± 1.1	14.00 ± 2.00	0.845
	Intragroup *P*-value	**0.001**	**0.001**	
	Subbasal CNFL (μm/mm²)	3285.6 ± 849.4	3626.4 ± 1097.7	0.465
	Intragroup *P*-value	**0.001**	**0.001**	
3-month post-op, Mean ± SD	**OSDI (score)**	13.3 ± 1.2	13.1 ± 1.9	**0.031**
	Intragroup *P*-value	0.173	0.142	
	Subbasal CNFL (μm/mm²)	7127.1 ± 465.6	6905.0 ± 553.3	0.368
	Intragroup *P*-value	**0.001**	**0.001**	

Abbreviations: OSDI, ocular surface disease index; subbasal CNFL, subbasal corneal nerve fiber length; SD, standard deviation; μm/mm², micrometer in square millimeter; post-op, postoperatively; ATs, artificial tears. *P*-values < 0.05 are shown in bold. Note: Group 1 was administered Systane® Hydration (Alcon Laboratories, Inc., Fort Worth, TX, USA); Group 2 was administered Systane® Ultra (Alcon Laboratories); Intragroup *P*-value, *P*-value from tests comparing each postoperative visit versus baseline data in Group 1 or 2; Intergroup *P*-value, *P*-value for the comparison between Groups 1 and 2 at specific time points.

Despite a significant decrease in the subbasal CNFL between the preoperative and 1-month postoperative visits (both $P < 0.05$), the subbasal CNFL showed a significant improvement between the preoperative and 3-month postoperative visits and between the 1- and 3-month postoperative visits in both study groups (all $P < 0.05$). Comparing the groups, only the baseline data showed a significant difference, with the SU group having a larger subbasal CNFL ($P < 0.05$), while at the 1- and 3-month postoperative visits, the difference was not significant (both $P > 0.05$). At the 3-month postoperative examination, SH-treated eyes had slightly better results in terms of regeneration of subbasal CNFL; despite having a significantly lower mean subbasal CNFL at baseline (8350.3 [1379.8] μm/mm² in SH group versus 10147.4 [1152.9] μm/mm² in SU group)

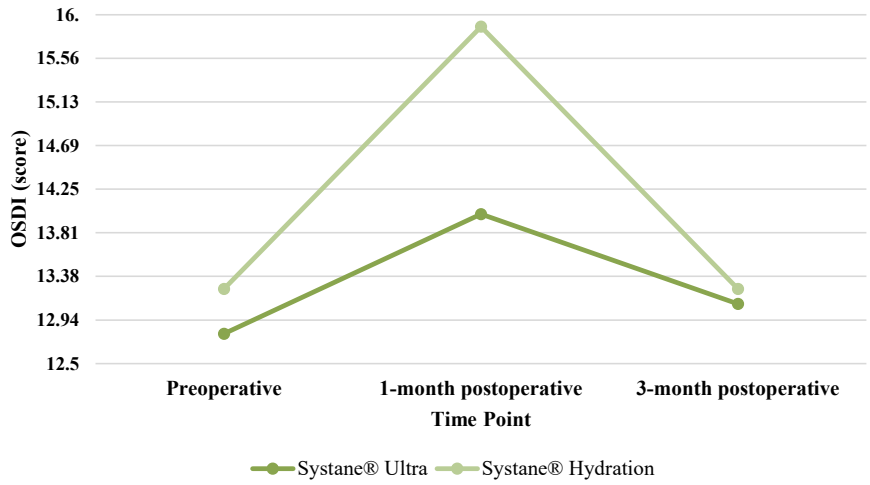

Figure 2. Changes in Ocular Surface Disease Index (OSDI) score in eyes treated with Systane® Hydration (Alcon Laboratories, Inc., Fort Worth, TX, USA) or Systane® Ultra (Alcon Laboratories) artificial tears over time.

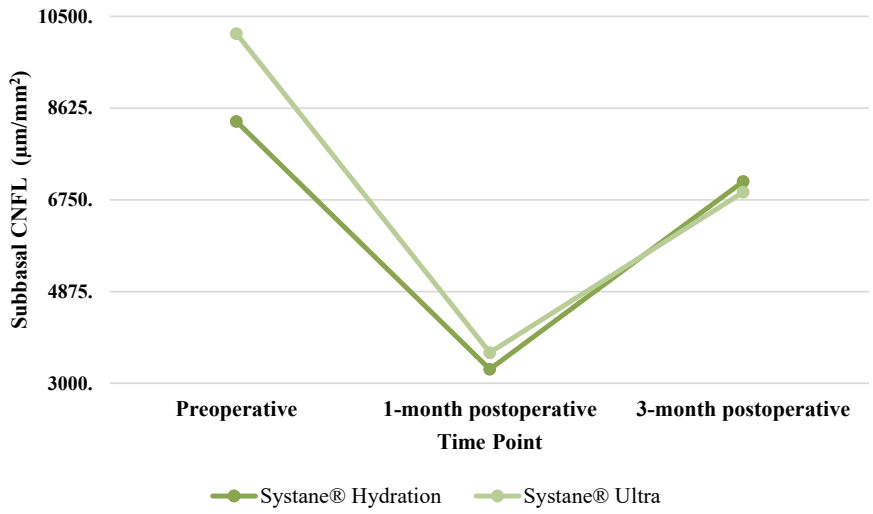

Figure 3. Changes in subbasal corneal nerve fiber length (CNFL) (µm/mm²) in eyes treated with Systane® Hydration (Alcon Laboratories, Inc., Fort Worth, TX, USA) or Systane® Ultra (Alcon Laboratories) artificial tears over time.

($P < 0.05$), at the 3-month postoperative visit the mean subbasal CNFL was higher in SH-treated eyes (7127.1 [465.6] µm/mm² in the SH group versus 6905.0 [553.3] µm/mm² in the SU group), although this difference was not statistically significant ($P > 0.05$). SH treatment yielded regeneration of the subbasal CNFL closer to the baseline levels compared to those of SU treatment (Table 1). Figure 3 illustrates the changes in subbasal CNFL throughout the study period. No treatment-related complications were observed at the end of the study period.

DISCUSSION

In this prospective, comparative, interventional study, both groups experienced significant improvements in the OSDI score and subbasal CNFL up to 3 months post-PRK.

The subbasal nerve plexus is found at the intersection of the basal epithelium and the anterior Bowman's layer. It consists of corneal nerves originating from the ophthalmic branch of the trigeminal nerve, enclosed in a thin network that contributes to epithelial innervation and intraepithelial nerves terminating on the ocular surface [9, 36]. Refractive error correction using the excimer laser photoablation of PRK at the corneal epithelial basement membrane and anterior stroma disrupts the subbasal and superficial sub-Bowman nerves [2], leading to the loss of corneal nerve endings. Likewise, we detected a significant decrease in subbasal CNFL in the early

postoperative visits in both study groups, in parallel with a deterioration in the OSDI scores as a quantitative measure of subjective symptoms of DED [37].

Loss of corneal nerve endings, with consequent ocular surface inflammation, can lead to DED [9]. Damage to the corneal nerves diminishes the afferent input to the lacrimal functional unit, reducing tear production and leading to an aqueous deficiency of the tear film [38]. Symptoms of DED, such as foreign body sensation, irritation, burning, and epiphora, are often reported by patients after refractive surgery; evidence of DED, including abnormal tear parameters and corneal fluorescein staining, are observed in eyes post-PRK [39]. Regeneration of corneal nerve fibers begins 1–7 days after surgery and is halfway complete by 3–6 months [7, 8]. This is consistent with the findings of the current study, as we observed marked reductions at the 1-month postoperative visit and steady increases thereafter in both groups.

The effects of oral [40] or topical [41-44] treatments on subbasal nerve regeneration post-PRK have been investigated in both animal and human studies. Oral supplementation with amino acids yielded significantly faster regeneration of subbasal nerves with a higher nerve fiber density and a more regular pattern in patients up to 12 months post-PRK compared to an untreated control group [40]. In an animal study administering twice-weekly treatments with docosahexaenoic acid (DHA), nerve growth factor (NGF), or NGF plus DHA delivered by collagen shield, at 2 months post-PRK, a significantly higher sub-basal nerve bundle area was detected in the DHA plus NGF-treated group than in the control and NGF- or DHA-alone groups [44]. Topical application of mitomycin C [41, 43] has promising effects on subbasal nerve regeneration post-PRK. To the best of our knowledge, this is the first prospective, interventional, comparative study to investigate the effects of two AT formulations on the restoration of subbasal CNFL post-PRK. As reported in the aforementioned studies, both AT formulations yielded significant improvements in the subbasal CNFL at 3 months post-PRK. However, owing to the lack of a placebo group, one cannot conclude whether this regeneration is solely due to the effects of ATs or is an element of the natural regeneration observed post-PRK [29].

ATs are considered the mainstay of therapy for DED because of their relatively low cost, immediate relief, and universally proven efficacy in enhancing tear film stability in most patients [38]. Other treatment options for DED include warm compression, lid wipes and systemic antibiotics for meibomian gland dysfunction, topical corticosteroids and cyclosporine as anti-inflammatory therapy, punctal occlusion for tear conservation in aqueous deficiency-type DED, and autologous serum for inflammation related to the autoimmune diseases such as Sjogren syndrome [45]. Previous authors [46] commented that although ATs temporarily alleviate dry eye symptoms, they do not address the underlying inflammatory process. However, with the advancement of technology, manufacturers have successfully developed better formulations and utilized more appropriate lubricants and ingredients to mimic natural human tears. The current study showed improvement in DED symptoms in post-PRK patients, as the OSDI scores decreased toward the normal range. The incorporation of sodium hyaluronate or hyaluronan (HA) into AT formulations has positive effects. HA is the viscoelastic sodium salt of hyaluronic acid; it is known for its avid water binding, dehydration resistance, and excellent biocompatibility [47]. HA-based ATs, such as SH and SU, have been reported to promote corneal epithelial migration and facilitate interactions with cytoskeletal proteins, thus promoting corneal wound healing [12, 48]. Therefore, these AT formulations offer the advantages of reduced dehydration-induced inflammation and improved ocular surface wettability and lubrication [49]. This may explain the observed improvement in both the OSDI scores and sub-basal CNFLs at 3 months post-PRK in both study groups.

DED symptoms, evaluated using the OSDI questionnaire, were reduced or improved after the intervention using both AT formulations. This indicates that the use of ATs does not exacerbate symptoms, thereby providing relief to patients. However, both groups showed a similar gradual increase in the OSDI score at 1 month postoperatively, when compared to baseline, before reaching their lowest scores at 3 months postoperatively. Thus, in comparing the SH and SU groups, OSDI scores were reduced, with SH yielding slightly better results, as OSDI scores were similar to the mean baseline values at the 3-month postoperative evaluation. This may imply a favorable effect of the ingredients in this particular AT formulation. Other studies have reported similar findings [38, 48].

Regarding subbasal CNFL regeneration, our study revealed no significant difference between the SH and SU groups postoperatively, suggesting similar efficacies of the two formulations. While both groups showed a significant improvement at 3 months postoperatively, the subbasal CNFL did not reach preoperative values. This outcome is consistent with that of a previous prospective study by Erie [29], who reported a significant post-PRK reduction in subbasal nerve fiber bundle density to 87%, 75%, and 60% of the baseline values at 3, 6, and 12 months, respectively; density was only restored to the preoperative value at the 24-month postoperative visit, and it remained stable at 36 months. In another prospective clinical trial, Erie et al. [8] observed a significant

reduction in mean subbasal nerve density by 59% at 1 year post-PRK compared to preoperative values. However, by 2 years, the density was not significantly different from the preoperative density and remained stable for 5 years [8]. Thus, the shorter follow-up period of our study may explain our findings. A previous study [50] revealed that one-third of eyes treated with PRK still displayed low corneal nerve fiber density even after 5 years of follow-up, leading the authors to postulate partial recovery of the cornea in some post-PRK patients. Likewise, a previous study [51] found that subbasal nerves were morphologically altered and that they still did not achieve the preoperative values even 5 years after PRK. In a 15–20 year follow-up study [52], reduced corneal subbasal nerve density was observed in post-PRK eyes compared to that of controls, which also indicates incomplete nerve regeneration.

We included only a single refractive surgeon in this study to minimize individual variations in the PRK technique, which may cause varying degrees of corneal nerve disruption. In addition, the use of a standardized instrument to evaluate dry eye symptoms—the OSDI questionnaire—ensured data validity. However, several limitations remain, and studies with larger sample sizes may provide further insights into this issue. Another limitation was that the patients recruited in this study were mostly in the normal category; thus, the effects could differ according to symptom severity of DED. Future studies should include a true placebo group to further establish the absolute interventional efficacy of ATs. Our short treatment period, compared to those of the existing studies of corneal subbasal nerve regeneration, might not reveal the full potential of the interventions. Long-term longitudinal clinical trials are required to verify these preliminary findings.

CONCLUSIONS

We found no significant difference in preoperative and 3-month postoperative OSDI scores in the SH- and SU-treated eyes. The groups had comparable OSDI scores at baseline and 1 month; however, there was a significant difference at 3 months postoperatively, despite being clinically insignificant. The observed subbasal CNFL regeneration indicated a positive effect of both AT formulations, with a longer mean CNFL noted in SH-treated eyes at the final visit. This finding suggests that SH may be a better option for improving corneal reinnervation after PRK. This plausible inference should be verified in future studies with longer follow-up periods and larger sample sizes.

ETHICAL DECLARATIONS

Ethical approval: Prior to commencement of the study, ethical approval was obtained from the IIUM Research Ethics Committee and the study conformed to the tenets of the Declaration of Helsinki. Participants were provided with adequate information regarding the methods and risks of all procedures conducted in the study. All participants voluntarily participated in the study and provided written informed consent.
Conflict of interests: None.

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