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Original Research Article

PRESERVATIVE FREE SODIUM HYALURONATE 0.15% IN DRY EYE DISEASE PATIENTS TREATED WITH PROSTAGLANDIN ANALOGUES FOR PRIMARY OPEN-ANGLE GLAUCOMA IN KASHMIR: A PROSPECTIVE STUDY

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Abstract

Purpose: Dry eye disease (DED) can be triggered using preserved ophthalmic formulations or prostaglandin analogues. In this prospective study, we evaluated the efficacy of a 0.15% hyaluronic acid (HA) non preserved ophthalmic formulation in decreasing DED symptoms in Kashmiri population with open-angle glaucoma treated with prostaglandin analogues.

Materials and Methods: 50 patients with DED receiving chronic treatment with prostaglandin analogues for primary open-angle glaucoma or ocular hypertension were administered ophthalmic formulations 3 times daily for 12 weeks. Foreign body sensation, burning, stinging, dryness, pain, frequency of symptoms, conjunctival hyperaemia, corneal fluorescein staining (CFS), tear film break-up time (TBUT), best-corrected visual acuity, Schirmer test results between the baseline and 4 and 12 weeks were evaluated.

Result: The analysis shows that all primary endpoints improved; in particular, burning sensation and the frequency of symptoms after 4 and 12 weeks of treatment ($p < 0.001$) and dryness and pain after 12 weeks of treatment ($p < 0.001$ and $p = 0.03$, respectively) were reduced significantly. Secondary outcomes confirmed the positive results, with a statistically significant change in the CFS between the baseline and 4 ($p = 0.02$ and $p < 0.001$, respectively) or 12 weeks (both $p < 0.001$) and TBUT after 4 weeks ($p = 0.01$). Conjunctival hyperaemia improved in both eyes in >90% of cases at 12 weeks of treatment.

Conclusion: The present study shows that the ophthalmic formulation containing 0.15% HA has a promising beneficial effect on reducing the signs and symptoms of DED in Kashmiri population treated with prostaglandin analogues.

INTRODUCTION

The ocular surface consists of a continuous epithelium hydrated by the tear film, which also contains protective antimicrobial factors (e.g., defensins, immunoglobulin A, lactoferrin, and lysozyme). Tear film stability is crucial for maintaining homeostasis of the ocular surface and is ensured in particular by the mucin-rich gel produced by epithelial cells.[1] In addition, goblet cells in the epithelium produce cytokines, epidermal growth factor, and retinoic acid, which together maintain immune tolerance.[2] When these protective mechanisms fail, tear deficiency results in alterations in the tear film and hyperosmolar stress, which lead to increased friction and mechanical irritation of the ocular surface.[3–5] In addition to these phenomena, activation of inflammatory processes further increases ocular discomfort.[6–9] According to the 2017 International Dry Eye Workshop II report, dry eye disease (DED) is a multifactorial condition characterized by increased osmolarity of the tear film and inflammation of the ocular surface.[10–12] The prevalence of DED has a wide range (5%–50%) and is estimated to be higher in women, with a tendency to increase with age.[13] Most of the symptoms associated with DED are non specific and common to other ocular diseases and include redness, burning, stinging, foreign body sensation, pruritus, and, in some cases, photophobia.[13] The clinical signs of ocular surface inflammation are a loss of conjunctival goblet cells

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and corneal epitheliopathy.[14] The course of the disease is persistent and characterized by an episodic pattern of symptoms (fares).[15]

Because of the enormous variability of clinical signs, there is no consensus on the diagnosis of DED; nevertheless, self-reported questionnaires, such as the Ocular Surface Disease Index (OSDI), are commonly used as tools for assessing the severity of the disease. In addition, other clinical tests are used by physicians, including the Schirmer test, tear break-up time (TBUT), corneal and conjunctival staining, and tear osmolarity.[16] Many causes underlie the occurrence of DED. The most common are the use of contact lenses, refractive laser cataract surgery, and the use of topical formulations containing preservatives and prostaglandin (PG) analogues for glaucoma and ocular hypertension.[17,18] Recent studies suggest that the use of topical formulations containing benzalkonium chloride (BAK) as a preservative may have adverse effects on the ocular surface.[19] BAK is a quaternary ammonium compound used in a variety of formulations,[20] although BAK destabilizes cell membranes, leading to bacterial death, its effect is nonspecific and may also affect mammalian cells, resulting in local side effects that are cumulative and become more severe with repeated exposure.[21,22] Instead, PG analogues have become the first-line therapy for treating patients with glaucoma due to their efficacy in lowering intraocular pressure (IOP).[18] While reducing IOP, PG analogues are associated with ocular side effects, such as a prominent feature of ocular irritation associated with dry eye disease and an increase in conjunctival hyperaemia.[23] A recent meta-analysis of glaucoma patients showed that the risk of conjunctival hyperaemia increases in patients treated with PG analogues compared to patients treated with other classes of drugs.[18,24] Conjunctival hyperaemia is thought to be caused by nitric oxide-mediated vasodilation in the conjunctiva. However, the relationship between PG analogues and ocular surface changes is complicated and remains unclear.[18] Hyaluronic acid (HA) is a linear polymer composed of N-acetyl-glucosamine and glucuronate units. Its use in ophthalmology has been studied since the early 1990s, and HA is known to increase tear film stability by stimulating mucin production.[26]

Consistent with this notion, existing studies suggest that HA is able to significantly alleviate the symptoms of DED and reduce ocular inflammation.[27,28]

Based on these findings and aiming to keep on providing the literature with increasing clinical data, the present prospective, study evaluated the efficacy of the formulation containing 0.15% sodium hyaluronate (as the main component) and amino acids in improving DED symptoms. Since such study has not been done in our institution, we aim to treat the symptomatic patients with the treatment concluded.

MATERIALS AND METHODS

Aim of the Study

The aim of this prospective study was to evaluate the efficacy of a topical HA-based formulation also containing amino acids in improving DED symptoms as an adjunctive treatment in patients with primary open-angle glaucoma or ocular hypertension undergoing treatment with PG analogues. Tis ophthalmic formulation is specifically designed to protect the corneal epithelium and helps increase the biological defence of the tear film by better stabilizing and preserving its properties.

The study was conducted in the outpatient department of SKIMS medical college from February 2022 to June 2022.

The inclusion criteria were as follows

1. Age ≥18 years
2. A diagnosis of primary open-angle glaucoma or ocular hypertension and current treatment with PG analogues as monotherapy .
3. A Schirmer test I result of ≥5 mm to avoid the inclusion of dry eye patients due to decreased tear production.
4. Conjunctival hyperaemia of ≥2.

Patients were excluded if they

1. Used artificial tear substitutes in 2 weeks before the start of the study,
2. Had a history of ocular trauma,
3. Had an active ocular surface infection of any type,
4. Had an ocular allergy, hypersensitivity to any component of the drug.
5. Had undergone ocular surgery within 30 days prior to enrolment,
6. Had another concurrent eye disease associated with ocular surface inflammation (e.g., pinguecula, pterygium, or corneal scarring associated with corneal irregularities),

We also excluded patients with DED linked to a systemic disease or therapeutic used to treat a systemic disease.

Treatment and Evaluations

Patients, already undergoing treatment with PG analogues therapy, were administered 1 drop of ancillary topical therapy containing HA, amino acids, 3 times daily for 12 consecutive weeks. The evaluation was considered at baseline, 4 (±1) weeks, and 12 (±1) weeks. At each visit, as per the TFOS DEWS II Diagnostic Methodology report [29], the parameters evaluated were (1) best-corrected visual acuity (BCVA) using a LogMAR chart; (2) IOP by Goldmann applanation tonometry; (3) conjunctival hyperaemia measured on a 4-point scale (0 = none, 1 =mild, 2 =moderate, and 3 =severe); (4) tear film break-up time (TBUT) measured after instillation of 1 drop of fluorescein sodium; specifically, one single drop of balanced salt solution (BSS) was applied at the tip of fluorescein strips and then

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instilled into the inferior fornix of the patients' eye; patients were then instructed to blink normally for approximately three times and then to stop blinking while TBUT was measured; (5) corneal fluorescein staining (CFS) measured after TBUT according to the National Eye Institute/Industry (NEI) scoring system; (6) ocular surface symptoms using a 10-point visual analogue scale (0–10 points) for foreign body sensation, burning, stinging, dryness, pain, and frequency of symptoms. All exams were performed in the same environmental settings to avoid potential DED evaluation bias,[30] thermostat-regulated room, dim room light, maximum slit-lamp illumination, same amount of fluoresceine, and patients were all evaluated by the same observer.

Outcomes

The primary outcome of this study was the change in ocular surface inflammatory symptoms for each item of the visual analogue scale (foreign body sensation, burning, stinging, dryness, pain, and frequency of symptoms) after 4 and 12 weeks of treatment. The secondary outcomes were the mean change in conjunctival hyperaemia, CFS, TBUT, BCVA, and Schirmer test result between baseline, 4 weeks, and 12 weeks after the start of the study.

Sample Size and Statistical Analysis

A medium clinically relevant effect size equal to −0.50 at 12 weeks for the dryness symptom has been considered primary outcome of this study; all other ocular surface DED symptoms of the visual analogue scale, such as foreign body sensation, burning, pain, and frequency of symptoms, were also primary outcomes but were not considered for sample size analysis. A sample size of 27 data pairs achieved a minimum of 80% power to reject the null hypothesis of zero effect size at 12 weeks at a significance level (alpha) of 0.10 using the two-sided paired t-test. As a rule of thumb, an anticipated 10% dropout rate has been assumed, and thus, the minimum number of evaluable subjects included in the study was N =30.

RESULTS

Demographics

Thirty patients were enrolled in this study; of these, 15 (50%) were female, and the mean age at the baseline was 64.2 years (standard deviation =10.5 years). Participating patients had been treated for an average of 9.1 years with PG analogues for glaucoma. All patients were diagnosed with primary open-angle glaucoma or ocular hypertension, and all had ocular surface inflammation and DED symptoms, such as foreign body sensation, burning, stinging, dryness, and pain at the baseline. All patients included in the study completed the entire treatment period; demographic and baseline diagnostic and treatment details are reported in [Table 1].

Table 1: Patients' characteristics at the baseline.

Characteristics	level	Statistics*
Sex	Male Female	15(50.0) 15(50.0)
Age (years)	Male Female overall	70.1(10.8) 64.2(10.5) 67.1(10.8)bc
Duration of glaucoma (years)		9.1 (5.0-12.0)
Duration of therapy (years)	Actual total	6.0 (3.0-10.0) 8.3(4.0 – 12.0)

* Statistics are displayed as count (%) for sex or mean (standard deviation) for age but mean (interquartile range) otherwise. b: Min =44.4, max =87.0, c: Male vs. female unpaired t-test, p =0.14.

Table 2: Summary statistics for secondary outcomes by time.

Outcome	Visit time	N	Score(SD)	Paired Difference With Baseline(SD)	P Value*
TBUT	Baseline 4 weeks 12 weeks	30 30 30	4.5(3.1) 6.3(3.8) 4.2(1.9)	 1.8(3.2) 0.3(2.2)	 0.01 0.40
CFS	Baseline 4 weeks 12 weeks	30 30 30	5.2(3.6) 3.7(2.4) 0.5(1.4)	 -1.5(2.3) -4.7(4.0)	 <0.001 <0.001
Schirmer test(mm)	Baseline 12 weeks	30 30	13.2(7.5) 15.9(5.7)	 2.7(5.2)	 0.05

* One-sample signed rank-sum test or 1-samplet-test as appropriate. Abbreviations: CFS, corneal fluorescein staining; TBUT, tear film break-up time

Primary Outcome

At both 4 and 12 weeks, all primary outcome treatment resulted in significant improvements in burning and frequency of symptoms. Indeed, the mean values (standard deviation; 95% CI; p value) of burning decreased by 2.50 (SD: 2.68; −3.95 to −1.21; $p < 0.001$) and 2.75 (SD: 2.56; −4.00 to −1.40; $p < 0.001$), and the mean values calculated for the frequency of symptoms decreased by 1.60 (SD: 2.51; −3.10 to −0.51; $p = 0.002$) and 2.79 (SD: 2.23; −3.82 to −1.69; $p < 0.001$) after 4 and 12 weeks of treatment compared to the baseline,

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respectively. After 12 weeks of treatment, dryness and pain significantly decreased by 2.28 (SD: 3.02; −3.79 to −0.67; $p < 0.001$) and 1.29 (SD: 2.53; −2.57 to 0.00; $p = 0.03$), respectively. We also observed a reduction in foreign body sensation after 12 weeks of treatment; however, the t-test yielded a borderline value, and the difference was not statistically significant (mean 1.42; SD: 2.76; −2.89 to 0.00; $p = 0.05$). differences in stinging values at 4 weeks (mean: 0.09; SD: 3.07; −1.67 to 1.58) and 12 weeks (mean: −1.00; SD:2.83; −2.40 to 0.49) compared to the baseline were also not statistically significant ($p = 0.10$ and $p = 0.20$, respectively). Age at the baseline was significantly and inversely correlated with burning in both univariate and multivariate analyses (regression coefficient =−0.09; standard error p= 0.03; $p = 0.01$) as well as the visit time (i.e., $p < 0.001$ for both 4 weeks vs. baseline and 12 weeks vs. baseline). No other factors were significantly associated with the observed changes in the primary outcome.

Secondary Outcomes

The OSDI score showed a monotonic and significant mean change between the baseline and 4 and 12 weeks. The mean change scores were −7.8 points ($p = 0.02$) and −8.1 points ($p = 0.04$) at 4 and 12 weeks, respectively [Table 2]. Interestingly, TBUT increased significantly ($p = 0.01$) by 1.8 seconds at 4 weeks of treatment compared to the baseline [Table 2]. A monotonic and significant decrease in CFS values by 1.5 at 4 weeks ($p < 0.001$) and 4.7 at 12 weeks ($p < 0.001$), respectively, was observed compared to the baseline [Table 2]. The results of the Schirmer test showed an increase from the baseline to 12 weeks (from 13.2 to 15.9 mm), which was not clearly statistically significant ($p = 0.05$) [Table 2]. Due to their distributional properties, a per-eye analysis was performed for conjunctival hyperaemia and BCVA changes at the baseline, with results categorized as worsening, no change, or improvement. Conjunctival hyperaemia improved in both eyes at 12 weeks of treatment in >93% of cases, while BCVA did not change from the baseline for most patients. Another secondary finding was a significant decrease by −2.2 mmHg in IOP between the baseline and 12 weeks ($p < 0.001$), which was included in the clinical parameters as a reference value to detect any clinical worsening or any influence of the HA based formulation on the effect of PG analogue therapy.

DISCUSSION

The results of the present study support the efficacy of an ophthalmic formulation containing HA and amino acids in the treatment of ocular symptoms associated with DED in patients undergoing treatment with PG analogues. The present study examined several outcomes, all of which may be representative of ocular surface changes. Indeed, daily use of the study ophthalmic formulation resulted in rapid improvement in inflammation-related symptoms and their frequency, with a significant decrease in burning sensation after only 4 weeks of treatment; foreign body sensation, dryness, and pain scores were also statistically significantly lower after 12 weeks of treatment than at the baseline. The improvement in these symptoms is crucial, since lower levels of inflammation help break or at least mitigate the typical vicious cycle of DED, in which inflammation is not only caused by the ocular surface but also becomes a key factor in damage to the eye.[31] Changes in objective parameters, such as tear stability (TBUT test), which is severely impaired in DED patients and is one of the concomitant phenomena leading to ocular surface stress, also mirrored the clinical results; conjunctival hyperaemia and basal tear secretion (Schirmer test) data. Considering the chronic nature of the disease, it is important to highlight that most of the effects promoted by the HA-based ophthalmic formulation in this study were visible after 4 weeks of treatment and persisted throughout the study period. These effects can be attributed to the distinctive composition of the ophthalmic formulation studied, as similar results have been observed in several previous clinical studies with HA-based eye drops.[32–34] Indeed, Molina-Solana et al. conducted a prospective, single-arm longitudinal intervention study to evaluate the efficacy of a preservative-free artificial tear containing 0.4% HA and found a significant improvement in signs and symptoms, such as hyperaemia, CFS, after 1 week and 1 month of treatment.[33] Similar results were also obtained in the study by Sanchez-Gonzalez et al., who recorded an improvement in Schirmer test results, TBUT, and OSDI score after artificial tears containing different concentrations of HA were administered.[34] Among others, Roberti et al. conducted a prospective, randomized, single-masked, parallel study to evaluate the efficacy of a preservative-free solution containing 0.4% HA and 0.5% taurine in glaucoma patients undergoing long term treatment with preserved hypotensive therapy. Teir results showed that the formulation greatly improved the signs and symptoms associated with DED.[35] Finally, the safety and efficacy of HA-based artificial tears were thoroughly investigated by Aragona et al. in a randomized, controlled, multi centre, 3-month study involving >460 patients.[36] An interesting point that emerged from this study is the possible synergistic effect of formulation components. Indeed, the formulation tested here was highly effective compared to those investigated in the aforementioned studies despite the lower concentration of HA.[28] Tus, such an effect could be due to the combination of HA with amino acids. Indeed, supplementation with amino acids, especially L-proline, L-lysine, L-glycine, and Leucine, is known to support the metabolism of the corneal epithelium, which is damaged in DED patients.[37] However, these results are still preliminary due to the limited sample of the study,

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and a future, more in-depth analysis of quality of life involving different types of questionnaires would be of great interest. Interestingly, a statistically significant decrease in IOP was observed in patients. It seems that improving ocular surface health in glaucoma patients allows for a better control of IOP values. However, the change in IOP could be due to (i) better adherence to glaucoma treatment, which is common in patients participating in a scientific study, (ii) better adherence to glaucoma treatment due to the patient's perceived improvement in symptoms of ocular discomfort, or (iii) treatment of the ocular surface disease that allows to reduce inflammation, thus improving both ocular surface health and IOP values.[33] In future studies, it would be useful to extend the follow-up period to assess how long the effect of the study formulation lasts. Although HA-based eyedrops have been used for many years, longer observation would allow further detection and monitoring of potential adverse effects. In addition, the presence of a control group and, as mentioned above, a larger cohort of patients would be useful to better study the effects of treatment on the patients' quality of life. We acknowledge that the presence of a placebo effect might have influenced the subjective results of our study given the lack of a control group,[40] and in addition, the relevant improvements in clinical signs seem to support the role of the studied supplementation in improving DED in patients treated with PG analogues. Despite the limitations mentioned above, the results of this study show that the beneficial effects of eye drops containing HA and amino acids, are rapid and persist throughout the treatment period (12 weeks). Since no such study has been done at our centre till date, we hope this brings relief to the patients suffering from the symptoms of dry eye using prostaglandin analogues chronically for glaucoma in kashmiri population.

CONCLUSION

The present study shows that the ophthalmic formulation containing 0.15% HA has a promising beneficial effect on reducing the signs and symptoms of DED in Kashmiri population treated with prostaglandin analogues.

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