HYDROXYPROPYL CELLULOSE OPHTHALMIC INSERTS (LACRISERT) REDUCE THE SIGNS AND SYMPTOMS OF DRY EYE SYNDROME AND IMPROVE PATIENT QUALITY OF LIFE

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ABSTRACT

Purpose: A multicenter, 2-visit, open-label, 4-week study was conducted to determine the acceptability of hydroxypropyl cellulose ophthalmic inserts in adult patients with a history of dry eye syndrome (DES).

Methods: At visit 1, patients (N = 520) were evaluated, screened by slit-lamp biomicroscopy, and completed the Ocular Surface Disease Index (OSDI), a validated measure of quality of life. Patients were trained in the proper placement and use of hydroxypropyl cellulose ophthalmic inserts and were contacted by telephone on day 3 of the study. At week 4, patients were given a clinical evaluation and completed a second questionnaire. Answers determined changes in symptoms and quality of life. Adverse events were monitored throughout the study.

Results: Four hundred eighteen patients completed the study and reported significant improvements in discomfort, burning, dryness, grittiness, stinging, and light sensitivity ($P = .05$) after 4 weeks use of hydroxypropyl cellulose ophthalmic inserts. Significant improvements in clinical signs (keratitis, conjunctival staining, and tear volume) were reported. Contact lens wearers reported significant improvements similar to nonwearers, with a strong trend toward improvement in light sensitivity. Mean OSDI total scores, measuring quality of life, significantly improved by 21.3% (from 41.8 ± 22.38 to 32.9 ± 21.97, $P \leq .0215$). The most commonly reported adverse event leading to discontinuation was blurred vision, observed in 8.7% of patients (n = 45). Compliance during the study was good; 41.5% of subjects were fully compliant. Of the 58.5% of subjects who missed doses, the majority (69.4%) missed only one to five.

Conclusions: Hydroxypropyl cellulose ophthalmic inserts significantly reduced symptoms and clinical signs of moderate to severe DES. They also significantly improved DES in patients wearing contact lenses. Patients experienced a statistically significant improvement in quality of life, as measured by the OSDI, of 21.3%.

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INTRODUCTION

Five million Americans are affected by dry eye syndrome (DES), a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, including burning, itching, foreign body sensation, soreness, dryness, photophobia, redness, and reduced visual acuity.[1,2] Approximately one-third of patients seeking treatment from an ophthalmologist have symptoms of DES.[2] It affects about 5 million Americans 50 years of age and older, and nearly twice as many women as men. The number of individuals with DES is expected to increase dramatically as the population of older Americans rises in the coming decades.[3] Furthermore, 52% of contact lens wearers experience symptoms of DES.

Its impact on patients' activities of daily living (ADLs) and quality of life is considerable, with many patients experiencing difficulty when reading, watching television, and using a computer.[2] In addition to tangible symptoms, intangible decreases in leisure time and social interactions, impaired physical functioning and quality of life, and declines in mental and general health, DES directly impacts costs of care due to increased health care system utilization, and indirectly contributes to lost work time and productivity.[3]

Often, patients' symptoms are at odds with the results of clinical tests, and no single repeatable, reliable test is in common use.[3] DES itself varies from patient to patient, its symptoms are subjective, and responses to questions about the physical sensations in the eyes may also vary.[3] Patients may even present with severe damage to the ocular surface with no or few symptoms of DES.[2]

Additionally, preservatives such as benzalkonium chloride used in many dry eye therapies cause inflammation of the ocular surface and damage to the corneal and conjunctival epithelium. Effective, preservative-free treatment options are absolutely necessary, particularly for patients with moderate to severe DES.[4]

Hydroxypropyl cellulose ophthalmic inserts (Lacrisert; Aton Pharma, Lawrenceville, New Jersey) are indicated in patients with moderate to severe DES, including keratoconjunctivitis sicca. They are indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions. They are also indicated for patients with exposure keratitis, decreased corneal sensitivity, and recurrent corneal erosions.[5]

Each hydroxypropyl cellulose ophthalmic insert is 5 mg of hydroxypropyl cellulose 1.27 mm in diameter by 3.5 mm long. The inserts are placed into the inferior cul-de-sac of each eye beneath the base of the tarsus, not in apposition to the cornea, nor beneath the eyelid at the level of the tarsal plate.[5]

Hydroxypropyl cellulose ophthalmic inserts act to stabilize the precorneal tear film and prolong tear film breakup time (TFBUT), which is usually accelerated in patients with DES. They also act to lubricate and protect the eye.[5]

The purpose of this study was to determine the acceptability of hydroxypropyl cellulose ophthalmic inserts in adult patients with a history of moderate to severe DES. It was hypothesized that patients would experience reduced symptoms and signs of DES, along with improvements in their quality of life.

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Bold type indicates AOS member.
From Ophthalmic Consultants of Long Island, Long Island, New York (Dr McDonald, Dr D'Aversa, Dr Perry, Dr Wittpenn, Dr Donnenfeld) and InterQuest Medical, Mountain Lakes, New Jersey (Dr Nelinson).

METHODS

STUDY DESIGN

This was a multicenter, open-label study consisting of 2 office visits. At visit 1 (day 0), the following was done: Patients read, signed, and dated an institutional review board–approved, HIPAA-compliant informed consent form. Patient information was collected. Best-corrected visual acuity (BCVA) was measured, slit-lamp biomicroscopy was performed, and a general dry eye evaluation was conducted (specific evaluation procedures were left to the discretion of the individual investigator and included, but were not limited to, fluorescein staining and Schirmer test). Participants completed Patient Questionnaire A, a panel of questions on a numerical/visual analog scale that assessed DES symptoms. Patients were instructed on how to properly place hydroxypropyl cellulose ophthalmic inserts into the cul-de-sac of each eye, which included viewing an instructional video, and the participants each placed one 5-mg insert bilaterally in the presence of the investigator or coordinator after training. Finally, patients were dispensed 58 5-mg hydroxypropyl cellulose ophthalmic inserts and scheduled for visit 2.

As a follow-up to visit 1, patients were contacted by telephone at day 3 (±1 day) for approximately 10 minutes to assess any adverse events and to determine whether hydroxypropyl cellulose ophthalmic inserts were being properly used. Reinstruction on correct use was given if necessary.

On day 28 (±3 days), patients returned for an approximately 1-hour follow-up visit. During this time, any adverse events were reviewed, BCVA was assessed, and slit-lamp biomicroscopy was performed. A general dry eye evaluation was conducted (as in visit 1), and participants completed Patient Questionnaires B and C, a panel of questions on a numerical/visual analog scale that assessed DES symptoms. Investigators completed the Physician Questionnaire at this time prior to exiting patients from the study.

MONITORING OF ADVERSE EVENTS

Adverse events (whether elicited or observed) were monitored throughout the study. All adverse events were promptly reviewed by the relevant investigator for accuracy and completeness and were documented appropriately.

PATIENT INCLUSION AND EXCLUSION CRITERIA

Only subjects who were at least 18 years of age who provided written informed consent and were willing and able to follow all instructions and attend all visits were enrolled in the study. All participating subjects had either a diagnosis of DES in both eyes with a history of intermittent or regular artificial tear use, or a desire to use artificial tears within the past week prior to study initiation.

Subjects were excluded from participation in this study if they were affected by any of the following: had clinically significant blepharitis, meibomian gland dysfunction, or lid margin inflammation and were currently taking systemic or topical medication used to treat any of these diagnoses; had a diagnosis of ongoing ocular infection (bacterial, viral, or fungal), active ocular inflammation (eg, follicular conjunctivitis), or preauricular lymphadenopathy; had laser in situ keratomileusis (LASIK) surgery within 12 months of visit 1; had ocular surgical intervention within 3 months prior to or during the study period; had a systemic disease or uncontrolled medical condition that, in the opinion of the investigator, could interfere with study measurements or subject compliance; used any new dry eye therapies throughout the duration of the trial; were currently taking any systemic medications known to cause ocular drying and had not been on a stable dose within 30 days of visit 1; had a known allergy and/or sensitivity to hydroxypropyl cellulose; had received an investigational drug or device within 30 days of visit 1.

STATISTICAL ANALYSES

Overall comparison of variables was performed by multivariate analysis of variance (MANOVA) using a standard software package for social sciences (SPSS Inc, Chicago, Illinois). After F tests univariate analyses were done using *t* tests. This enabled the investigators to isolate the strength of impact of the treatment on specific clinical and quality of life outcomes. Confidence intervals (CIs) were reported at 95% to provide a practical structure for reporting such diverse findings with large numbers of variables..

RESULTS

PATIENT CHARACTERISTICS

This study enrolled 520 patients across 49 sites throughout the United States. Of the 520 patients who enrolled in the study, 418 (80.4%) completed through visit 2. The majority (n = 337, 64.8%) of patients participating were women, and 54.6% (n = 284) were 50 years of age or older. Twenty-six patients (5.0%) withdrew consent or were lost to follow-up prior to completion of the study.

CHANGE IN DRY EYE SYNDROME SYMPTOMS

At each visit, patients were asked to rate the average severity of their DES symptoms over the past month (eg, the month prior to visit 1 and the 28 days between visit 1 and visit 2). Patients scored the severity of their symptoms on a numerical/visual analog scale ranging from 1 (least severe) to 5 (most severe). After 1 month of treatment with hydroxypropyl cellulose ophthalmic inserts, significant reductions in the mean severity of DES symptoms, including discomfort, burning, dryness, grittiness, sensitivity to light, and stinging, were reported (Figure 1). Patient-reported severity of discomfort was reduced by 24.9% (mean change -0.87, 95% CI 3.50 ± 1.10 to 2.63 ± 1.31; $P = .05$), burning improved by 34.9% (mean change -1.03, 95% CI 2.95 ± 1.34 to 1.92 ± 1.21; $P = .05$), severity of dryness improved by 41.9% (mean change -1.64, 95% CI 3.91 ± 1.05 to 2.27 ± 1.25; $P = .05$), feeling of grittiness was reduced by 29.0% (mean change -0.85, 95% CI 2.93 ± 1.38 to 2.08 ± 1.25; $P = .05$), sensitivity to light improved by 18.9% (mean

change -0.53, 95% CI 2.81 ± 1.52 to 2.28 ± 1.37; *P* = .05), and severity of stinging improved by 28.5% (mean change -0.73, 95% CI 2.56 ± 1.31 to 1.83 ± 1.11; *P* = .05).

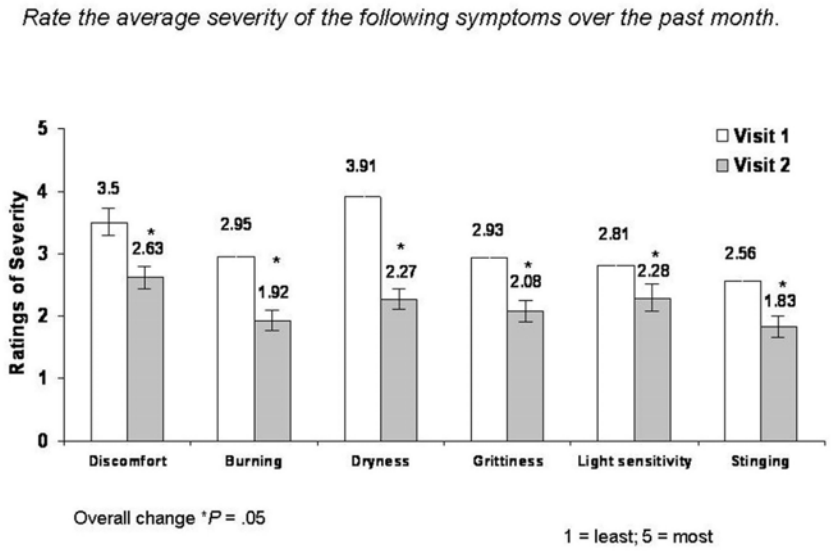

FIGURE 1

Mean change in severity of DES symptoms reported in the past month from visit 1 to visit 2.

CHANGE IN OCULAR SURFACE DISEASE INDEX

The Ocular Surface Disease Index (OSDI) is a validated instrument that measures patient quality of life. It consists of 12 individual questions separated into 3 categories, including DES symptoms, performance of ADLs, and environmental conditions that contribute to or cause DES. Respondents rank the frequency of occurrence of symptoms, limitations in performing ADLs due to DES, and ocular discomfort over the past week on a numerical/visual analog scale ranging from 0 (none of the time) to 4 (all of the time). The OSDI was incorporated into Patient Questionnaires A and B that patients completed at visit 1 and visit 2. After 1 month of treatment with hydroxypropyl cellulose ophthalmic inserts, significant mean improvement was observed in the majority of OSDI components.

Patients reported significantly fewer occurrences of most DES symptoms scored by the OSDI (Figure 2). Patient-reported occurrence of sensitivity to light was significantly reduced (by 22.3%; mean change -0.39, 95% CI 1.75 ± 1.45 to 1.36 ± 1.32; *P* = .05), 36.5% fewer incidences of sensations of grittiness were observed (mean change -0.62, 95% CI 1.70 ± 1.27 to 1.08 ± 1.14; *P* = .05), and significant reductions (41.8%) in occurrence of painful or sore eyes occurred (mean change -0.69, 95% CI 1.65 ± 1.31 to 0.96 ± 1.09; *P* = .05). Occurrence of blurred vision, the most commonly reported adverse event associated with hydroxypropyl cellulose ophthalmic inserts, increased by 16.6% (mean change 0.27, 95% CI 1.63 ± 1.29 to 1.90 ± 1.32; *P* = .05). No significant difference was reported for the occurrence of poor vision between visit 1 and visit 2.

Significant reductions in frequency of difficulty performing daily tasks as measured by the OSDI were also reported (Figure 3). A significant (12.2%) reduction in occurrence of difficulty when reading was reported (mean change -0.19, 95% CI 1.56 ± 1.35 to 1.37 ± 1.28; *P* = .05). Incidence of difficulty driving at night was significantly reduced (by 26.6%; mean change -0.41, 95% CI 1.54 ± 1.39 to 1.13 ± 1.27; *P* = .05). Incidence of difficulty working with a computer or automated teller machine (ATM) was significantly reduced (by 16.9%; mean change -0.26, 95% CI 1.54 ± 1.31 to 1.28 ± 1.25; *P* = .05), and occurrence of difficulty watching television was significantly reduced (by 18.4%; mean change -0.23, 95% CI 1.25 ± 1.22 to 1.02 ± 1.17; *P* = .05).

Significant reductions in occurrence of discomfort in certain environmental conditions as measured by the OSDI were also observed (Figure 4). Patients experienced a significant (33.2%) reduction in occurrence of discomfort in windy conditions (mean change -0.77, 95% CI 2.32 ± 1.38 to 1.55 ± 1.41; *P* = .05), 40.2% fewer incidences of discomfort in areas of low humidity (mean change -0.94, 95% CI 2.34 ± 1.33 to 1.40 ± 1.33; *P* = .05), and a significant (35.2%) reduction in occurrence of discomfort in areas that are air-conditioned (mean change -0.69, 95% CI 1.96±1.37 to 1.27±1.35; *P* = .05).

After 1 month of therapy with hydroxypropyl cellulose ophthalmic inserts, mean OSDI total scores improved by 21.3% (from 41.8 ± 22.38 at visit 1 to 32.9 ± 21.97 at visit 2; *P* ≤ .0215).

CHANGE IN ACTIVITIES OF DAILY LIVING

At each visit, patients were asked to rate how troubled they had been during the past week in performing daily tasks due to their DES symptoms. Any difficulty was rated on a numerical/visual analog scale ranging from 0 (minimal, slight discomfort when performing a task) to 3 (severe, ability to perform a task is prevented). Significant improvements in patients' ability to perform ADLs were reported after 1 month of treatment with hydroxypropyl cellulose ophthalmic inserts (Figure 5). Patients experienced a significant (13.6%) reduction in difficulty reading (mean change -0.18, 95% CI 1.32 ± 0.99 to 1.14 ± 1.04; *P* = .05), a 27.0% improvement in ability to watch television or movies (mean change -0.30, 95% CI 1.11 ± 0.95 to 0.81 ± 0.94; *P* = .05), a 30.9% reduction in problems while

shopping in retail stores (mean change -0.30, 95% CI 0.97 ± 0.97 to 0.67 ± 0.89; *P* = .05), a 36.5% improvement in ability to perform housework (mean change -0.42, 95% CI 1.15 ± 1.01 to 0.73 ± 0.88; *P* = .05), and a 43.1% reduction in difficulty performing tasks in heated areas (mean change -0.94, 95% CI 2.18 ± 1.89 to 1.24 ± 1.59; *P* = .05).

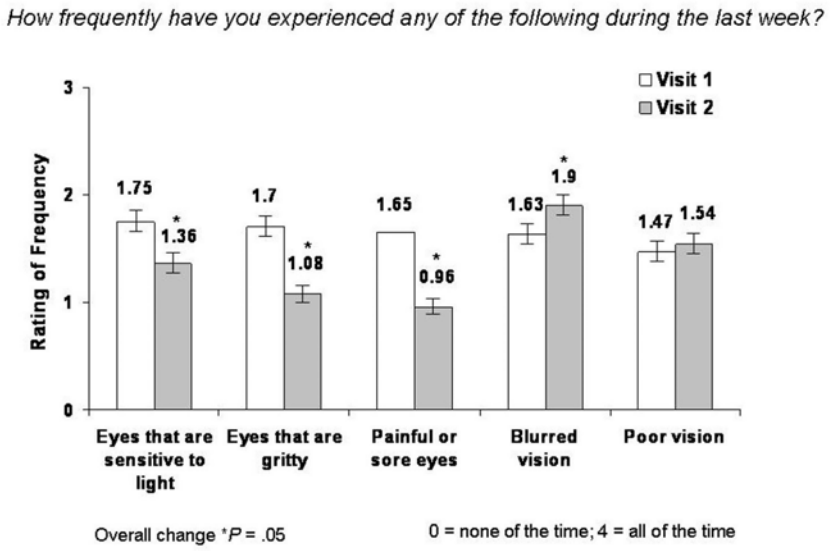

FIGURE 2

Mean change in frequency of DES symptoms from visit 1 to visit 2 as scored by the OSDI.

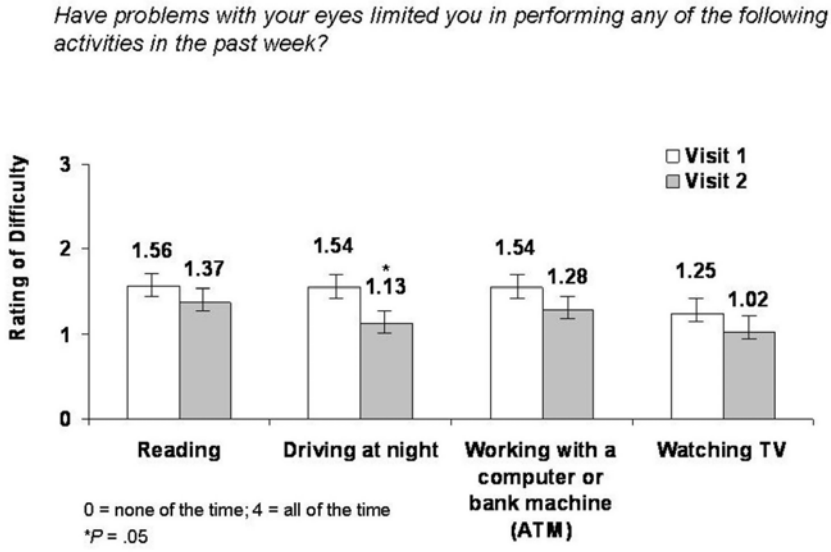

FIGURE 3

Mean change in occurrence of difficulty when performing daily tasks from visit 1 to visit 2 as scored by the OSDI..

CHANGE IN CLINICAL SIGNS

Investigators conducted a general dry eye evaluation at visit 1 and visit 2 to measure changes in TFBUT, fluorescein staining, and tear volume as measured by the Schirmer test (Figure 6). Mean TFBUT increased bilaterally, reaching statistical significance in the right eye, with a strong trend for improvement observed in the left eye. Mean tear volume also increased bilaterally, reaching significance in the right eye, with a trend toward improvement seen in the left eye. A strong trend toward reduced mean fluorescein staining was observed in the right eye, with staining in the nasal region reaching statistical significance. Mean fluorescein staining in the left eye was reduced significantly in most areas, with a trend for improvement in the central and superior regions.

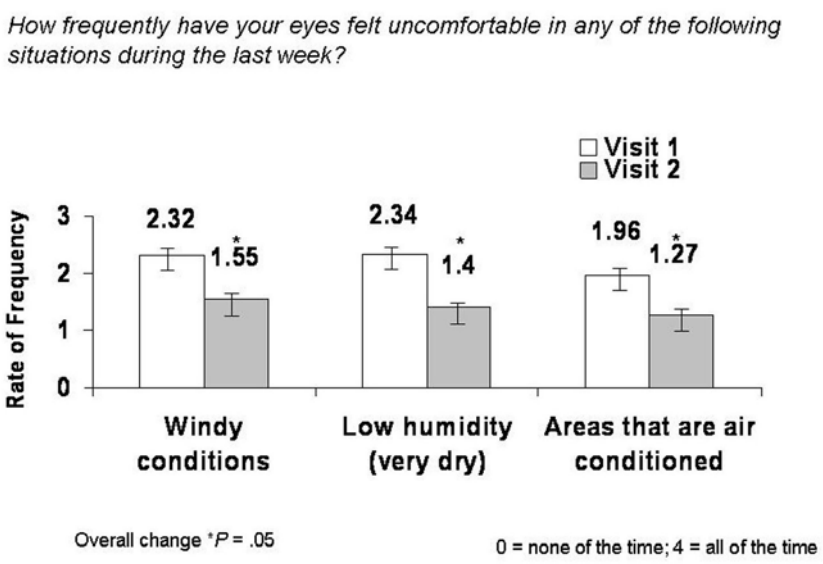

FIGURE 4

Mean change in frequency of discomfort in various environmental conditions from visit 1 to visit 2 as scored by the OSDI.

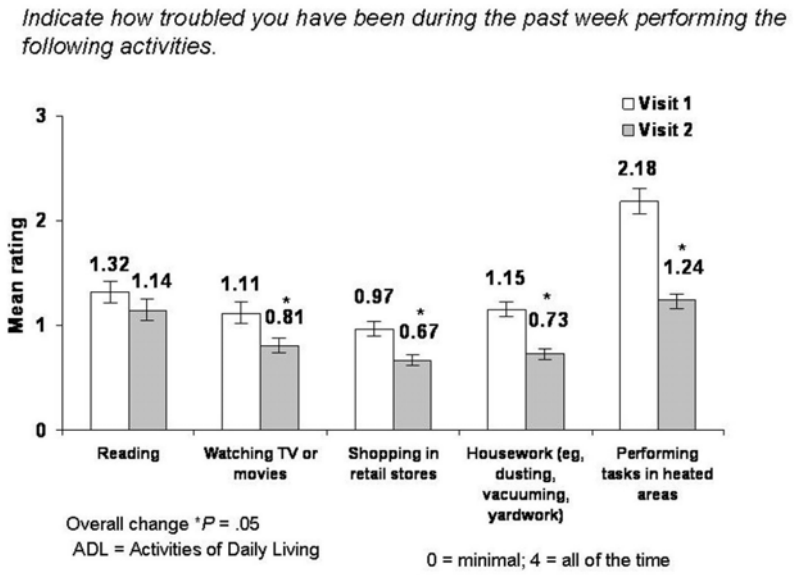

FIGURE 5

Mean change in difficulty in performing activities of daily living in the past week from visit 1 to visit 2.

CONTACT LENS WEARERS

Of the 520 patients enrolled in the study, 107 reported that they wore contact lenses throughout the 1-month treatment period. Similar to nonwearers, patients wearing contact lenses experienced significant reductions in the severity of feelings of discomfort, burning, dryness, grittiness, and stinging after 1 month of treatment with hydroxypropyl cellulose ophthalmic inserts. A strong trend for reduction in the severity of sensitivity to light was observed in lens wearers (Figure 7).

ADHERENCE/COMPLIANCE

Overall, compliance during the study was good; 41.2% (n = 179) of patients for whom this information was available indicated that they did not miss any hydroxypropyl cellulose ophthalmic insert doses. Of the 58.5% of patients (n = 255) who missed doses, the majority (69.4%, n = 177) indicated that they missed only one to five doses.

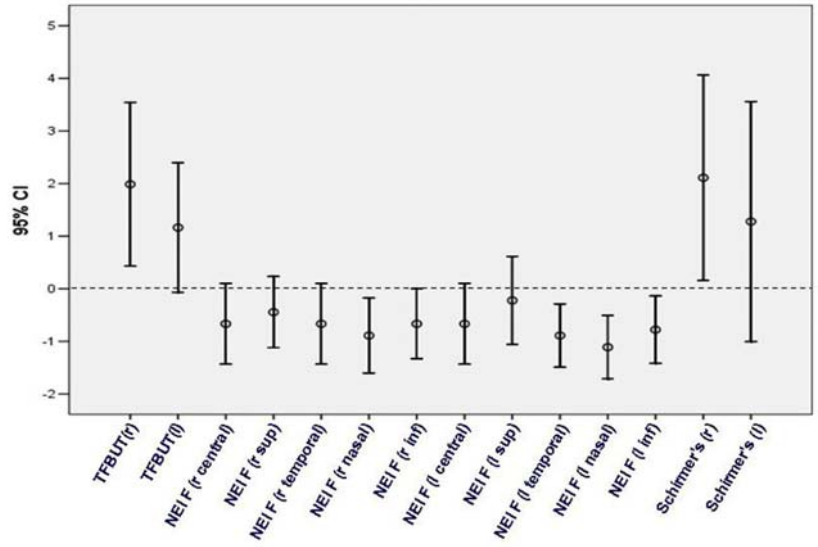

FIGURE 6

Mean change in clinical signs from visit 1 to visit 2. NEI F, National Eye Institute fluorescein staining; Schirmer's, Schirmer's test of tear volume; TFBUT, tear film breakup time.

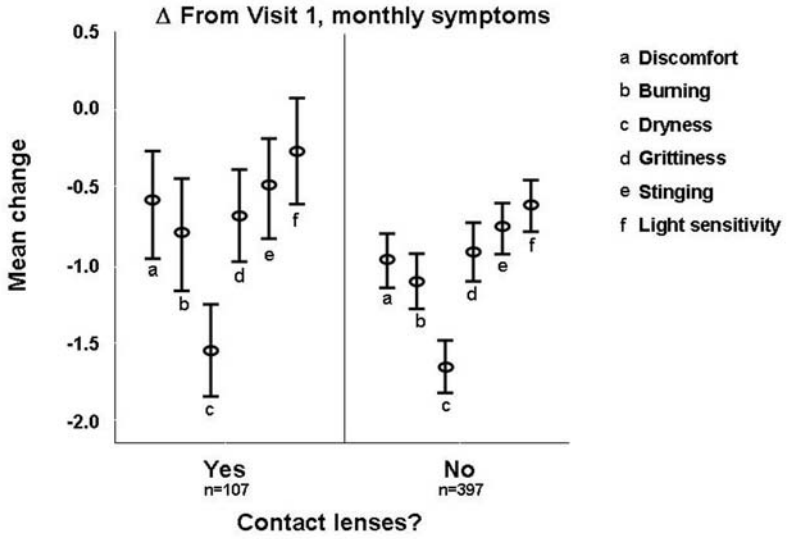

FIGURE 7

Mean change in severity of DES symptoms reported in the past month from visit 1 to visit 2 among contact lens wearers vs nonwearers.

SAFETY

The most commonly reported adverse event associated with hydroxypropyl cellulose ophthalmic inserts was blurred vision. Blurred vision led to discontinuation in 8.7% of patients (n = 45). Incidence of additional adverse events leading to discontinuation was low—less than 1.0% of patients (Table). One corneal abrasion was reported during this study; however, it was unrelated to treatment with hydroxypropyl cellulose ophthalmic inserts. The abrasion occurred when a participating patient who was attempting to remove a

gas-permeable contact lens inadvertently self-inflicted a corneal abrasion. The patient was not using hydroxypropyl cellulose ophthalmic inserts at the time of the incident.

TABLE. INCIDENCE OF ADVERSE EVENTS AND OTHER CAUSES FOR DISCONTINUATION*

ADVERSE EVENT	PERCENT (N)
Blurred vision	8.7 % (45)
Ocular discomfort	0.96% (5)
Foreign body sensation	0.96% (5)
Ocular stinging/grittiness/ache	0.58% (3)
Ocular irritation	0.38% (2)
Swollen lids	0.38% (2)
Excessive tearing	0.38% (2)
Eyelash crusting/stickiness	0.38% (2)
Other	0.58% (3)
Withdrew consent	3.5% (18)
Lost to follow-up	1.54% (8)
Did not complete visit 2 outcome questions	1.34% (7)

*One incidence per patient.

DISCUSSION

After only 1 month of treatment with hydroxypropyl cellulose ophthalmic inserts as an adjunct to ongoing therapy, participants in this study experienced significant reductions in the severity of DES symptoms, fewer occurrences of DES symptoms, less difficulty when performing daily tasks, and reduced discomfort in environmental conditions that exacerbate DES symptoms. Investigators reported improvements in clinical signs of DES, including increased TFBUT and tear volume, along with decreased fluorescein staining.

Patients reported a significant and dramatic improvement in overall quality of life as scored by the OSDI. Significant improvements were reported in incidence of sensitivity to light, feelings of grittiness, and painful or sore eyes. No significant changes were reported in occurrence of poor vision. Blurred vision, the most commonly reported adverse event associated with hydroxypropyl cellulose ophthalmic inserts, was reported to occur with increased frequency. This is likely due to the thickened precorneal tear film observed after placement of the inserts. Immediate, transient blurring can be managed by instilling a drop of artificial tears to thin the tear film. Some patients may find that blurred vision is eliminated if hydroxypropyl cellulose ophthalmic inserts are emplaced at night and removed in the morning.

If blurring does not occur immediately after placement but is observed later in the day, patients can remove the inserts and replace them with a new pair. Blurring several hours after placement may be caused by the softened, bleb-shaped insert. Most patients will not experience blurred vision; however, if blurring is observed, it can be easily managed.

Of interest, while the incidence of blurred vision did increase in this analysis, patients reported significant improvement in ADLs that require a high degree of visual acuity, particularly reading, watching television or movies, working with a computer or ATM, and driving at night. It is likely that hydroxypropyl cellulose ophthalmic inserts provide significant enough relief of additional DES symptoms that offset any inconvenience experienced by transient, manageable blurred vision. This is reflected in the significant, dramatic 21.3% improvement in OSDI total score.

A large number of contact lens wearers participated in this study. Lens wearers experienced relief of DES symptoms that was comparable to patients who do not wear contact lenses, with a strong trend toward improvement in sensitivity to light. Additional analyses are under way to determine the activity of hydroxypropyl cellulose ophthalmic inserts in further subsets of patients (ie, those with glaucoma, cataracts, or previous refractive surgery). Once-daily use of hydroxypropyl cellulose ophthalmic inserts is an effective, preservative-free option for the treatment of moderate to severe DES.

ACKNOWLEDGMENTS

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Author Contributions: *Design of the study* (M.M.); *Conduct of the study* (M.M., G.D., H.P., J.W.); *Management, analysis, and interpretation of data* (D.N.); *Preparation, review, or approval of manuscript* (M.M., G.D., H.P., J.W., E.D., D.N.).

Conformity With Author Information: Upon enrollment in the study, patients read, signed, and dated an IRB-approved, HIPAA-compliant informed consent form. This study was conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). IRB approval of the protocol and informed consent documents was obtained prior to study initiation.

Other Acknowledgments: The authors would like to thank Frederick Parente, PhD, and Norman Nagl, PhD, for assistance with data analysis and editorial support.

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PEER DISCUSSION

DR. ANDREW J. W. HUANG: The authors conducted a multi-center, open-label study consisting of 2 visits in 4 weeks regarding the use of hydroxypropyl cellulose ophthalmic inserts (LACRISERT®) for treating patients with moderate to severe dry eye syndrome (DES). The study re-examined the clinical efficacy of a less utilized therapy for DES, which has been available for more than two decades. A total of 520 patients from 49 sites were enrolled in the study. Of the 520, 102 (19.6%) patients who did not complete the study, but only 95 patients were accounted for in the table, entitled "Incidence of Adverse Events Leading to Discontinuation". The reason for discontinuing the treatment in the remaining 7 patients is unclear. It is concerning that nearly 20% of patients failed to complete the study. The demographic information regarding the participants and drop-outs was not readily available. The severity of DES was not stratified. It is unclear if those patients that dropped out of the study might have had worse DES and experienced more adverse effects or if they might have had fewer symptoms and did not experience as much improvement.

While a large number of patients were enrolled in this study, the criteria for inclusion and exclusion were not well defined. There was no specific wash-out period for those patients with DES currently being treated with artificial tears. As some of the regimens contain polymers or cellulose-based lubricants, concurrent use of these medications may affect the outcome and validity of the study. Current consensus favors the use of anti-inflammatory agents such as 0.05% cyclosporine A for DES. It is unclear if the enrolled patients were allowed to continue the use of topical cyclosporine or other topical ocular medications, such as glaucoma medications. Concurrent use of hydroxypropyl cellulose inserts and other topical medications may have an impact on pharmacodynamics of those medications. Prior history of punctal occlusion was not clearly delineated; as such a procedure may prolong the retention time of hydroxypropyl cellulose inserts and have potentiating or adverse impact on the therapeutic effects of these inserts. It is also unclear if contraceptive or hormonal use was allowed or excluded for the female patients.

The compliance rate of using hydroxypropyl cellulose inserts was seemingly low. Only 41.5% reported full compliance with daily use. For those patients that missed one or multiple doses, it is not clear if the poor compliance was due to significant side-effects or no perceivable benefits being experienced. Blurred vision was the most reported adverse effect in 45 (8.7%) patients leading to discontinuation of the treatment. In addition to the previously validated OSDI (ocular surface disease index), the authors also evaluated the "Change in Activities of Daily Living" in this group of patients. As most of the ADL changes have already been assessed in OSDI in Figures 3 and 4, the results in Figure 5 are repetitive of the findings.

While acknowledging there has been no single test which can be used reliably and repeatedly to evaluate DES, the authors reported improvement in the tear film breakup time (TFBUT), fluorscein staining and tear volume by Schirmer's test. Only 95% CI were presented in Figure 6. The actual readings of those tests were not listed or described, which makes it difficult to interpret their findings. The NEI F (National Eye Institute fluorscein staining) are usually aggregated as one score rather than individually listed for each zone as in Figure 6. There was no information regarding the use of vital stains, such as rose bengal or lissamine green for evaluating the ocular surface. This renders a somewhat incomplete evaluation of ocular surface.

While the authors observed improvements in subjective symptoms and objective clinical signs, there were no adequate control groups for comparison. There was also no evident dose-dependent response. Ideally, there should be cross-over studies or treatment with a placebo or varied dosage of hydroxypropyl cellulose inserts (e.g. 2 mg vs. 5 mg inserts) to validate the therapeutic effects. There was no follow-up after 4 weeks of treatment. It is unclear how soon the patients' DES start to deteriorate after treatment is discontinued. While the treatment is seemingly non-invasive, the long-term efficacy remains elusive.

A large number of contact lens wearers (107 patients) were included in this study. However, the demographic information regarding the contact lens users was not described. Presumably, younger patients are expected in this group and they may have different responses to the treatment (e.g. better tolerance of inserts or less severity in DES). While the authors reported the improvement of DES symptoms in contact lens users, it remains unclear if their visual clarity and/or the rate of compliance are

affected by the inserts.

The citation of references is inadequate. Only 5 references are listed, of which one is the LACRISERT® package insert. The package insert of a pharmaceutical product should not be used as a scientific reference. In essence the authors only referenced one paper by a single author and three subcommittee reports from of the International Dry Eye Workshop. While the current study demonstrates some improvements in DES symptoms and quality of life in treated patients, the cost-effectiveness and long-term patient compliance of using hydroxypropyl cellulose inserts await further validation.

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DR. ALLAN J. FLACH: Marguerite, thank you for the survey. When this product was first commercially available, many patients complained it was difficult to insert. Secondly, they did not like the ocular sensation, and thirdly some of them did not have enough tears to dissolve the insert. How are those three problems circumvented now?

DR. IRENE H. LUDWIG: In some of my strabismus patients with resections or stretch scar repairs in the muscles located rather inferiorly, I have trouble with the development of corneal dellen. One actually led to an ulcer. Do you think the prophylactic use of Lacrisert® would be helpful in these cases?

DR. RICHARD K. FORSTER: I have no conflict of interest. I have a question. Was there any placebo Lacrisert® used in this study? How do we know that the Lacrisert® was any better than adding another tear or any other treatment?

DR. J. DANIEL NELSON: No conflict. Lacrisert® has been around for a long time. They initially disappeared during Operation Dessert Storm when they were sent for the soldiers to use. I have patients who would swear and kill to get their Lacriserts®. Some patients complain about blurred vision, and I wonder if that was reported in your study. My patients serendipitously told me that they would use them two or three times each day and remove them when the vision became blurred and apply a new Lacrisert® that relieved the blurring.

DR. DENNIS P. HAN**:** No disclosures. I was wondering, in patients with pre-existing blurred vision as a symptom of their dry eye, what effect did Lacrisert® have on their pre-existing symptoms? Were patients in that particular group more likely to have improvement or worsening of their symptoms?

DR. MARGUERITE MCDONALD: Thank you to Dr. Huang and to all of you for your excellent comments. A significant large number of patients did not complete the study. You should remember that most of the18% dropped out after signing the consent, but before they took any medicine. They were terrified by the consent. There was no washout crossover or dose dependent aspect to the study because it was not a formal clinical trial. It was a registry, no more and no less. With respect to the references, referring to a package insert, an FDA approved package insert, is allowed in peer reviewed journals. Of course, that was not the only reference; however, it is appropriate. I believe that in this instance, if you are talking about the package insert. We had no abrasions in our study. Regarding tricks for inserting the original formulation, I determined 20 years ago that if you asked the patients put the inserts in the freezer and to hit them with a hammer to make it flat little discs, that it was easier for them to insert. They could more easily place a flat disc in their inferior conjunctival cul de sac than a little rod. After the product reappeared on the market, I tried that technique and it really did not work well. The formulation is ever so slightly different than it was 20 years ago. The manufacturer is working on developing easier ways for patients to insert these devices. It helps many patients to show them the pictures in the package insert and for them to visit the website. You can also demonstrate insertion yourself. The best technique is to begin by instilling a drop of artificial tears to moisten the insert and to grab the Lacrisert ®off center with the inserter. The patient then makes a little triangular pocket out of the lateral inferior cul-de-sac by pinching the skin and puts in the insert. The patient must pin the Lacrisert® in the cul de sac before removing the applicator, otherwise it will come out with the applicator. This application is terrific for preventing dellen formation. Irene, we frequently use this after pterygium surgery.

There was no placebo because this was not a clinical trial. When something is made of hydroxypropyl cellulose, it is difficult to develop a placebo, because the material itself is almost a placebo. You know the insert does not contain an antibiotic or a steroid

Regarding blurred vision, insertion at night instead of in the morning makes a huge difference because a burst of gooey material comes out of the device. It is less bothersome if the burst comes out at night and has reached a steady state concentration by the morning. I have quite a few people who tell me that the Lacrisert® goes in as a tiny insert, smaller than a grain of rice, which then swells and starts to melt again. When it reaches a critical size it dislocates from the cul de sac and can be seen in inferior tear meniscus. They state that this happens at the same time every day. I tell those people an hour before that occurs to remove it and put a fresh one.

With respect to blurred vision before treatment, we studied that issue. There was no statistically significant difference in the number of patients predisposed to blurred vision before treatment. I showed you there was a little worsening of blurred vision while reading and that was statistically significant. Thank you.