Clinical Optometry

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ORIGINAL RESEARCH

# Evaluation of carboxymethylcellulose 0.5%/glycerin 0.9% and sodium hyaluronate 0.18% artificial tears in patients with mild to moderate dry eye



This article was published in the following Dove Press journal:
Clinical Optometry
24 November 2011
Number of times this article has been viewed

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**Background:** Artificial tears are commonly used for the symptomatic treatment of dry eye. This study compared the efficacy and safety of two preservative-free formulations of artificial tears, carboxymethylcellulose 0.5%/glycerin 0.9% (CMC/glycerin) and sodium hyaluronate 0.18% (sodium hyaluronate), in patients with mild to moderate dry eye symptoms.

**Methods:** This multicenter, investigator-masked, randomized, parallel-group, active-controlled, clinical study enrolled patients with mild to moderate dry eye symptoms. At baseline, patients received both treatments (one in each eye) and completed an Acute Preference Questionnaire. Patients were then randomized 1:1 to treatment with one drop of CMC/glycerin or sodium hyaluronate at least three times per day for 2 weeks. Efficacy outcomes included Ocular Surface Disease Index (OSDI), tear break-up time (TBUT), corneal staining, conjunctival staining, conjunctival hyperemia, Dry Eye Symptom and Bothersomeness Survey, Patient Acceptability Questionnaire, and Patient Global Assessment of Change. Safety outcomes included the number and frequency of adverse events.

**Results:** CMC/glycerin and sodium hyaluronate produced statistically significant improvements in OSDI ($P < 0.0001$), TBUT ($P < 0.0001$), corneal staining ($P < 0.0001$), conjunctival staining ($P < 0.0001$ at Week 1; $P < 0.01$ at Week 2), and conjunctival hyperemia ($P < 0.0001$ at Week 1; $P < 0.05$ at Week 2) relative to baseline. No statistically significant between-group differences in any evaluated variable, including clinical and patient-reported outcomes, were observed. Following a single-drop instillation, there was a trend in favor of sodium hyaluronate for which each drop produced less blurring ($P = 0.055$). At Day 14, there were trends in favor of CMC/glycerin for questions about how many hours the eyedrops controlled symptoms ($P = 0.057$), whether the eyedrops effectively relieved dryness ($P = 0.053$), and which drop provided a cushion of moisture on eyes ($P = 0.052$). No treatment-related adverse events were reported.

**Conclusion:** Both CMC/glycerin and sodium hyaluronate effectively relieved dry eye symptoms. Scores were consistently similar across all measures, and both artificial tears were highly acceptable to patients.

**Keywords:** artificial tears, dry eye, safety, efficacy, carboxymethylcellulose 0.5%/glycerin 0.9%, sodium hyaluronate 0.18%

## Introduction

The ocular surface is maintained and protected by the tear film. Adequate tear secretion and subsequent distribution by blinking is essential to ocular comfort and vision. Dry eye can manifest upon dysfunction or inflammation in any component of the lacrimal functional unit (lacrimal glands, ocular surface, eyelids, meibomian glands, and the

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interconnecting neural reflex loop) and is often exacerbated by immunologic, hormonal, and environmental factors.[1] Ocular symptoms such as irritation, foreign-body sensation, and burning may arise when native tears are insufficient in quantity and/or quality. Tear film alterations in the setting of dry eye include a decrease in volume, an increase in inflammatory cytokines and matrix metalloproteinases, and an increase in osmolarity.[1] Dry eye syndrome has been shown to have substantial impact on quality of life, particularly in the activities of daily living.[2]

The treatment goal for dry eye syndrome is to improve comfort and quality of life, as well as to restore the tear film and ocular surface to its normal state.[1,3] Artificial tears are the most common initial treatment approach to relieve symptoms in patients with mild to moderate disease, although artificial tears alone do not directly address the underlying ocular surface inflammation.[4,5] Preservative-free carboxymethylcellulose 0.5%/glycerin 0.9% (CMC/glycerin; Refresh® Optive™ Sensitive; Allergan, Inc, Irvine, CA) is a next-generation artificial tear that was designed with a dual mechanism of action to provide lubrication as well as hydration and protection of corneal epithelial cells. Sodium hyaluronate is widely used outside the United States as a tear-replacement eyedrop for patients with dry eye. Theoretically, the mucoadhesive properties of sodium hyaluronate provide longer residence times on the precorneal tear film.

The purpose of this study was to evaluate the safety and efficacy of preservative-free formulations of CMC/glycerin and sodium hyaluronate 0.18% (Vismed®; TRB Chemedica SA Société, Vouvry, Switzerland) in the symptomatic treatment of patients with dry eye. The clinical hypothesis for this study was to determine whether CMC/glycerin was as effective as, or more effective than, sodium hyaluronate eyedrops for treating the symptoms and signs of dry eye.

## Methods

This multicenter, investigator-masked, randomized, parallel-group, active-controlled clinical study was conducted at nine sites in Germany in June 2009. The study protocol and informed consent forms were approved by all institutional review boards. All patients or legally authorized representatives signed a written consent form before initiation of study-specific procedures.

At the initial visit, patients underwent an acute comfort evaluation in which patients received one drop of CMC/glycerin in one eye and one drop of sodium hyaluronate in the other eye by study personnel; patients were masked to treatment. Following that evaluation, patients were randomly assigned 1:1 to bilateral treatment with one of the treatments for 2 weeks. Patients instilled study formulations as one drop as needed at least three times daily for 2 weeks and remained masked to treatment. Patients were permitted to use additional drops of the same medication more frequently as needed to relieve dry eye symptoms. The investigator was masked to study treatment.

This study enrolled adult patients (≥18 years of age) with mild to moderate dry eye symptoms. At baseline, patients had an average tear break-up time (TBUT) ≤10 seconds in at least one eye and a baseline Ocular Surface Disease Index (OSDI)[6] score of ≥13 (on a scale of 0 to 100), and were currently using an artificial tear for dry eye. Patients were excluded if they: had used any other topical ophthalmic medications within 14 days (other than artificial tears); had a corneal or conjunctival staining grade ≥3 (using the Oxford scale of grading[7]) in any area of either eye; had uncontrolled systemic disease; had undergone refractive surgery within 12 months; required chronic use of systemic medications that would affect dry eye unless medications were stable for 3 months; had punctal plugs (temporary or permanent); had active ocular infection or ocular allergy; had a history of recurrent herpetic keratitis; had severe blepharitis; or had dry eye secondary to destruction of conjunctival goblet cells.

The primary efficacy outcome measure was the OSDI,[6] which evaluated the frequency of various dry eye symptoms using a 5-point scale: 0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, and 4 = all of the time. Secondary clinical efficacy measures included TBUT and corneal and conjunctival staining (Oxford scale[7]). Clinical outcomes were assessed at baseline, Week 1, and Week 2. Safety outcomes included the frequency and severity of adverse events.

Patient-reported efficacy outcomes included the Acute Preference Questionnaire, Dry Eye Symptom and Bothersomeness Survey (using 5-point scales to evaluate frequency and bothersomeness of symptoms), Patient Acceptability Questionnaire, and the Patient Global Assessment of Change (using a 5-point scale: 0 = much worse, 1 = worse, 2 = about the same, 3 = improved, and 4 = much improved). The assessments included: the Acute Preference Questionnaire only at baseline; the Dry Eye Symptom and Bothersomeness Survey at baseline and Weeks 1 and 2; and both the Patient Acceptability Questionnaire and the Patient Global Assessment of Change at Week 2.

Approximately 66 patients (33 per treatment group) were planned to ensure that at least 60 patients completed the study, allowing for a 10% drop-out rate. The mean value

for both eyes was used for TBUT, corneal and conjunctival staining, and conjunctival hyperemia analyses. Continuous data were analyzed with nonparametric tests. Nominal data were evaluated with $\chi^2$ or Fisher exact tests.

## Results

A total of 71 patients were enrolled and 70 successfully completed the study: 33 patients received CMC/glycerin and 37 patients received sodium hyaluronate. One patient was excluded from the analyses because of a protocol violation at randomization. Patient demographics were balanced between treatment groups (Table 1).

At baseline, no statistically significant differences between treatment arms in OSDI or other clinical measures were observed (Table 1, Figure 1). In this 2-week study, improvements in objective clinical measures were seen in both arms. Additionally, OSDI scores significantly improved from baseline at Weeks 1 and 2 ($P < 0.0001$ for both groups at each time point). There was no significant between-group difference for OSDI at any time point (Figure 1).

TBUT results were similar between treatment groups at baseline and after treatment (Table 2); significant improvements from baseline in TBUT were observed at Weeks 1 and 2 ($P < 0.0001$ for both groups at each time point). There were no statistically significant differences between groups in mean corneal staining or in mean change from baseline at any follow-up. Improvements in corneal staining were observed with both treatments ($P < 0.0001$ for both groups at each time point). Similarly, there were no significant differences in temporal or nasal conjunctival staining or conjunctival hyperemia between treatment groups. The two treatments improved temporal conjunctival staining at Week 1 ($P < 0.0001$ for both groups) and at Week 2 (CMC/glycerin: $P = 0.0002$; sodium hyaluronate: $P = 0.0029$). Both treatments improved nasal conjunctival staining at Week 1 ($P < 0.0001$ for both groups) and Week 2 (CMC/glycerin: $P = 0.0016$; sodium hyaluronate: $P = 0.0008$). Both treatments improved conjunctival hyperemia at Week 1 ($P < 0.0001$ for each group) and at Week 2 (CMC/glycerin: $P = 0.0054$; sodium hyaluronate: $P = 0.0419$).

**Table 1** Patient demographics

| | CMC/glycerin n = 33 | Sodium hyaluronate n = 37 | *P*-value[a] |
|---|---|---|---|
| Sex, n (%) | | | 0.575 |
| Female | 23 (70) | 28 (76) | |
| Male | 10 (30) | 9 (24) | |
| Age, mean years (SD) | 54.4 (19.4) | 48.8 (16.2) | 0.193 |
| Range | 20.3–87.5 | 18.9–84.5 | |
| Race, n (%) | | | > 0.999 |
| White | 32 (97) | 36 (97) | |
| Asian | 1 (3) | 1 (3) | |

**Note:** [a]*P*-value for comparison between groups.
**Abbreviations:** CMC, carboxymethylcellulose; SD, standard deviation.

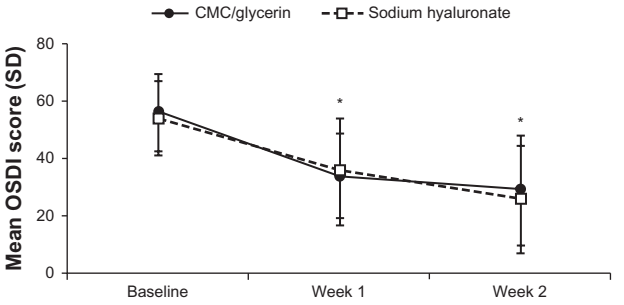


**Figure 1** Ocular Surface Disease Index (OSDI) scores. Mean OSDI scores for patients receiving carboxymethylcellulose 0.5%/glycerin 0.9% (circles) or sodium hyaluronate (squares) from baseline through Week 2 are shown.
**Notes:** Error bars represent standard deviations (SDs). *$P < 0.0001$ for change from baseline (both treatments).

No statistically significant differences were observed between groups in patient responses to the Acute Preference Questionnaire performed following a single-drop installation, although in the area of blurring there was a trend in favor of sodium hyaluronate ($P = 0.055$). Similarly, there were no statistically significant differences between groups in frequency or bothersomeness of dry eye symptoms (ie, stinging, dryness, foreign-body sensation, itching, light sensitivity, pain/soreness, blurred vision, tiredness/fatigue, or frequent blinking) at baseline or after 2 weeks of treatment, although improvements were noted in both groups following treatment. There were also no significant differences between treatment groups in responses to the Patient Acceptability Questionnaire (Table 3); however, trends favored CMC/glycerin in symptom control in terms of how many hours the eyedrops controlled dry eye symptoms ($P = 0.057$), whether the eyedrops effectively relieved dryness ($P = 0.053$), and which drop provided a cushion of moisture on the eyes ($P = 0.052$). The mean (standard deviation) Global Assessment of Change score at Week 2 was 3.00 (0.67) for patients receiving CMC/glycerin and 2.84 (0.93) for patients receiving sodium hyaluronate at Week 2.

A single nontreatment-related adverse event was reported in a patient receiving CMC/glycerin: vitreous hemorrhage secondary to diabetes. No serious adverse events were reported.

## Discussion

The results of this study demonstrated that both preservative-free CMC/glycerin[8] and sodium hyaluronate[9] relieved the

**Table 2** Secondary clinical efficacy outcomes

| | CMC/ glycerin n = 33 | Sodium hyaluronate n = 37 | *P*-value[a] |
|---|---|---|---|
| TBUT, mean seconds (SD) | | | |
| Baseline | 6.5 (1.7) | 5.9 (1.6) | 0.138 |
| Week 1 | 7.9 (2.7) | 7.2 (2.4) | 0.251 |
| Week 2 | 9.4 (2.6) | 8.5 (3.2) | 0.279 |
| Change from baseline at Week 2, mean seconds | 2.9 | 2.6 | 0.634 |
| Change from baseline *P*-value[b] | < 0.0001 | < 0.0001 | |
| Corneal staining, mean grade (SD) | | | |
| Baseline | 1.82 (0.78) | 1.61 (0.94) | 0.203 |
| Week 1 | 0.80 (0.75) | 0.61 (0.76) | 0.203 |
| Week 2 | 0.53 (0.61) | 0.38 (0.63) | 0.181 |
| Change from baseline at Week 2, mean grade | −1.29 | −1.23 | 0.556 |
| Change from baseline *P*-value[b] | < 0.0001 | < 0.0001 | |
| Conjunctival staining – temporal, mean grade (SD) | | | |
| Baseline | 1.82 (0.95) | 1.92 (1.01) | 0.670 |
| Week 1 | 1.21 (0.86) | 1.08 (0.72) | 0.490 |
| Week 2 | 0.67 (0.74) | 0.70 (0.78) | 0.843 |
| Change from baseline at Week 2, mean grade | −1.15 | −1.22 | 0.794 |
| Change from baseline at Week 2 *P*-value[b] | 0.0002 | 0.0029 | |
| Conjunctival staining – nasal, mean grade (SD) | | | |
| Baseline | 1.76 (0.90) | 2.00 (0.91) | 0.269 |
| Week 1 | 1.12 (0.78) | 1.03 (0.76) | 0.612 |
| Week 2 | 0.70 (0.68) | 0.54 (0.65) | 0.330 |
| Change from baseline at Week 2 | −1.06 | −1.46 | 0.093 |
| Change from baseline *P*-value[b] | 0.0016 | 0.0008 | |
| Conjunctival hyperemia, mean grade (SD) | | | |
| Baseline | 0.76 (0.59) | 0.99 (0.72) | 0.141 |
| Week 1 | 0.39 (0.38) | 0.42 (0.48) | 0.810 |
| Week 2 | 0.21 (0.42) | 0.24 (0.33) | 0.665 |
| Change from baseline at Week 2 | −0.55 | −0.75 | 0.208 |
| Change from baseline *P*-value[b] | 0.0054 | 0.0419 | |

**Notes:** [a]*P*-value for comparison between groups; [b]*P*-value for change from baseline within group.
**Abbreviations:** CMC, carboxymethylcellulose; SD, standard deviation; TBUT, tear break-up time.

symptoms of dry eye. In this head-to-head comparative study, there were no statistically significant differences in measures of clinical efficacy between the two formulations. Similarly, no statistically significant differences in patient-reported outcomes were noted. These observations are consistent with the clinical hypothesis that CMC/glycerin was at least as effective as sodium hyaluronate eyedrops for the treatment of the signs and symptoms of dry eye.

Studies have shown that clinical outcomes are often not concordant with patient-reported symptoms of dry eye disease.[2] Therefore, it is important to consider patient-reported symptoms to assess severity and response to treatment.[2] To address this issue, we used the OSDI, which has been validated in patients with dry eye,[6] to evaluate patient symptoms. The mean improvement in OSDI at Week 1 was 21.8 in patients receiving CMC/glycerin and 18.9 in patients receiving sodium hyaluronate. Patients in both treatment arms, therefore, achieved the minimal clinically important difference in OSDI score (ie, 4.5 to 7.3) for patients with mild to moderate disease[10] within 1 week of treatment.

Several patient-reported outcomes were used in this study. The OSDI provided information on ocular symptoms (ie, light sensitivity, grittiness, pain, blurred and poor vision), vision-related functioning (ie, ability to read, drive at night, work on a computer, watch television), and environmental factors (ie, exposure to wind, humidity, air conditioning) from the patient's perspective. The questionnaire is simple to administer and is validated for use in patients with dry eye. The Dry Eye Symptom and Bothersomeness Survey, which assesses additional symptoms (ie, stinging, dryness, foreign-body sensation, itching, tiredness/fatigue, and frequent blinking), warrants further study and validation for use in clinical studies. The Acute Preference Questionnaire was devised to provide a direct comparison between the two products and was implemented in this study following only a single-drop instillation. Together, these tools provide a broad patient perspective on dry eye treatment.

Several numerical trends were observed in response to some elements of these questionnaires that approached statistical significance. In particular, questions on the effectiveness and duration of relief appeared to favor CMC/glycerin when these questions were asked after 2 weeks of treatment, though the results were less apparent following a single-drop instillation. A trend favoring sodium hyaluronate in regards to less blurring was seen on the Acute Preference Questionnaire following treatment with a single drop, although any immediate difference in blurring did not necessarily persist; similar numbers of patients in both groups reported their vision was normal within 5 minutes or less after drop application as reported at 2 weeks.

This study was ultimately only 2 weeks in duration, although similar in duration to the phase 3 study conducted for 0.18% sodium hyaluronate in the United States.[9]

**Table 3** Acceptability questionnaire results

| Patient responses, n (%)[a] | CMC/glycerin n = 33 | Sodium hyaluronate n = 37 | *P*-value[b] |
|---|---|---|---|
| Overall, liked using drops | | | 0.856 |
| Strongly agree or agree | 28 (85) | 32 (86) | |
| Neither agree nor disagree | 4 (12) | 3 (8) | |
| Disagree or strongly disagree | 1 (3) | 2 (5) | |
| Overall, drops made eyes feel comfortable | | | 0.584 |
| Strongly agree or agree | 29 (88) | 31 (84) | |
| Neither agree nor disagree | 3 (9) | 4 (11) | |
| Disagree or strongly disagree | 1 (3) | 2 (5) | |
| Drops were soothing to eyes | | | 0.486 |
| Strongly agree or agree | 30 (91) | 28 (76) | |
| Neither agree nor disagree | 3 (9) | 7 (19) | |
| Disagree or strongly disagree | 0 | 2 (5) | |
| Drops provided long-lasting relief of dry eye discomfort | | | 0.820 |
| Strongly agree or agree | 21 (64) | 19 (51) | |
| Neither agree nor disagree | 6 (18) | 11 (30) | |
| Disagree or strongly disagree | 6 (18) | 7 (19) | |
| Number of hours that drops controlled dry eye symptoms | | | 0.057 |
| < 1 | 1 (3) | 5 (14) | |
| 1–3 | 13 (39) | 17 (47) | |
| 4–6 | 16 (48) | 13 (36) | |
| 6–10 | 2 (6) | 1 (3) | |
| < 10 | 1 (3) | 0 | |
| Drops effectively relieved dryness | | | 0.053 |
| Strongly agree or agree | 26 (79) | 20 (54) | |
| Neither agree nor disagree | 6 (18) | 12 (32) | |
| Disagree or strongly disagree | 1 (3) | 5 (14) | |
| Drops did not interfere with vision when first applied | | | 0.189 |
| Strongly agree or agree | 23 (70) | 31 (86) | |
| Neither agree nor disagree | 6 (18) | 2 (6) | |
| Disagree or strongly disagree | 4 (12) | 3 (8) | |
| Vision was normal within 5 minutes or less after drops were applied | | | 0.547 |
| Strongly agree or agree | 28 (85) | 30 (83) | |
| Neither agree nor disagree | 3 (9) | 3 (8) | |
| Disagree or strongly disagree | 2 (6) | 3 (8) | |
| Drops did not cause eyes or eyelashes to become matted or crusty | | | 0.918 |
| Strongly agree or agree | 29 (88) | 29 (81) | |
| Neither agree nor disagree | 1 (3) | 5 (14) | |
| Disagree or strongly disagree | 3 (9) | 2 (5) | |
| Drops provided a cushion of moisture on eyes | | | 0.052 |
| Strongly agree or agree | 23 (70) | 15 (41) | |
| Neither agree nor disagree | 9 (27) | 15 (41) | |
| Disagree or strongly disagree | 1 (3) | 7 (19) | |

**Notes:** [a]Some patients did not provide responses to all questions, so n values vary; [b]*P*-value for comparison between groups.
**Abbreviation:** CMC, carboxymethylcellulose.

Additional long-term studies are necessary to more fully compare the long-term efficacy and safety of these two formulations. In addition, this study was primarily designed to evaluate patients with mild to moderate dry eye, and further comparisons are warranted to compare these formulations in patients with more severe dry eye disease.

Although artificial tears have been shown to provide relief of many signs and symptoms of dry eye disease, they do not treat inflammation or increase the volume of natural tears.[5] In addition to using preservative-free artificial tears for Level 2 dry eye disease, current treatment guidelines also recommend cyclosporine A and/or corticosteroids.[3,4] In the present study, CMC/glycerin and sodium hyaluronate effectively relieved the symptoms in patients with mild to moderate symptoms of dry eye. Additional studies are also warranted in the future to compare these artificial tear formulations in conjunction with anti-inflammatory therapies in the treatment of dry eye disease.

## Acknowledgments

We thank Melissa Earl MPH (IMEDS, Inc, Riverside, CA) for her assistance with the statistical analyses. Editorial assistance in the preparation of this manuscript was provided by Julia R Gage PhD of Gage Medical Writing LLC and by SCI Scientific Communication & Information. Support for this assistance was funded by Allergan, Inc. This study was funded by Allergan, Inc.

## Disclosure

Dr Roth has no conflicts of interest to disclose. Ms Conway and Dr Hollander are employees and shareholders of Allergan, Inc.

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