# Effect of a hyaluronic acid and carboxymethylcellulose ophthalmic solution on ocular comfort and tear-film instability after cataract surgery

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**PURPOSE:** To evaluate the efficacy and safety of using sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% artificial tears for ocular discomfort and tear-film stability in eyes after cataract surgery.

**SETTING:** Twenty ophthalmic centers in Italy.

**DESIGN:** Prospective randomized case series.

**METHODS:** This study enrolled patients scheduled for unilateral cataract surgery. After surgery, patients received artificial tears and a topical steroid–antibiotic (study group) or topical steroid–antibiotic alone (control group) and were assessed postoperatively at 1 and 5 weeks. Outcome measures were tear breakup time (TBUT), ocular surface disease index (OSDI), frequency of dry-eye symptoms evaluated using a visual analog scale (VAS), and corneal fluorescein staining.

**RESULTS:** The study comprised 282 patients. At 5 weeks, the mean TBUT was statistically significantly higher in the study group than in the control group ($P = .0003$). The mean OSDI score statistically significantly improved in both groups from 1 to 5 weeks ($P < .0001$ for both groups); however, there was no statistically significant difference between the groups at these timepoints. The artificial tears statistically significantly improved VAS-assessed dry-eye symptoms in the study group compared with the control group at 5 weeks ($P < .001$). The mean corneal fluorescein staining was significantly reduced in the study group compared with the control group at 5 weeks ($P = .002$ versus $P = .05$, respectively). No treatment-related adverse events were reported.

**CONCLUSION:** Sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% ophthalmic solution was effective and well tolerated in reducing dry-eye disease symptoms and improving the clinical outcome after cataract surgery.

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Symptoms of dry-eye disease, such as foreign-body sensation and irritation, frequently occur after cataract surgery.[1,2] Surgery might also exacerbate preexisting dry-eye disease.[3] Several factors might contribute to tear-film instability after cataract surgery. For example, damage to corneal structures as a result of surgery, adverse effects of topical anesthesia and benzalkonium chloride–containing eyedrops, and exposure to intense light from the operating microscope can adversely affect the ocular surface environment.[3,4] This can lead the tear film into a vicious cycle of tear-film instability, tear/cell hyperosmolarity, apoptosis of conjunctival and corneal cells, and inflammation.[5]

Dry-eye disease symptoms can reduce patients' quality of life, affecting their ability to perform daily activities[6]; therefore, timely and effective treatment is necessary in cataract patients.[7] Artificial tears are widely used for the treatment of dry-eye disease[8] and are recommended for dry-eye disease prevention after phacoemulsification.[4] Sodium hyaluronate 0.1%

and carboxymethylcellulose 0.5% (Optive Fusion) is a new ophthalmic solution for the treatment of dry-eye disease that has the potential to optimize ocular hydration and improve ocular surface comfort. Hyaluronate is a naturally occurring polysaccharide that retains water and hydrates the ocular surface,[9] helping to protect the corneal endothelium during cataract surgery if used as an ophthalmic viscosurgical device.[10] Carboxymethylcellulose has lubrication and cell-binding properties that allow it to remain on the ocular surface for an extended period of time.[11] Together, carboxymethylcellulose and sodium hyaluronate form a bridged matrix of polymers that protects the ocular surface by maintaining hydration and stabilizing the tear film.

The objective of this study was to evaluate the efficacy and safety of using sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% artificial tears to treat ocular discomfort and tear-film stability in eyes after cataract surgery.

## PATIENTS AND METHODS

### Study Design

This was a prospective randomized comparative open-label 5-week study performed from September 1, 2013, to October 31, 2013. Study participants were recruited at 20 ophthalmic centers in Italy. The study was performed in compliance with good clinical practices and was consistent with the tenets outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants. No institutional review board approval was required.

### Study Population

Patients enrolled in the study were adults 18 years or older who were scheduled for unilateral cataract surgery. Exclusion criteria were severe dry-eye disease (defined as a Schirmer test without anesthesia result of <5.0 mm after 5 minutes at the preoperative visit), concurrent ocular diseases that could affect the study results (eg, anatomic or functional eyelid abnormalities, lagophthalmos, floppy eyelid syndrome), concurrent administration of topical eyedrops not included in the protocol, use of systemic drugs that may contribute to dry-eye disease (antihistamines, decongestants, spasmolytics, and antidepressants), modification of topical and systemic therapy during the course of the study, complicated cataract surgery and/or use of sutures during surgery, punctate keratopathy linked to dry-eye disease, and anterior corneal dystrophy. Contact lens wearers were also excluded.

### Surgical Technique, Treatment, and Assessment

The surgical procedures used were consistent among centers and involved a 2.2 mm sutureless clear corneal incision made at the 12 o'clock position and standard phacoemulsification with intraocular lens implantation. Table 1 shows the preoperative and postoperative assessments. At the preoperative visit (within 90 days of surgery), patients were assessed for eligibility and tear breakup time (TBUT). There was a 10-minute interval between the TBUT and the Schirmer test. Eligible patients were enrolled and randomly assigned by a computer-generated randomization list in a 1:1 ratio to the study group or the control group. Both groups were given a topical steroid–antibiotic (tobramycin 0.3% and dexamethasone acetate 0.1%) in a 4-week tapered regimen (4 times a day for 1 week, then 3 times a day for 1 week, twice a day for 1 week, and once a day for 1 week). The study group was also prescribed lubricant eyedrops containing sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% to instill 4 times daily for 5 weeks. Study group patients were instructed to instill the lubricant eyedrops at least 10 minutes after the tobramycin–dexamethasone eyedrops.

Study visits were scheduled for 1 week (7 days ± 2 [SD]) and 5 weeks (35 ± 7 days) postoperatively. At the postoperative visits, patients were asked about compliance with the assigned treatment.

### Outcome Measures

A 10.0 mm visual analog scale (VAS) was used to assess the following 3 co-primary outcome measurements: TBUT; ocular surface disease index (OSDI), a validated and reliable tool that uses a 5-point scale to measuring the

**Table 1.** Preoperative and postoperative assessment.

| Assessment | Preoperative | Postoperative | |
|---|---|---|---|
| | | Week 1 | Week 5 |
| Inclusion/exclusion criteria | + | – | – |
| Schirmer test | + | – | – |
| TBUT | + | + | + |
| OSDI | – | + | + |
| VAS | – | + | + |
| Corneal fluorescein staining | – | + | + |

OSDI = ocular surface disease index; TBUT = tear breakup time; VAS = visual analog scale

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frequency of various dry-eye symptoms[12]; and frequency of dry-eye disease symptoms (foreign-body sensation, puncture sensation, stinging, discomfort in blinking, and desire to close eyes).

At 1 week and 5 weeks, corneal fluorescein staining was evaluated as a secondary outcome measurement. The National Eye Institute staining grid was used to grade the corneal staining and assign a score of 0 (normal) to 3 (severe) to each of 5 corneal regions (nasal, central, temporal, inferior, and superior), with a maximum possible score of 15.

### Statistical Analysis

Data were calculated as the mean ± SD for continuous variables and as frequencies for categorical variables. The effect of treatment on variables of interest over time was analyzed using multivariate analysis of variance for repeated measures, with time, treatment, and their interaction as effects. Between-group comparisons were performed using independent *t* tests or Mann-Whitney *U* tests. Within-group comparisons were made using paired *t* tests or Wilcoxon signed-rank tests where appropriate after Shapiro-Wilk tests were used to check data normality. A *P* value less than 0.05 was considered statistically significant.

## RESULTS

A total of 298 patients (298 eyes) were randomized to the study group and the control group in a 1:1 ratio. Sixteen patients (16 eyes) discontinued the study for personal reasons unrelated to the study treatment. Results are reported for the patients who completed the study and for whom all data were obtained for the 1-week and 5-week postoperative visits. In this per-protocol dataset comprising 282 patients (282 eyes), the study group contained 146 patients (88 women [60.3%] and 58 men [39.7%]) and the control group contained 136 patients (80 women [58.8%] and 56 men [41.2%]). The mean age in the study group was 71.2 years and in the control group was 70.3 years (no significant difference between groups, $P > .05$).

At the preoperative visit, the mean Schirmer test scores were similar between the study group and the control group (11.9 mm and 11.6 mm, respectively; not statistically significant). The mean TBUT was significantly lower in the study group (8.9 seconds) than in the control group (9.8 seconds) ($P = .04$, Wilcoxon signed-rank test) (Figure 1). One week postoperatively, there were no statistically significant differences between the groups in TBUT, OSDI, VAS, or corneal fluorescein staining results. Between the preoperative and 1-week postoperative visits, the decrease in the mean TBUT (1.4 seconds) was statistically significant in the control group ($P < .0001$) but not in the study group (Figure 1). At 5 weeks, the mean TBUT was statistically significantly higher by 1.4 seconds in the study group than in the control group (10.7 seconds and 9.3 seconds, respectively) ($P = .0003$, Wilcoxon test) (Figure 1).

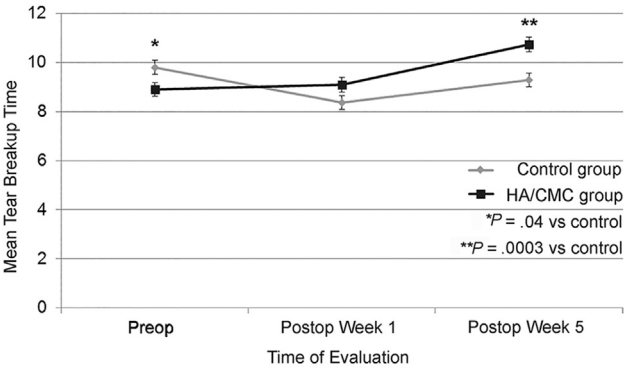


**Figure 1.** Mean TBUT preoperatively and 1 week and 5 weeks postoperatively. The error bars represent standard errors of the mean (CMC = carboxymethylcellulose; HA = hyaluronic acid; TBUT = tear breakup time).

The mean OSDI score significantly improved in both groups from 1 week to 5 weeks (a mean decrease of 4.82 in the study group and of 4.34 in the control group) (both $P < .0001$, paired *t* test) (Figure 2). The mean OSDI scores were numerically lower in the study group than in the control group at 1 week by 2.23 and 5 weeks by 2.21 (Figure 2); however, these differences were not statistically significant (both $P > .05$, Wilcoxon signed-rank test).

The sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% resulted in significant improvements in symptoms of foreign-body sensation and puncture sensation in the study group compared with the control group as measured using the VAS (Figure 3). At 5 weeks, the mean score for foreign-body sensation

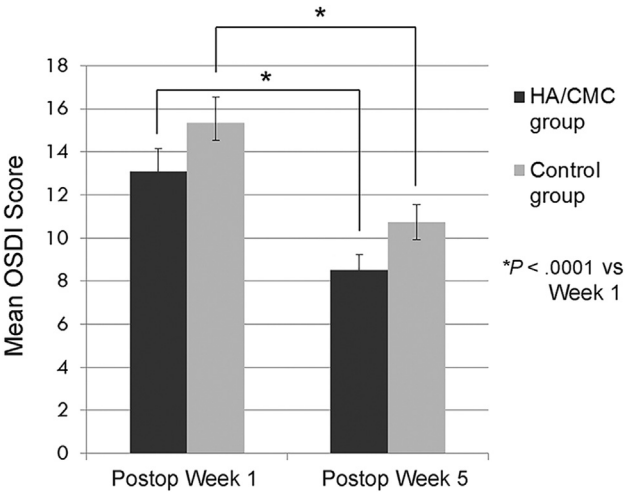


**Figure 2.** Mean OSDI scores 1 week and 5 weeks postoperatively. The error bars represent standard errors of the mean (CMC = carboxymethylcellulose; HA = hyaluronic acid; OSDI = ocular surface disease index).

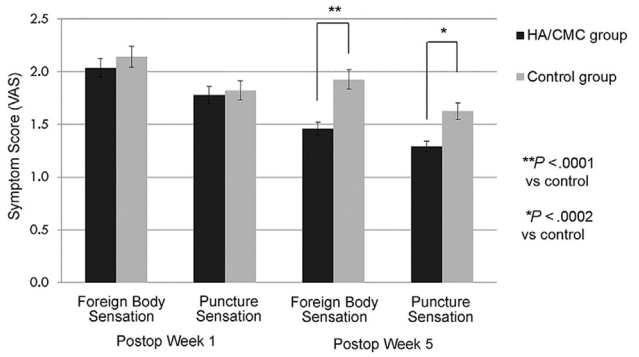


**Figure 3.** The symptom score as assessed by VAS at 1 week and 5 weeks. The error bars represent standard errors of the mean (CMC = carboxymethylcellulose; HA = hyaluronic acid; VAS = visual analog scale).

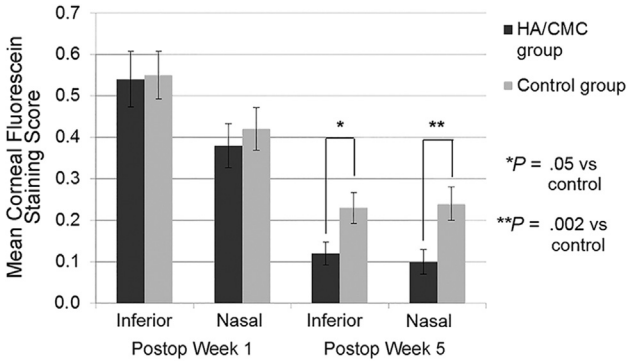


**Figure 4.** Corneal fluorescein staining scores at 1 week and 5 weeks (CMC = carboxymethylcellulose; HA = hyaluronic acid).

symptoms was 0.46 lower in the study group than in the control group (1.46 and 1.92, respectively) ($P < .0001$, Wilcoxon signed-rank test). The mean score for puncture-sensation symptoms was 0.34 lower in the study group than in the control group (1.29 and 1.63, respectively) ($P = .0002$, Wilcoxon signed-rank test). Additionally, the mean score in discomfort in blinking was 0.21 lower in the study group than in the control group (1.56 and 1.35, respectively), although this difference was of borderline significance ($P = .05$, Wilcoxon signed-rank test,).

Five weeks postoperatively, the mean corneal fluorescein staining value was significantly improved in the study group compared with the control group in the inferior and nasal corneal regions ($P = .05$ and $P = .002$, respectively; Wilcoxon signed-rank test) (Figure 4). No treatment-related adverse events were reported.

## DISCUSSION

Patients might experience dry-eye symptoms soon after cataract surgery, and these symptoms can persist late into the postoperative period. In 1 study,[4] dry-eye symptoms appeared 1 week postoperatively and peaked at 1 month. This highlights the importance of preventing or effectively managing post-cataract surgery dry-eye symptoms at an early stage.

In the present study, sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% ophthalmic solution administered after cataract surgery was more effective than a topical steroid–antibiotic alone in reducing dry-eye disease symptoms that developed gradually over the postoperative period. One week postoperatively, there was no statistically significant difference in dry-eye disease symptoms between the 2 groups; however, at 5 weeks, the treatment with sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% had significantly improved the dry-eye disease symptoms of foreign-body sensation and puncture sensation in the study group compared with the control group, as measured using a VAS. However, using the OSDI scale, no statistically significant difference was detected between the 2 groups.

The subjective improvements in dry-eye disease symptoms observed in this study were supported by improvements in clinical outcome measures. The TBUT is considered a surrogate measure of tear-film stability and is a test for evaporative dry-eye disease. The improvements in TBUT with use of sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% in the study group compared with the control group suggest improved integrity of the tear film, which can prevent evaporation, hyperosmolarity, and progression of dry-eye disease. Corneal fluorescein staining is a measurement of corneal tissue cell damage, and these improvements in the study group compared with the control group at 5 weeks showed that sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% objectively improved the health of the ocular surface. This is consistent with reports that carboxymethylcellulose-containing eyedrops stimulate healing of the corneal epithelium.[13]

Effective postoperative management of the ocular surface might increase patient satisfaction with the surgical outcome.[14] As shown in this study, sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% ophthalmic solution might be effective in reducing or preventing dry-eye disease symptoms after cataract surgery. This result has the potential to improve quality of life; however, that outcome was not measured as part of this study. Sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% were well tolerated, and no treatment-related adverse events were reported.

Limitations of this study included the short duration, which was insufficient to evaluate the impact of the artificial tear treatment on long-term dry-eye

disease, and the lack of a placebo for the sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% ophthalmic solution; moreover, the OSDI test was not performed at baseline. There was also an imbalance in the mean TBUT score at the preoperative visit, with patients allocated to sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% having a lower mean TBUT. This would be expected to lead to an underestimation of the effects of sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% in the study group.

In conclusion, in this study, sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% ophthalmic solution was effective and well tolerated in reducing dry-eye disease symptoms following cataract surgery. Compared with the control treatment, sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% improved the clinical outcome measures of tear-film stability and ocular surface health. In addition, long-term studies are necessary to more fully assess the long-term postoperative efficacy and safety of sodium hyaluronate 0.1% and carboxymethylcellulose 0.5%.

### WHAT WAS KNOWN

- Symptoms of dry-eye disease are common after cataract surgery and can have a negative impact on patients' quality of life. Timely and effective management of the ocular surface environment with artificial tears is necessary to improve outcomes in post-cataract surgery patients.

### WHAT THIS PAPER ADDS

- In patients having phacoemulsification, sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% ophthalmic solution reduced dry-eye disease symptoms compared with a control group treated with a topical steroid–antibiotic only.
- Sodium hyaluronate 0.1% and carboxymethylcellulose 0.5% improved objective measurements of tear-film stability and ocular surface health compared with controls.

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## APPENDIX

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