Hydroxypropyl Methylcellulose for the Treatment of Severe Dry Eye Associated with Sjögren's Syndrome

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Our purpose was to evaluate the efficacy of a new formulation of methylcellulose, preservative-free 0.5% hydroxypropyl methylcellulose (HPMC), for the treatment of dry eye. In the clinical part of our study, two groups of dry-eye patients, those with Sjögren's syndrome (SS) and those without (non-SS), were treated topically with 0.5% HPMC and evaluated for symptoms, ocular surface vital staining, tear breakup time (BUT), and tear evaporation rate from the ocular surface at 40% ambient humidity (TEROS40). In the in vitro part of the study, rose bengal uptake was measured in human conjunctival epithelial cells, which were cultured and incubated with or without 0.5% HPMC. Although symptoms improved in both groups, rose bengal and fluorescein staining and BUT improved significantly only in the SS group. TEROS40 increased for 30 min after instillation of 0.5% HPMC, but not after the use of 0.1% sodium hyaluronate or saline-based artificial tears. Rose bengal uptake by cultured conjunctival epithelial cells was blocked by 0.5% HPMC. These findings suggest that 0.5% HPMC provides long coverage of and protection for the ocular surface. Patients with severe dry eye, such as in SS, are good candidates for this treatment.

Key Words: Hydroxypropyl methylcellulose—Sjögren's syndrome—Dry eye.

Dry eye is a common, chronic, and often debilitating disease. Despite its high prevalence, dry eye does not always have a definite treatment. Generally, mild or early dry eye can be controlled by artificial tears, spectacles with side covers (1), or punctum plugs (2). However, in severe cases, especially with Sjögren's syndrome (SS), symptoms and ocular surface damage are sometimes uncontrollable and the patients' quality of life is greatly limited. The severity of ocular surface damage may depend on the presence of stimulated tears, which reflects the maximal ability of the lacrimal gland to moisten the eye. In SS this gland typically is infiltrated and destroyed by lymphocytes. Tsubota (3) introduced a nasal stimulation method to obtain the maximal stimulated tearing and reported a lack of stimulated tearing in SS, accompanied by severe rose bengal staining of the ocular surface. Treatment of SS dry eye is thus complicated because tear components, which are crucial for wound healing and maintenance of ocular surface integrity, are not well supplied.

Several investigators have tried to develop new treatments based on the immunologic pathogenesis of SS. Cyclosporin A improved severe dry eye in dogs, presumably by inhibiting T cells in lacrimal glands (4). There are many reports that suggest that Epstein–Barr virus (EBV) plays a role in SS (5,6). Interferon-α, an inhibitor of EBV, was used to treat dry mouth in SS patients and was found to improve saliva secretion (7). However, further work is required to determine the safety and efficacy of these drugs for clinical application. In the present study, we were interested in finding a better artificial tear preparation using currently available materials to improve the quality of life of SS patients.

Many kinds of artificial tears with a variety of formulations have been developed. Some were intended only to supplement aqueous tears, whereas others, such as fibronectin (8) and hyaluronate (9,10), were designed to accelerate ocular surface wound healing. However, most of these formulations provide only transient relief for SS dry eye,
since they don’t remain on the ocular surface for long and require frequent instillation. Many viscous agents, such as polyvinyl alcohol (PVA) and methylcellulose (MC), have been employed to prolong drug retention on the ocular surface (11,12) and are now widely used as lubricants for dry eye. Even though biochemical and rheological studies (13–15) suggest that these agents are good tear substitutes, there have been very few clinical reports (16,17) that have shown a significant improvement in symptoms as well as in ocular surface damage with these drugs.

The ability of these polymers to remain on the ocular surface depends on their concentration, which determines their viscosity. However, increasing viscosity lessens patients’ tolerance because the drops may become too sticky, cause discomfort, and temporarily interfere with vision (14). These effects also depend on the severity of dry eye.

MC, the most commonly available ophthalmic polymer solution, includes several kinds of compounds, which share a polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units. The properties of each MC vary depending on substitutions to the backbone (data from Alcon). Grene et al. reported that a carboxy methylcellulose (CMC)-based solution is more beneficial for dry eye than a hydroxypropyl methylcellulose (HPMC)-based solution (16). Feenstra and Tseng observed that CMC blocked uptake of rose bengal by cultured epithelial cells (18). In contrast, the advantage of HPMC has not been well elucidated. In this study, we used a new formulation of MC, preservative-free 0.5% HPMC, to treat SS and non-SS dry-eye patients and also examined some of its in vitro properties.

MATERIALS AND METHODS

Patients

Twenty-four dry-eye patients (47 eyes, one enucleated) were recruited into this study. They were divided into two groups according to their ocular and systemic conditions: dry eye associated with SS (27 eyes in 14 patients; three men and 11 women, 50.4 ± 9.1 years old) and dry eye not associated with SS (non-SS; 20 eyes in 10 patients; five men and five women, 53.7 ± 16.4 years old). SS was diagnosed according to the criteria of Fox et al. (19). Non-SS was diagnosed based on our criteria (20), which required the presence of chronic dry-eye symptoms, positive vital staining of the ocular surface (rose bengal score = 3 or fluorescein score ≥ 1), and the presence of tear dynamics abnormality (Schirmer test ≤ 5 mm, phenol red thread tear test (21) ≤ 10 mm, tear clearance test (22) ≤ 1:4, or tear breakup time ≤ 5 s).

Basic and stimulated tear secretions, which were determined by the Schirmer test, with anesthesia and with nasal stimulation (3), respectively, were 3.9 ± 3.3 mm and 5.1 ± 6.4 mm for SS and 6.2 ± 5.1 mm and 15.8 ± 12.3 mm for non-SS, indicating that maximal tear secretion from the lacrimal gland was suppressed in SS.

Drug Protocol

The patients were instructed to use a preservative-free 0.5% HPMC (Alcon, Osaka, Japan) four times a day. Symptoms and signs were compared before and 1 month after beginning treatment. Any previous treatments, such as use of protective eye-glasses or other artificial tears, were continued in all patients.

Symptoms

Dry-eye symptoms were evaluated using a questionnaire (Table 1). Fourteen symptoms were scored 0–5 according to their severity: 0, none; 1, occasional; 2, constant, but mild and putting no restriction on activities of daily living (ADLs); 3, constant and moderate, but no restriction of ADLs; 4, constant and severe, with some restrictions of ADLs; 5, severe restrictions of ADLs. The total score of the three major symptoms in each patient were compared before and after treatment.

Vital Staining of the Ocular Surface

Double vital staining with rose bengal and fluorescein (23) was used to assess ocular surface damage. Two microliters of preservative-free, 1% rose bengal and 1% fluorescein were applied with a micropipette. The ocular surface was divided into seven areas for rose bengal and three areas for fluorescein and scored 0–3 according to the staining intensity. Total scores for each eye were the sums of the rose bengal and fluorescein scores.

Tear Breakup Time (BUT)

BUT was measured with the instillation of 2 μl of 1% fluorescein. Patients were instructed to keep their eyes open until the first dry spot was observed in the central cornea. The period between the eye opening and the appearance of the first dry spot was measured three times and averaged.
TABLE 1. Dry eye questionnaire

Please check your symptoms according to their severity

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>most common (check 3)</th>
<th>before</th>
<th>after</th>
</tr>
</thead>
<tbody>
<tr>
<td>ocular fatigue</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>dryness</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
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<tr>
<td>foreign body sensation</td>
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<tr>
<td>pain</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>blurred vision</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>brightness</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
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<tr>
<td>red eye</td>
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<td>0, 1, 2, 3, 4, 5</td>
<td></td>
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<tr>
<td>discharge</td>
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<tr>
<td>heavy sensation</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>discomfort</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>difficulty opening eyes in the morning</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
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<tr>
<td>excess tearing</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>itching</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>burning</td>
<td>0, 1, 2, 3, 4, 5</td>
<td>0, 1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
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</tbody>
</table>

Tear Evaporation Rate from the Ocular Surface

In seven SS patients (seven eyes), we measured the tear evaporation rate from the ocular surface at 40% ambient humidity (TEROS40) before and after applying three different kinds of artificial tears: 0.5% HPMC, 0.1% sodium hyaluronate, and Soft-san tear (0.4% sodium chloride and 0.1% sodium potassium; Santen, Osaka, Japan). TEROS40 was measured using a system developed by Tsubota and Yamada (24), which consisted of a closed chamber with humidity and temperature sensors, a micro-computer, and a display. The chamber completely covered the patient’s eye, and the change in humidity inside the chamber was measured over 120 s. TEROS40 was calculated by the computer, which adjusts the temperature, the environmental humidity, and the evaporation from the eyelid skin. The measurements were done before and 10 min, 30 min, and 45 min after instillation of each solution.

Rose Bengal Uptake by the Conjunctival Epithelium

Feenstra and Tseng reported that 1% CMC (Celluvisc; Allergan, Irvine, CA, U.S.A.) blocks rose bengal uptake by cultured rabbit corneal epithelium (18). We wanted to confirm this effect for 0.5% HPMC using cultured human conjunctival epithelium.

Human conjunctival epithelial cells were collected from a healthy volunteer using a brush cytology technique (25) that enabled us to take 5,000–10,000 cells. Cells were released in 800 µl of culture medium (Hams F12/Dulbecco’s Modified Eagle Medium, 15% fetal calf serum, dimethyl sulfoxide, NaCO3, 5 µg/ml insulin, 10 ng/ml human epidermal growth factor, 0.1 ng/ml cholera toxin, 5 mg/ml amphotericin-B, 20 µg/ml penicillin, 0.2 g/µl streptomycin), delivered into an eight-well (each 200 µl) LabTek chamber (5 × 5 mm²; Nunc Inc., Naperville, IL, U.S.A.). This procedure was done twice to fill all eight wells. After adding 200 µl of the medium to each well, the cells were incubated for 48 h at 37°C.

After the semiconfluent cells were washed three times with phosphate-buffered saline (PBS), four of the cell cultures were preincubated with 50 µl of 5% HPMC and the other four (controls) with 50 µl of PBS. Twenty microliters of 0.2% rose bengal solution was added to the top of this fluid layer. Following a 1-min incubation, the cells were washed three times with PBS, examined with a microscope.
(IMT2; Olympus, Tokyo, Japan), and photographed. Blocked uptake was defined as ≥80% of the cells in one field (x40) not stained by rose bengal. Three areas in each well were observed, to determine the blocking effect.

**Statistical Analysis**

The Student's *t* test was used for the statistical analysis of BUT and TEROS40. The Mann-Whitney U-test was used for subjective scores and rose bengal and fluorescein scores.

**RESULTS**

**Symptoms**

We were able to obtain subjective scores both before and after treatment in nine cases of non-SS and 11 cases of SS. Eight non-SS patients (88.9%) and 10 SS patients (90.9%) reported improvement in their symptoms (Fig. 1A). Although the subjective scores declined in most instances, improvement in the three major symptoms was more significant in SS patients (*p* < 0.01 for non-SS, *p* < 0.001 for SS; Fig. 1B).

**Vital Staining and BUT**

Rose bengal and fluorescein staining significantly improved in SS (*p* < 0.01; Fig. 2), but not in non-SS. BUT also improved only in SS (*p* < 0.01, Fig. 3).

**CASE REPORT**

A 56-year-old man was referred to our clinic with a 1-year history of severe ocular dryness, foreign body sensation, and discomfort, which were refractory to treatment. He had cut back his working hours since the onset of disease because he often needed eyedrops owing to the severity of his symptoms. His total subjective score was 41, and the total score of the three major symptoms (dryness, foreign body sensation, and pain) was 14. Slit-lamp examination showed that the ocular surface was damaged, with massive staining with rose bengal (score: right/left eyes, 8/8) and fluorescein (score: 9/9) and severe filamentary keratitis (Fig. 4A). Both basic and stimulated tears decreased; a Schirmer test with anesthesia gave a result of 3 mm/3 mm and with nasal stimulation, 6 mm/4 mm. BUT was not measurable (0/0 s) because there was not enough tear film.

The patient had increased serum autoantibodies: rheumatoid factor, ×320; antinuclear antibody, ×160; anti-SSA, ×16. There was moderate lymphocytic infiltration into the lacrimal gland. He was diagnosed with SS, and topical 0.5% HPMC four times a day was added to his previous regimen of saline-based artificial tears, 1% chondroitin sulfate,
FIG. 2. Vital staining of the ocular surface. Vital staining with rose bengal and fluorescein significantly improved in SS. A: Rose bengal scores were 2.8 ± 1.6 in non-SS and 6.5 ± 2.2 in SS before treatment and 2.3 ± 2.8 (p > 0.05) in non-SS and 4.1 ± 2.5 (* * p < 0.01) in SS after treatment. B: Fluorescein scores were 3.9 ± 3.7 in non-SS and 6.8 ± 2.2 in SS before treatment and 2.1 ± 3.0 (p > 0.05) in non-SS and 2.6 ± 2.3 (** p < 0.01) in SS after treatment.

and use of eyeglasses with moisture inserts. After 1 month of treatment his symptoms significantly improved, with a total subjective score of 17 and a total score in the three major symptoms of 5. The vital staining scores dramatically improved, to 4/4 for rose bengal and 2/2 for fluorescein, and the filamentary keratitis totally disappeared (Fig. 4B). BUT was 2/2 s. The patient was very satisfied with 0.5% HPMC, which lessened the required frequency of instillation of artificial tears and enabled him to resume his usual work schedule.

TEROS40

TEROS40 significantly increased to 30 min after instillation of 0.5% HPMC, but not after 0.1% sodium hyaluronate or Softsantear, indicating that 0.5% HPMC remains on the ocular surface for a long time and maintains tear stability (Fig. 5).

Blocking Effect of Rose Bengal Cell Uptake

The conjunctival epithelial cells uncovered by 0.5% HPMC took up rose bengal in all four wells (Fig. 6A). In contrast, >90% of cells in all four wells preincubated with 0.5% HPMC did not take up the dye (Fig. 6B).

DISCUSSION

Although many different kinds of MC eye lubricants have been used to treat dry-eye patients, there have been very few studies (16,17) that showed the clinical efficacy of MCs. Moreover, there has been no report that specifically focused upon which type of dry eye is most responsive to
such treatment. In this study, we showed that 0.5% HPMC eyedrops markedly improved dry-eye signs and symptoms, especially in SS patients, who could not be stimulated to produce tears.

The ocular surface damage in SS dry eye is severe owing to poor protection by tear components. Aqueous tear substitutes are ineffective because of their short retention time on the eye. We found that 0.5% HPMC increased the TEROS40 for a longer time compared with 0.1% sodium hyaluronate or saline-based artificial tears (Softsantear), indicating that 0.5% HPMC remains on the ocular surface longer and maintains its wetness. This finding is in agreement with those of previous studies that examined BUT (26), argyrol marker (27), gamma scintigraphy (28), and fluorophotometry (15) to show that MCs prolong tear retention time. This prolongation may contribute to patients’ convenience by lessening the frequency of eyedrop use. Our patients used 0.5% HPMC drops only four times a day.

Preservatives are well known to adversely affect the corneal epithelium (29,30). Adams et al. evaluated the morphologic and physiologic effects of four commercially available artificial tears with or without preservatives and concluded that the preserved formulations caused more damage to the epithelial cells than did the unpreserved ones (31). Recently, unpreserved and single-unit artificial tears have been marketed, although there is no preservative-free 0.5% HPMC. Additives, such as benzalkonium chloride and edetate disodium, are more harmful to SS than non-SS dry-eye patients, since the latter can wash out these additives with stimulated tears. Furthermore, SS patients need to use artificial tears more often, which causes greater accumulation of additives. Even though unpreserved 0.5% HPMC is effective when used only four times per day, it may be safe for SS patients to use more drops if needed.

The benefits of 0.5% HPMC are less dramatic for non-SS dry-eye patients. The viscosity of 0.5% HPMC is ~4,000 cps, which may cause discomfort owing to stickiness and blurred vision (32). Non-SS patients may be more satisfied with conventional dry-eye treatments and thus have higher expectations for new drugs. Moreover, discomfort causes stimulated tearing, which only exacerbates the problem. Since 0.5% HPMC has more benefits than side effects for SS patients, they can more readily accept it. Indeed, even though the vital staining scores of SS patients after treatment were still higher than those of non-SS patients, there was greater improvement of symptoms in the former group. Some previous reports may have failed to confirm the efficacy of HPMC-based solutions (33).
FIG. 6. Rose bengal uptake by cultured conjunctival epithelial cells. A: Rose bengal was taken up by exposed conjunctival epithelial cells. B: When preincubated with 0.5% HPMC, rose bengal uptake was blocked.
because these studies probably recruited patients with non-SS dry eye in the initial stages of the disease. Selection of patients is important for both the objective and subjective success of HPMC therapy.

That 0.5% HPMC blocked rose bengal uptake by cultured human conjunctival epithelial cells suggests a mechanical effect similar to that of mucin. Feenstra and Tseng observed this blocking effect in cultured rabbit corneal epithelial cells using either 1% porcine stomach mucin or 1% CMC (18). Epithelial cells are protected from desiccation and exogenous stimuli by 0.5% HPMC. Although we did not measure how long 0.5% HPMC covers the epithelial cells, it may be at least several hours, because its use four times per day improved the rose bengal scores. Adhesion to cells apparently lasts longer than the 45 min after instillation of 0.5% HPMC because it takes the TEROS40 45 min to return to its initial level.

Several investigators have emphasized the advantage of anionic polymers (16,28), such as CMC, which are more bioadhesive than neutral polymers, such as HPMC. Grene et al. (16) compared two commercially available MC eyedrops—a 1% CMC-based solution (Celluvisc; Allergan) and a 0.3% HPMC-based solution (Tears Naturale II; Alcon)—and found that CMC was more beneficial. However, this study was limited because Tears Naturale II contains preservatives. The punctate keratitis of the dry-eye patients improved more during the first week in the Tear Naturale II group, but Celluvisc was more effective after 8 weeks of treatment. The reduced efficacy of Tears Naturale II may be due to preservatives.

Although there are benefits of anionic polymers, such as providing electrolytes that maintain ocular surface health (34), charged polymers may complex with metabolites or debris in tears and form insoluble precipitates (data from Alcon). These precipitates can be especially harmful in SS patients with poor tear clearance. Neutral polymers, such as HPMC, are highly water soluble and are less likely to form insoluble precipitates. This property of HPMC allows for a high viscosity in artificial tears, enhancing their stability on the ocular surface. However, high viscosity also produces discomfort. Although possibly thousands of formulations of eyedrops are made using various combinations of concentrations and types of MCs, viscosity should be carefully chosen based on both objective and subjective factors. Unfortunately, the behavior of MC solutions on the ocular surface does not always reflect their rheologic and biochemical properties in vitro or correlate with subjective acceptance (14).

In conclusion, preservative-free 0.5% HPMC, a new formulation of MC, improved the subjective scores and ocular surface damage of SS dry-eye patients. These effects may be explained by extended retention time, nonpreserved preparation, and the mechanical protection of epithelial cells. Since only severe types of dry eye without reflex tears responded well to this therapy, dry-eye patients with these symptoms are good candidates for this treatment.

REFERENCES