Comparison of Efficacy and Ocular Surface Toxicity of Topical Preservative-free Methylprednisolone and Preserved Prednisolone in the Treatment of Acute Anterior Uveitis

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Purpose: The aim of this study was to compare the antiinflammatory effect and ocular surface toxicity of topical nonpreserved methylprednisolone sodium succinate 1% and preserved prednisolone acetate suspension 1% for the management of acute anterior uveitis (AAU).

Methods: In this prospective, randomized, investigator-masked, comparative clinical trial, patients with mild-to-moderate noninfectious AAU were assigned randomly to receive either hourly nonpreserved methylprednisolone 1% (group A) or preserved prednisolone 1% (group B) eye drops followed by a 2-week tapering regimen. Anterior chamber cells and flare were clinically evaluated for the objective comparison of the antiinflammatory effect. The main outcome measure was the percentage of patients with a resolution of inflammation (anterior chamber cells $<$1+) on day 14. Ocular surface toxicity was assessed by means of the corneal fluorescein staining score, tear breakup time, Schirmer I test, and questionnaire-based grading of ocular discomfort parameters.

Results: Seventy-two eyes of 68 patients were studied, of which 38 eyes were enrolled in group A and 34 eyes were enrolled in group B. On day 14, 76.3% of the patients in group A had resolution of inflammation compared with 70.6% of the patients in group B, proving noninferiority ($\chi^2 = 0.303$, $P = 0.582$). The mean anterior chamber cell grade reduction for patients in group A was similar to that in group B (2.52 vs. 2.86, respectively; $P = 0.92$). Group A patients showed significantly lower corneal fluorescein staining scores ($P < 0.001$) and reported milder subjective ocular discomfort (0.55 vs. 1.43, $P = 0.01$) as compared with group B.

Conclusions: Both preparations demonstrated equal antiinflammatory effects for the treatment of AAU. Nonpreserved methylprednisolone eye drops exhibited a significantly lower ocular surface toxicity profile and milder subjective discomfort when compared with that exhibited by preserved prednisolone.

Key Words: clinical trial, inflammation, ocular surface, treatment medical

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Topical steroids are the standard treatment for noninfectious acute anterior uveitis (AAU). Current clinical practice emphasizes aggressive treatment to bring uveitis under control as rapidly as possible. With frequent topical eye drop instillation, ocular surface epitheliopathy related to preservatives in topical ophthalmic preparations is a major concern. The toxic action of preservatives on the ocular surface has been widely demonstrated in vitro and in vivo, in both humans and animals.[1] Besides, it was shown that the frequency of symptoms and objective signs of ocular surface irritation was higher with preserved eye drops than with preservative-free eye drops.[2] For the treatment to be effective, side effects need to be minimized to promote compliance and allow continuation of therapy.

Topical nonpreserved methylprednisolone has been used successfully to treat keratoconjunctivitis sicca associated with Sjögren syndrome.[3] As a nonpreserved preparation, it is proven to be a safe and effective treatment to improve subjective and objective dry eye factors in Sjögren syndrome.[4] Based on its well-documented, antiinflammatory, and safety profile, we conducted this study to evaluate the efficacy of this nonpreserved steroid preparation to treat AAU and compare its antiinflammatory and ocular surface toxicity with that of commercially available prednisolone acetate suspension 1%, which was used in several large clinical trials, as the comparator arm.[5–7]

MATERIALS AND METHODS

This prospective, randomized, investigator-masked, comparative clinical study was conducted from November 2011 to February 2013 at the Noor Eye Hospital, Tehran. The

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study protocol was approved and registered by the Iranian Registry of Clinical Trials (IRCT2012101511125N1) in accordance with the International Clinical Trials Registry Platform, which complied with the Declaration of Helsinki. Written informed consents were obtained from all the patients before enrollment in the study.

Patients with unilateral AAU and at least 2+ anterior chamber cells based on the Standardization of Uveitis Nomenclature (SUN) Working Group Classification were assigned randomly to receive either hourly nonpreserved methylprednisolone sodium succinate 1% (group A) or preserved prednisolone acetate 1% (group B) followed by a 2-week tapering regimen.[8] Eligibility criteria were age 16 years or older, attack duration less than a 1-week period, intraocular pressure (IOP) ≤21 mm Hg at presentation, and negative evidence for infectious (eg, corneal scars, iris atrophy) or granulomatous (eg, granulomatous keratic precipitate or iris nodule) inflammation. The following exclusion criteria were used: eyes with hypopyon or florid fibrin formation, previous unsuccessful topical treatment, known cases of Behçet disease, cases with evidence for the other causes attributable to their uveitis (eg, positive skin tuberculin test), any slit-lamp evidence of significant blepharitis or meibomian gland dysfunction, concomitant topical eye drops for chronic eye disease (eg, glaucoma medication, artificial tear), and the recent use of contact lenses.

At presentation, a detailed history of recent illness along with the course, treatment, and outcome of previous attack(s) was taken. Known cases of "idiopathic" or "HLA B_{27}-related" anterior uveitis that had experienced previous attack(s) were treated without further investigation. New cases with typical nongranulomatous AAU were checked only for HLA B_{27} positivity. Atypical cases underwent further investigation and were excluded, if positive clues for other attributable causes were found (eg, positive skin tuberculin test). Ocular examination, including a dilated fundus examination, was performed in a semidark room to classify the anatomic location and histopathologic type of inflammation. If the media opacity obscured funduscopy, B-scan ultrasonography assisted the clinician to rule out vitreous involvement. Optical coherence tomography was obtained when macular edema was suspected. Ocular inflammatory parameters (anterior chamber cell and flare) and corneal toxicity and tear film stability indices [corneal fluorescein staining scores, fluorescein tear breakup time (TBUT), and Schirmer I test] were determined. The IOP was measured by Goldman applanation tonometry at the end of the examination. At each follow-up visit (weeks 1 and 2), in addition to the above-mentioned examination and measurement, a questionnaire-based grading system was used to evaluate the amount of subjective discomfort experienced by patient. The questionnaire is in the following section named "measurements of subjective ocular discomfort."

Randomization and Study Medications

In this prospective, randomized, investigator-masked, comparative study, the eyes of qualified patients were assigned in a 1:1 ratio to 1 of the treatment groups using the balanced blocked randomization method. The study medications were nonpreserved methylprednisolone sodium succinate 1% (group A) or preserved prednisolone acetate suspension 1% (group B). The preserved prednisolone (Pred Forte 1%, Allergan, Inc) eye drops contain benzalkonium chloride (BAC) 0.004%. A topical solution of nonpreserved methylprednisolone was prepared by the Laboratory of the Noor Eye Hospital by diluting intravenous methylprednisolone sodium succinate in sterile balanced salt solution to final concentrations of 1%. The process was performed under clean conditions of a laminar hood, and the solution was filtered through a 0.2-μm cellulose acetate filter papers. The patients were dispensed bottles containing 10 mL of the steroid solution and were asked to keep these refrigerated and to discard these after 4 weeks. The patients were instructed to instil 1 drop of study medications hourly in the affected eyes for the first 72 hours and then every 2 hours for the rest of the week. During sleep time, betamethasone 0.1% topical ointment (Betamethasone, preservative: BAC 0.004%; Sina-Darou Pharmaceutical Co, Tehran, Iran) was applied instead of eye drops. Homatropine 2% eye drops (Homydrin, preservative: BAC 0.004%; Sina-Darou Pharmaceutical Co) were prescribed for all the patients every 8 hours. The patients were instructed to come back to the clinic immediately if their symptoms aggravated. Except for the coordinator distributing the study medications, all the investigators remained blinded to the allocation throughout the entire study. The participants were not masked because of ethical and feasibility constraints.

At the first-week follow-up visit, the patients who did not improve clinically (at least a 2-step reduction of anterior chamber cell grade) were considered "refractory to topical treatment," and an additional regional steroid injection or oral prednisolone was given to them. The refractory to topical treatment cases were considered as part of treatment failure and were treated by preserved prednisolone eye drops for the rest of the study. Patients with a good response in the first week of treatment were encouraged to continue the eye drops in a tapering regimen according to clinical response. All the patients were visited again 2 weeks after the treatment to evaluate the success of the treatment. Successful treatment was defined as aqueous cells equal or less than grade 1. Treatment failure includes cases that did not fulfill the 2-week endpoint goal together with refractory to topical treatment cases.

Measurements of Inflammatory Parameters

Anterior Chamber Cell

The intensity of the cellular reaction in the anterior chamber was assessed based on the number of inflammatory cells seen in a 1- × 1-mm full intensity beam at 45 to 60 degrees and were graded according to the SUN Working Group Classification.

Anterior Chamber Flare

Anterior chamber flare was assessed using the laser flare photometer (FM-600; Kowa, Tokyo, Japan). Seven consecutive laser flare readings at the lower third of the anterior chamber were obtained, with a background scatter

of <20%. The highest and lowest readings were discarded, and the remaining 5 were averaged to obtain the flare measurement.

Measurements of Corneal Toxicity and Tear Film Stability Indices

Fluorescein Tear Breakup Time

The fluorescein TBUT was measured as follows: 2 μL of fluorescein solution 1% was instilled in a lower cul-de-sac using a micropipette. The patient was instructed to blink several times to distribute the fluorescein evenly on the corneal surface. The patient was then asked to stare directly ahead without blinking. The tear film was examined under blue light illumination of a biomicroscope, and any breakup of the tear film was noted. A digital timer recorded the time from the blink until a dark spot appeared in the tear fluorescein layer.

Corneal Fluorescein Staining Scores

After the instillation of fluorescein solution and measurement of TBUT, corneal fluorescein staining was scored according to the protocol described by Shimmura et al.[9] The cornea was divided into 3 equal areas of upper, middle, and inferior compartments and examined by means of a slit lamp using blue light illumination. Based on the number and extent of punctate epithelial erosions visible, each compartment was graded on a scale of 0 (no staining) to 3 points (intense staining) with a maximum staining score of 9 points for each cornea examined.

Schirmer I Test

Tear production was determined by the Schirmer I test. The Schirmer test was performed after corneal staining, because it may affect the staining pattern of the cornea with fluorescein. The eye was anesthetized by instilling 1 drop of tetracaine hydrochloride 0.5% (Anestocaine 0.5%, preservative: BAC 0.004%; Sina-Darou Pharm Co). A standard filter paper strip was placed inside the margin of the inferolateral third of the lower eyelid, taking care to prevent the paper from contacting the cornea. After 5 minutes, the level of strip wetting (in millimeters) was measured.

Measurements of Subjective Ocular Discomfort

This parameter was evaluated before the slit-lamp examination and consisted of questioning about (1) discomfort or pain upon the instillation of eye drops; (2) stinging or burning sensation between instillations of eye drops; (3) foreign body or gritty sensation; and (4) tearing. Each parameter was scored by the patient as follows: 0, absent; 1, mild; 2, moderate (patient continued using eye drops); and 3, intolerable (the patient stopped using eye drops). Subjective discomfort score was determined by the summation of the scores given to each question (min = 0, max = 12).

Safety Parameter

The IOP was measured as the last step in the examination using applanation tonometry, and the values were recorded in millimeters of mercury.

Statistical Analysis

Quantitative variables were expressed as the mean, standard deviation, and confidence interval. Statistical testing of the noninferiority hypothesis was based on 95% confidence intervals on the parameter of interest. The repeated measures analysis of variance was used to check quantitative variables for changes over time. The independent sample t test was used for testing quantitative variables, and the χ^2 test was applied for qualitative variables. $P < 0.05$ was considered statistically significant.

RESULTS

Of the 78 eligible eyes (74 patients) enrolled, 40 and 38 eyes were randomly assigned to the preservative-free methylprednisolone (group A) and preserved prednisolone (group B) treatment groups, respectively. Two patients in group A and 4 in the group B did not complete the study because of protocol violation or were lost to follow-up (Fig. 1). The demographic profile of the patients is shown in Table 1.

In the first week of follow-up, 7 of 38 cases in group A (18.4%) and 6 of 34 patients (17.6%) in group B were withdrawn because the investigator determined that the patients were refractory to topical treatment (anterior chamber cell grade improvement was less than a 2-step reduction), and an additional regional steroid injection or oral prednisolone was required for them ($\chi^2 = 0.007$, $P = 0.932$). At the second-week follow-up visit, 29 of the 38 patients (76.3%) in group A and 24 of the 34 patients (70.6%) in group B had an anterior chamber cell grade equal or less than grade 1 ($\chi^2 = 0.303$, $P = 0.582$). This proves noninferiority of methylprednisolone therapy for achieving a resolution of inflammation as the endpoint goal in this study.

Measurements of Inflammatory Parameter

Anterior Chamber Cells

For the individual treatment groups, there was a significant reduction of the mean anterior chamber cell grades from baseline to the first and second follow-up weeks (Fig. 2). Mean anterior chamber cell grades were not significantly different between the 2 groups ($P = 0.60$ and $P = 0.88$; at the first- and second-week follow-up visits, respectively). On day 14, the mean anterior chamber cell grade improvement for group A was similar to that for group B (2.52 vs. 2.86, respectively; $P = 0.092$), proving noninferiority.

Anterior Chamber Flare

The reduction in flare values on day 14 was comparable between groups A and B (188.4 vs. 240.1 respectively; $P = 0.141$). At baseline and during the follow-up, there was no significant difference between the treatment groups concerning mean flare values ($P = 0.19$, $P = 0.60$, and $P = 0.56$ at

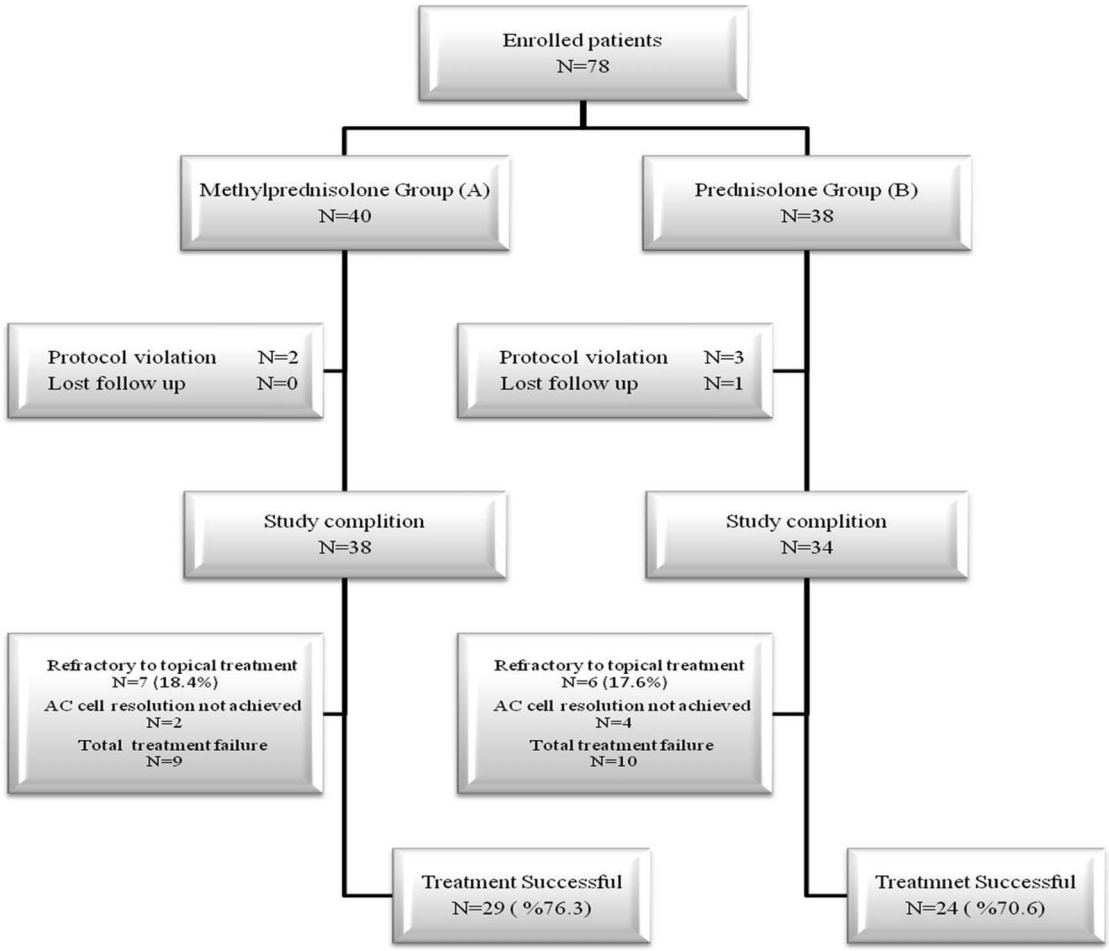

FIGURE 1. Randomization and allocation schema and treatment outcome in group A (nonpreserved methylprednisolone) and in group B (preserved prednisolone).

baseline and at the first and second weeks, respectively). Within individual groups, the flare values showed a significant decrease at each follow-up visit (Fig. 2).

Measurements of Corneal Toxicity and Tear Film Stability Indices

Corneal Fluorescein Staining Scores

Before treatment, the fluorescein staining score was not different between the 2 groups (1.38 vs.1.29, $P = 0.82$). The scores remained relatively stable in group A, whereas these increased in group B over follow-up time (Fig. 3). The preserved prednisolone group showed significantly higher values in posttreatment visits compared with the nonpreserved methylprednisolone group (1.67 vs. 2.65, $P = 0.02$ and 1.81 vs. 3.54, $P < 0.001$ at 1 and 2 weeks, respectively).

Schirmer I Test

The Schirmer strip wetting length (in millimeters) decreased in the first and second follow-up times in both the groups (Fig. 4). The Schirmer score was not different at baseline and posttreatment visits between the 2 treatment groups ($P = 0.64$, $P = 0.12$, and $P = 0.93$ at baseline and at the first and second weeks, respectively).

Fluorescein TBUT

The subjects in both the groups had a higher mean fluorescein TBUT at pretreatment compared with that at the first and second posttreatment visits, but the difference was not statistically significant (Fig. 4). Between groups, the mean fluorescein TBUT was not different at baseline or at the follow-up visit ($P = 0.22$, $P = 0.50$, and $P = 0.65$ at baseline and at the first and second weeks, respectively).

Measurements of Subjective Ocular Discomfort

In the group of subjects receiving preservative-free methylprednisolone, the scores for subjective discomfort decreased, whereas the subjects using preserved prednisolone eye drops experienced increased scores from the first to the second week of the follow-up (Fig. 3). At the second-week follow-up visit, preservative-free methylprednisolone-treated patients reported a significantly lower subjective discomfort compared with that of the control group (0.55 vs.1.43, $P = 0.01$).

TABLE 1. Patient Demographics and Clinical Profiles at Baseline in Groups A and B

	Methylprednisolone (Group A)	Prednisolone (Group B)
Mean age (range), yrs	41.2 (16–63)	36.4 (20–52)
Gender		
Male, %	78.9	70.6
Total number of episodes (mean)	2.4	3.6
Interval between the beginning of the attack and entering into the study (mean days)	4.7	4.4
Days received topical medication before entering into the study (mean)	2.1	1.9
Percent of HLA_{27} positivity, %	18.4	29.4
Baseline inflammatory parameter		
Mean anterior chamber flare, ph/ms	210.8	267.2
Mean anterior chamber cells	3.38	3.65
Baseline corneal irritation and tear film stability parameters		
Corneal fluorescein staining scores (mean)	1.38	1.29
Fluorescein TBUT (mean), s	17.5	16.2
Schirmer strip wetting length (mean), mm	14.4	13.2
Mean baseline IOP ± SD, mm Hg	11.7 ± 3.3	11.1 ± 3.9

ph/ms, photons per millisecond.

Safety Parameters

Intraocular Pressure

The IOP of the 2 patients in group A and 1 patient in group B started rising during the first 2 weeks of treatment but did not exceed 21 mm Hg, and none of them required antiglaucoma medication. The difference in the IOP was not significant between groups A and B at the follow-up visits (Fig. 5).

DISCUSSION

In humans, interesting experimental studies have shown deleterious effects of preservatives after the use of antiglaucoma preserved eye drops, but there are few studies, if any, to compare preserved and unpreserved steroid solutions for the treatment of anterior uveitis.[10–12] Our preliminary experience with the successful use of nonpreserved topical methylprednisolone for the treatment of noninfectious anterior uveitis encouraged us to conduct this study to evaluate and compare its antiinflammatory effect and ocular surface toxicity profile with prednisolone acetate suspension 1% as the standard care for AAU.

In our study, nonpreserved methylprednisolone 1% was found to be noninferior to prednisolone acetate 1% for the treatment of noninfectious AAU with comparable results for multiple objective efficacy endpoints. On the basis of an analysis of the means, the results for patients on methylprednisolone were equivalent to those on prednisolone acetate at the same dosing frequency.

The preserved prednisolone eye drops used in our study contain BAC, a quaternary ammonium compound that is the most commonly used preservative in topical ophthalmic preparations. BAC has been demonstrated to have adverse effects on the cornea and conjunctiva.[1,13] Three mechanisms of BAC toxicity have been described: a detergent effect, causing loss of tear film stability; direct damage to the corneal and conjunctival epithelium; and immunoallergic reaction.[13]

Our results showed that corneal fluorescein staining scores, which reflect the extent of punctuate epithelial erosion, were significantly lower in the preservative-free methylprednisolone group than in the control group. However, patients treated with preservative-free eye drops experienced less subjective discomfort during the follow-up examination when compared with preserved prednisolone. In fact, a steady increase in the corneal fluorescein staining and subjective discomfort scores was found when applying the preservative eye drops, but this was only minimal for the preservative-free eye drops.

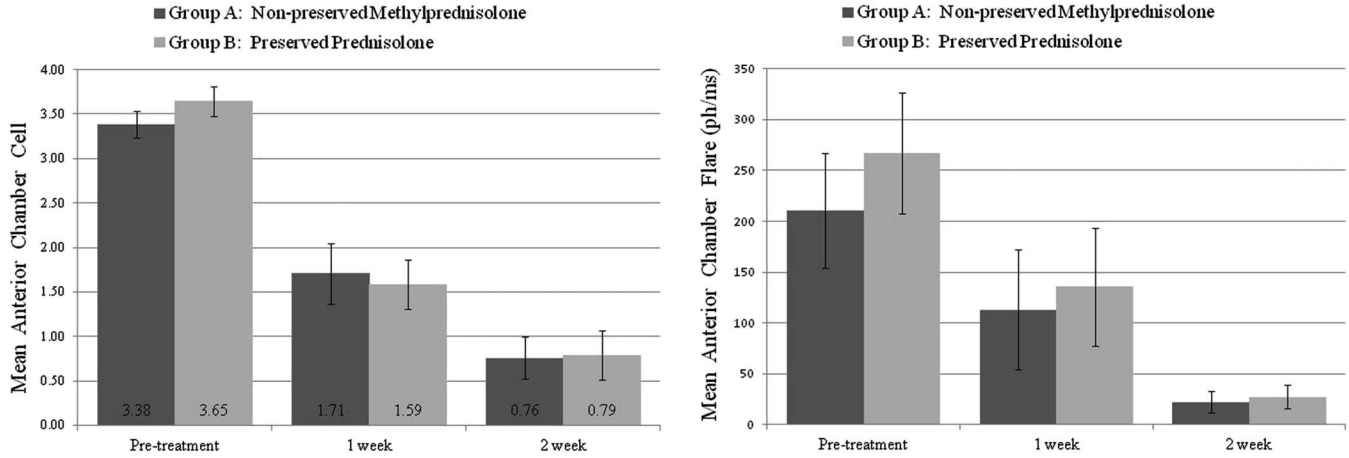

FIGURE 2. Mean anterior chamber cell (left) and flare (right) with the corresponding error bar depicting the 95% confidence interval before the treatment and 1 and 2 weeks after the treatment in groups A and B. ph/ms, photons per millisecond.

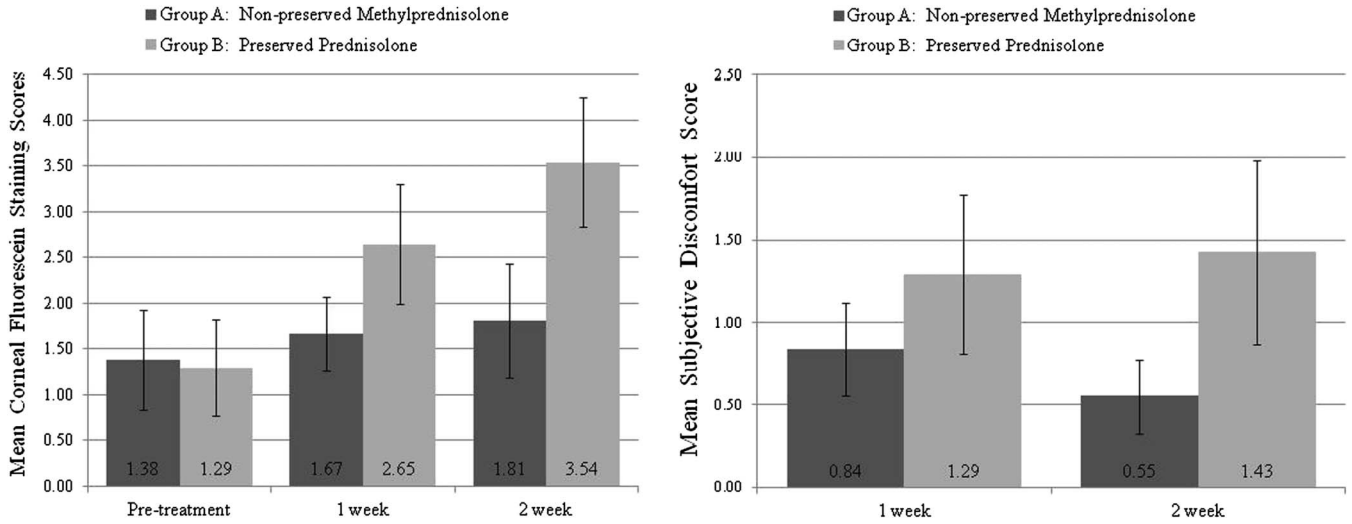

FIGURE 3. Mean corneal fluorescein staining scores before the treatment and 1 and 2 weeks after the treatment in groups A and B (left). Mean subjective discomfort score 1 and 2 weeks after the treatment in groups A and B (right). The corresponding error bars depict the 95% confidence interval.

In addition to the induction of punctuate epithelial erosion, the reduction in tear production and shortening of the TBUT are other parameters that could potentially reflect the toxic effects of BAC on the ocular surface.[14–16] In our study, the shortening of the TBUT did not show statistically significant differences between the preservative and preservative-free medication groups. This fact could be explained by a short period of treatment, which was probably not long enough for the preservative to induce measurable changes on tear structure.

Basic tear production (as measured by the Schirmer test) was not different in the preservative and preservative-free groups as well. Tearing during the acute stage of inflammation may play a confounding role for the assessment of the amount of basic tear production. It was expected that by a resolution of inflammation, the amount of tearing would decrease, which was shown by a significantly shorter length of the Schirmer strip wetting in the first and second weeks compared with that in the pretreatment state in both groups.

Pflugfelder et al reported that only 1 of their 21 patients receiving topical nonpreserved methylprednisolone had an increased IOP at 3 months while treating their dry eye condition. Although the patients in our study received a more frequent regimen of steroid treatment, we did not observe any significant rise in the IOP that necessitated antiglaucoma medication, which is assumed to be the result of both the short duration of treatment and a lower secretion of aqueous during inflammation.

Although several clinical trials have compared different preserved topical steroid preparations for the treatment of anterior uveitis,[6,17–19] this is the first study that evaluates and

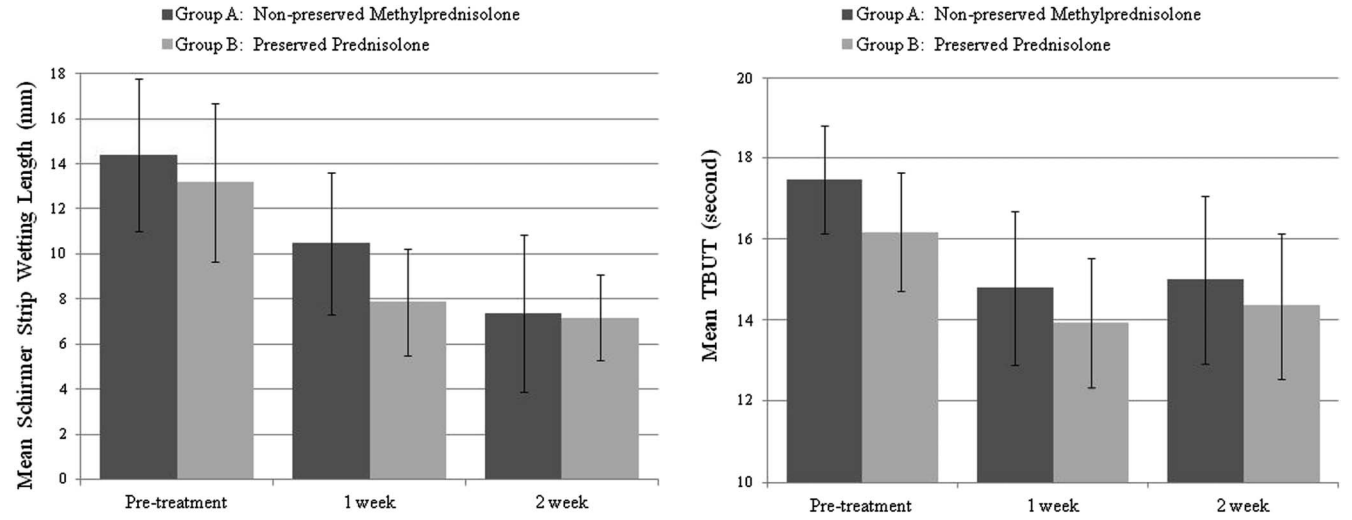

FIGURE 4. Mean Schirmer strip wetting length (left) and TBUT (right) with the corresponding error bar depicting the 95% confidence interval before the treatment and 1 and 2 weeks after the treatment in groups A and B.

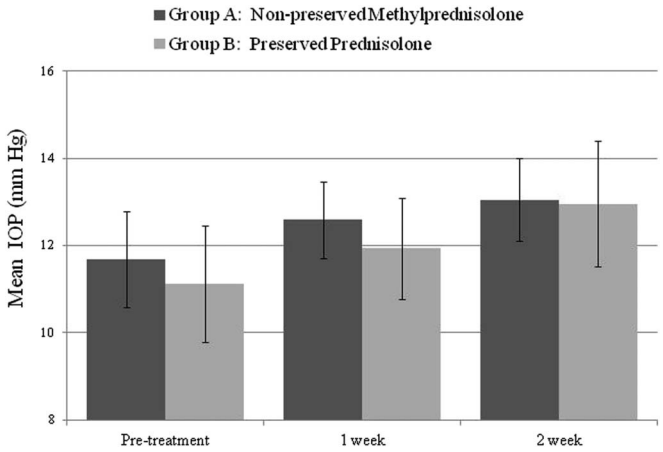

FIGURE 5. The mean IOP and the corresponding error bar depicting the 95% confidence interval before the treatment and 1 and 2 weeks after the treatment in groups A and B.

compares the efficacy and safety profile of nonpreserved methylprednisolone topical treatment. The strengths of this study include its rather uniform target population and the use of robust methods for ascertaining clinical outcomes. We only included patients with pure anterior uveitis (idiopathic and HLA B_{27} related) to provide a more uniform population for comparison. Besides, patients with severe inflammation (including patients with hypopyon or fibrin formation) and those who did not respond to topical treatment in previous episodes were excluded because it was deemed unethical to subject them to a treatment regimen that is most likely not effective. Moreover, the trial was conducted in 1 center, and all observations were made by 1 investigator and measurement devices were similar for all the participants.

As in other clinical studies, there are some limitations with our study that should be addressed: First, the sample size is rather small. This is a direct consequence of using restricted inclusion/exclusion criteria for entering into the study. Second, more HLA B_{27} positive patients were allocated in the prednisolone group than in the methylprednisolone group (29.4% vs. 18.4%). This may potentially cause a more severe and more resistant kind of anterior uveitis in the prednisolone-treated group. However, because we have already excluded cases with severe inflammation at presentation, this difference may barely affect our results. Finally, our patients were not masked to the treatment group they had been randomized to and were aware of which medication they were using. Because the study only looks at patients with mild-to-moderate disease, patients with severe disease should be evaluated in future studies, because these are the patients who might benefit the most from preservative-free treatment.

In conclusion, preservative-free methylprednisolone 1% preparation was shown to be at least as effective as prednisolone acetonide 1% suspension in resolving the inflammation associated with mild-to-moderate noninfectious AAU with less corneal toxicity and lower subjective discomfort.

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