



Add-on therapy with different non-steroidal anti-inflammatory agents in the management of non-infectious, non-necrotizing episcleritis

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ABSTRACT

Background: Episcleritis is a common ocular inflammatory disease that can cause red eye. It is usually managed using single or combined topical corticosteroids and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) as directed by clinical response. However, recurrence is possible. This study aimed to compare the effects of add-on therapies using different topical NSAIDs in the management of treatment-naïve, non-infectious, non-necrotizing episcleritis.

Methods: Seventy-five eyes of 75 patients with non-infectious, non-necrotizing unilateral episcleritis were included in this study. Patients were allocated to one of three groups based on the NSAID used as add-on therapy: topical diclofenac sodium 0.1% (group D), topical nepafenac 0.1% (group N1), and topical nepafenac 0.3% (group N3). The time to symptom disappearance was defined as the recovery time.

Results: There were no statistically significant differences in age, sex, initial best-corrected distance visual acuity, and intraocular pressure between groups (all $P > 0.05$). The mean recovery times of groups D and N1 were comparable (12.86 ± 5.35 days and 11.45 ± 5.42 days, respectively) ($P > 0.05$). However, the mean recovery time of group N3 was significantly shorter (9.70 ± 3.80 days, $P < 0.05$). Recurrence was observed in only one patient in group N1 at 3 months, and symptoms resolved when the same medication was reinstated. Furthermore, we noted no side effects during the follow-up period for any of the treatment modalities.

Conclusions: All three topical NSAIDs were effective add-on therapies in the management of non-infectious, non-necrotizing unilateral episcleritis. However, once-daily administration of topical nepafenac 0.3% had a shorter recovery time than topical diclofenac 0.1% and topical nepafenac 0.1%.

KEY WORDS

Anti-inflammatory agents, episcleritis, non-infectious, non-necrotizing, ocular surface, red eye, treatment

INTRODUCTION


Episcleritis is a common, usually idiopathic, acute, benign, and recurrent condition that more often affects young to middle-aged women. Typically, it is self-limiting and presents as diffuse, sectoral, or nodular episcleral inflammation. Clinical manifestations of episcleritis include eye tenderness or mild pain with no photophobia or reduced visual acuity [1]. According to the modified Honik criteria, episcleritis is characterized by superficial

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venous injection with minimal pain and tenderness. Scleritis is another form of scleral inflammation; episcleritis is typically superficial and benign, while scleritis is usually more severe with inflammation extending into the deep scleral layer [2].

There are four criteria for the diagnosis of scleritis. These include (1) injection of vessels with dark red or violet hue, (2) severe pain that interferes with sleep or is associated with marked tenderness on palpation, (3) no bleaching of veins when 2.5% or 10% phenylephrine is instilled, and (4) persistent active inflammation during at least one month of follow-up after initial presentation, or sudden relapse after discontinuation of treatment. Scleritis is diagnosed in the presence of at least three of these criteria [2]. To differentiate episcleritis from scleritis, instillation of one drop of 10% phenylephrine causes vasoconstriction of the superficial vessels, conjunctival and episcleral vessels, within a few seconds and at maximum effect in 1 min, without affecting the deep episcleral plexus. As a result, episcleritic hyperemia is eliminated, but scleritic hyperemia persists [3].

In epidemiological studies, the overall incidence of episcleritis was 41 per 100,000 people, with an annual prevalence of 52.6 per 100,000 people. In addition, this disease was more common among older adults and women [4]. In another study, the incidence of scleritis was found to be 4.1 per 100,000 people, and the incidence of episcleritis was 21.7 per 100,000 [5]. Episcleritis is usually managed using single or combined topical corticosteroids or topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), as determined by clinical response [1]. However, recurrence is possible [6, 7].

This study aimed to compare the effectiveness of three different topical NSAIDs as add-on therapy for non-infectious, non-necrotizing, treatment-naive episcleritis, based on rates of resolution and recurrence.

METHODS

This open-label, comparative, interventional study included 75 eyes of 75 patients with non-infectious, non-necrotizing, unilateral episcleritis. This study was approved by the Rize Training and Research Hospital Clinical Research Ethics Committee (17/Feb/2022-28). Written informed consent was obtained from all patients, and the principles of the Declaration of Helsinki were adhered to throughout this study.

All participants demonstrated the typical clinical features of episcleritis, with nodular or diffuse episcleral injection with or without overlying conjunctival injection. Therefore, further systemic investigations were deemed unnecessary. The inclusion criteria were as follows: 1) age over 18 years, 2) no previous episodes of episcleritis, 3) no previous ocular surgery, 4) non-smoking, 5) no NSAID use, for any reason, before and during treatment, 6) no history of atopy, known bowel disease, or inflammatory joint disease. Patients with bilateral episcleritis, intestinal discomfort, morning joint stiffness, joint pain, NSAID allergy, scleral involvement, other ocular pathologies, use of topical eye drops for another disease, other known systemic diseases, and contact lens users were excluded from this study. All included patients with episcleritis were treatment-naive.

The patients were allocated to one of three equal subgroups based on sex distribution. All patients received oral diclofenac sodium 100 mg (Voltaren® Retard, Novartis Pharma AG, Basel, Switzerland) three times a day, artificial tears (Refresh® single-dose, Allergan, Westport, Ireland) hourly, and eye drops containing loteprednol acetate (0.5%) (Lotemax®, Bausch & Lomb Inc., Florida, USA) four times a day. Additionally, they received one of three topical NSAID treatments. Of the 75 patients, 67 (89.3%) had diffuse episcleritis and 8 (10.7%) had nodular episcleritis. As the success of treatment was determined by the disappearance of symptoms, the severity of the initial symptoms was not classified. Treatment responses were evaluated weekly until symptom resolution, with a total follow-up period of 3 months. The time to symptom disappearance was defined as the recovery time.

All patients underwent complete ophthalmological examination, measurement of best-corrected distance visual acuity (BCDVA) using a Snellen chart (auto chart projector ACP-8; Topcon Corporation, Tokyo, Japan), intraocular pressure (IOP) measurement using a Goldmann applanation tonometer (AT900, Haag-Streit, Koeniz, Switzerland), and undilated and dilated slit-lamp biomicroscopy examination (Photo-Slit Lamp BX 900; Nidek Co., Ltd, Gamagori, Japan). All participants were examined by two ophthalmologists (O. O. and M. L. T.) on the same day.

Eligible participants were allocated to one of three subgroups according to the add-on therapy administered. Patients in group D received topical diclofenac sodium 0.1% (Inflased®, Bilim Ilac, Istanbul, Turkey) four times a day, those in group N1 received topical nepafenac 0.1% (Nevanac®, Alcon Couvreur, Puurs, Belgium) three times a day, and those in group N3 received topical nepafenac 0.3% (Apfecto®, World Medicine, Istanbul, Turkey) once a day as add-on therapy. This treatment protocol was developed and scheduled based on the clinical experience of the authors.

When starting treatment, we advised patients to return earlier than the scheduled follow-up if symptoms worsened. During treatment, the patients were examined weekly until episcleritis resolved. At each follow-up

visit, we performed a complete ophthalmological examination and evaluated the IOP and state of the corneal epithelium. Ten days after complete disappearance of symptoms, treatment was tapered and discontinued. Based on the study protocol, systemic examination, consultation with the Department of Rheumatology, and addition of oral corticosteroid administration were planned for patients not responding to treatment and/or whose symptoms worsened despite treatment; however, no patient required these arrangements during follow-up.

All collected data were analyzed using IBM SPSS Statistics for Windows (version 23.0; IBM Corp., Armonk, NY, USA). Normality of distribution of continuous variables was determined using the Shapiro–Wilk test. Continuous variables are presented as means \pm standard deviations. The Student's t-test was used to compare the means of two independent groups with normally distributed variables. The means of more than two independent groups were compared using analysis of variance (ANOVA). The means of independent groups of variables without normal distribution were compared using the Kruskal–Wallis method. Categorical variables are expressed as numbers and percentages. The relationships between categorical variables were analyzed using the chi-squared test. Statistical significance was set at $P < 0.05$.

RESULTS

Of the 75 patients with unilateral episcleritis, 25 were allocated to each treatment group, and all were followed until complete recovery. The mean age of patients in group D was 36.3 ± 7.4 years; 11 (44%) were men, and 14 (56%) were women. In group N1, the mean age was 33.2 ± 5.7 years; 12 (48%) were men, and 13 (52%) were women. In group N3, the mean age was 34.9 ± 5.1 years; 11 (44%) were men, and 14 (56%) were women. **Table 1** presents the baseline data and treatment responses of the study participants. There were no statistically significant differences in age, sex, laterality of involvement, initial BCDVA, and IOP between the three groups (all $P > 0.05$) (**Table 1**).

The mean recovery time was not significantly different between groups D and N1 (12.86 ± 5.35 days and 11.45 ± 5.42 days, respectively) ($P > 0.05$). However, for group N3, the mean recovery time was significantly shorter (9.70 ± 3.80 days, $P < 0.05$). Recurrence was seen in only one patient in group N1 at the 3-month follow-up examination, and symptoms disappeared when the same drug treatment was reinstated. Nevertheless, no statistically significant difference was observed in the recurrence rate at the final follow-up between the treatment groups ($P > 0.05$). We noted no treatment-related side effects during the follow-up period for any of the three topical treatments (**Table 1**).

DISCUSSION

To our knowledge, this is the first study to compare the effects of three different topical NSAID add-on therapies on the resolution and recurrence of non-infectious, non-necrotizing, treatment-naïve episcleritis. The recovery time was not significantly different between topical diclofenac 0.1% and topical nepafenac 0.1%; however, for topical nepafenac 0.3%, the mean recovery time was significantly shorter. No significant difference was observed in the recurrence rate; symptoms recurred in only one patient in group N1 and resolved when the same drug treatment was reinstated. No treatment-related side effects were documented during the 3-month follow-up.

Considering the vision-threatening side effects of topical steroids, such as cataracts and increased IOP [8–10],

Table 1. Baseline data and treatment responses of the study participants

Variable	Group D (n = 25)	Group N1 (n = 25)	Group N3 (n = 25)	P-value
Age (y), Mean \pm SD (Range)	36.3 \pm 7.4 (18–61)	33.2 \pm 5.7 (16–55)	34.9 \pm 5.1 (21–57)	0.204
Sex (Male/Female), n (%)	11 (44) / 14 (56)	12 (48) / 13 (52)	11 (44) / 14 (56)	0.948
BCDVA (Snellen), Mean \pm SD	0.86 \pm 0.13	0.89 \pm 0.11	0.88 \pm 0.13	0.355
IOP (mmHg), Mean \pm SD	14.7 \pm 2.5	13.6 \pm 2.4	14.8 \pm 2.6	0.079
Right eye / Left eye, n (%)	16 (64) / 9 (36)	8 (32) / 17 (68)	11 (44) / 14 (56)	0.073
Recovery time (days), Mean \pm SD	12.86 \pm 5.35	11.45 \pm 5.42	9.70 \pm 3.80	0.021
Recurrence, n (%)	0 (0)	1 (4)	0 (0)	0.363
Treatment-related side effects, n (%)	0 (0)	0 (0)	0 (0)	1.000

Abbreviations: n, number; y, years; SD, standard deviation; BCDVA, best-corrected distance visual acuity; mmHg, millimeters of mercury. Note: Group D, topical diclofenac sodium 0.1% (Inflased[®], Bilim Ilac, Istanbul, Turkey) four times a day was administered; Group N1, topical nepafenac 0.1% (Nevanac[®], Alcon Couvreur, Puurs, Belgium) three times a day was administered; Group N3, topical nepafenac 0.3% (Apfecto[®], World Medicine, Istanbul, Turkey) once a day was administered.

steroid-sparing treatments are a viable and safe alternative to corticosteroids in treating episcleritis, although symptoms can recur despite treatment [6, 7]. We found that combined oral and topical NSAID treatment regimens were safe and effective for the management of non-infectious treatment-naïve unilateral episcleritis.

Smoking is known to affect treatment response in ocular diseases [11, 12]. A retrospective review of 2,676 patients with active ocular inflammation revealed that smoking increases the possibility of bilateral ocular inflammation and reduced visual acuity upon presentation, and it increases the risk of recurrence [13]. In a study of 103 patients with either episcleritis or scleritis, patients who smoked during treatment required more intensive treatment than did non-smokers [14]. Therefore, smokers were excluded from the present study. Perhaps a reason for the complete recovery of the patients in almost two weeks, with nearly no recurrence in 3 months of follow-up, was that our patients had never smoked.

In a study by Williams et al. involving 38 eyes, topical ketorolac and artificial tears were compared in the treatment of episcleritis. No statistical difference was found in the post-treatment status of patients with similar baseline symptoms [15]. In our study, all patients were taking artificial tears and topical or oral NSAIDs. Studies have revealed that concurrent administration of topical and systemic agents has a synergistic effect, resulting in more rapid resolution of some ocular diseases [16, 17]. Therefore, we believe that the use of systemic drugs increases the success of episcleritis treatment because of this synergistic effect. However, the main purpose of our study was to compare the efficacies of three different topical NSAIDs. To obtain more precise results, studies of different combinations of drug groups with different routes of administration are needed to confirm synergistic effects.

In a 12-year follow-up study by Jabs et al., fluoromethalone 1% was administered to all patients with episcleritis, and more potent steroids were used in cases of poor treatment response. Oral indomethacin was administered if symptoms remained refractory [18]. Oral NSAIDs were used in 16.7% of patients in the study. Although it included a relatively small number of patients, topical corticosteroid therapy was inadequate in a significant proportion of patients when used alone [18]. In the treatment protocol of the current study, almost all patients recovered. In addition, none of the patients required potent corticosteroid eye drop therapy. No NSAID-related side effects were observed in any patient.

In a study by Kolomeyer et al., selective ($n = 37$) or non-selective ($n = 32$) cyclooxygenase (COX) inhibitors were administered to 69 patients for the treatment of scleritis or episcleritis. Additional oral corticosteroids were administered to 17 patients (24.6%) whose symptoms did not regress with this treatment protocol. After the symptoms resolved, the dose was tapered [19]. One may infer that oral treatment alone led to relatively low success rates in that study [19]. In our treatment protocol, topical drugs were administered in addition to oral NSAIDs. The treatment responses were good for all three topical NSAIDs subgroups. Therefore, topical eye drops should be considered as an add-on therapy when designing a treatment protocol.

In our study, all patients received oral diclofenac sodium as a standard. Although all three additional topical NSAIDs provided relief of symptoms, the shortest recovery time was noted in the group treated with topical nepafenac 0.3%. Studies comparing nepafenac 0.1% to nepafenac 0.3% demonstrated equal efficacy, with a slightly increased side effect rate with the 0.3% formulation [20]. The present study showed greater effectiveness of topical nepafenac 0.3% compared to topical diclofenac sodium 0.1% and topical nepafenac 0.1%, while none caused side effects up to the 3-month follow-up. Future studies with robust design, such as head-to-head clinical trials, may resolve this discrepancy between the results of the present study and those of previous studies.

This is the first study to compare the add-on effects of three topical NSAIDs on symptoms of episcleritis. Our proposed protocol was beneficial, especially in providing effective and safe treatment. Formulations that facilitate patient compliance could be useful as other options. However, limitations of the study include the relatively small number of patients and the absence of a patient group administered other oral NSAIDs. We failed to document indicators of disease severity, such as episcleral injection and the number of clock hours affected at baseline and follow-up examinations, because we defined treatment success as the resolution of all symptoms and signs. In future studies, documenting the subjective pain and redness scores, intensity of episcleral injection, and the area of episcleral injection measured as the number of clock hours affected at both baseline and follow-up could better determine the effectiveness of topical NSAIDs as add-on therapy in the management of episcleritis. To achieve more precise and reliable results, studies with different treatment protocols in a larger population are needed.

CONCLUSIONS

All three topical NSAIDs in this study were effective and safe for the management of non-infectious, non-necrotizing unilateral episcleritis. However, once-daily administration of topical nepafenac 0.3% produced a shorter recovery time than topical diclofenac 0.1% or topical nepafenac 0.1%.

ETHICAL DECLARATIONS

Ethical approval: This study was approved by the Rize Training and Research Hospital Clinical Research Ethics Committee (17/Feb/2022-28). Written informed consent was obtained from all patients in this study, and the principles of the Declaration of Helsinki were adhered to throughout the study.

Conflict of interests: None

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