RESEARCH PAPER

Cryotherapy versus Topical Corticosteroid Eye Drop versus Topical Non-Steroidal Anti-Inflammatory Eye Drop in Management of Moderate Cases of Vernal Keratoconjunctivitis

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ABSTRACT
Background: Vernal keratoconjunctivitis (VKC) is a chronic, recurrent allergic ocular illness that might result in corneal complications and vision loss. Various treatment options exist, but the optimal management strategy for moderate cases remains unclear. The purpose of this research is to compare the effectiveness and safety of cryotherapy, topical corticosteroid eye drops, and topical non-steroidal anti-inflammatory eye drops (NSAIDs) in the treatment of moderate VKC. Methods: This prospective randomized research involved sixty cases with moderate VKC, separated equally into 3 groups: Group A (cryotherapy), Group B (fluorometholone 0.1% suspension), and Group C (nepafenac 0.1% eye drops). Cases have been followed for six months, and outcomes assessed included resolution of symptoms and signs, recurrence, and complications. Results: At three months, no significant intergroup differences were observed in symptoms, conjunctival hyperemia, papillae, or keratitis ($p > 0.05$), except for Trantas dots distribution ($p = 0.0375$). At six months, all groups demonstrated significant improvement. Group C showed the highest resolution of palpebral papillae (70%) and the lowest relapse rate (35%), compared with Group A (80% relapse) and Group B (50% relapse). No serious treatment-related complications occurred in any group. Conclusion: Cryotherapy, corticosteroids, and NSAIDs are all effective in managing moderate VKC. However, cryotherapy remains a safe and useful non-pharmacological option, particularly for refractory cases.
Keywords: Vernal keratoconjunctivitis, cryotherapy, corticosteroids, nepafenac, ocular allergy
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INTRODUCTION

VKC is a distinctive disorder within the range of allergic ocular illnesses. It is a bilateral, chronic, inflammatory condition most frequently of the upper tarsal conjunctiva. It more frequently influences young male cases; however, it is often found in tropical regions where it could influence both genders equally [1].

Vernal keratoconjunctivitis is marked by the infiltration of the conjunctiva by several inflammatory cell types, particularly eosinophils. Whereas it was previously seen as an IgE-mediated illness, various additional immunologic pathways were additionally implicated [2].

Cases of vernal keratoconjunctivitis frequently presented with symptoms of watering eyes, redness, intense itching, and foreign body sensation, in addition to photophobia. Clinical signs of vernal keratoconjunctivitis involve a papillary reaction of the upper tarsal conjunctiva and the limbus. Additional typical signs of VKC involve a thick mucus discharge, bulbar conjunctival hyperemia, as well as corneal involvement, involving shield ulcers, superficial punctate keratitis, plaques, or epithelial erosions [3].

Vernal keratoconjunctivitis is categorized as tarsal, bulbar, or mixed according to its site, with papillae varying in size from one millimeter to giant cobblestone papillae [2].

A clinical grading system dependent on clinical signs and symptoms was suggested to aid in management and to recognize cases at elevated risk for recurrences, vision loss, and corneal complications [4].

At present, the diagnostic testing for VKC has limited utility.Skin testing and IgE concentrations are infrequently beneficial and might have negative results in fifty percent of cases with vernal keratoconjunctivitis [2].

Currently, there is no recognized gold-standard management algorithm for vernal keratoconjunctivitis; nevertheless, numerous options are accessible, and management must be tailored for every person [5].

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Regardless of the specified treatment regimen, it must be started promptly without delay, and the case must be closely followed up for the development of any corneal complications [5].

Topical corticosteroids are essential in the care of VKC, especially during exacerbations of vernal keratoconjunctivitis; nevertheless, they have significant side effect profiles, involving the potential for developing cataracts and glaucoma [6].

Topical non-steroidal anti-inflammatories might additionally be a beneficial therapeutic choice in vernal keratoconjunctivitis [7].

Surgical treatment involves cryotherapy and/or excision of giant papillae, with or without amniotic membrane transplantation (AMT). Additional invasive techniques involve surgical excision with oral mucous membrane grafting (MMG). Cryotherapy without excision of giant papillae is a non-invasive, relatively simple, daycare procedure that might be conducted under topical or local anesthesia [8].

The purpose of this research was to compare the safety and effectiveness of using cryotherapy versus topical fluorometholone 0.1% suspension eye drops versus topical depafenac 0.1% eye drops in the management of moderate cases of vernal keratoconjunctivitis.

PATIENTS AND METHODS

This comparative, prospective randomized research has been performed on 60 cases that had moderate to severe VKC. The patients involved in the investigation have been divided into three groups: Group A involved twenty cases that were managed by cryotherapy; group B involved twenty cases that were managed by topical fluorometholone 0.1 percent suspension eye drops; and group C included twenty cases that were treated by topical nepafenac 0.1% eye drops.

Inclusion criteria: Moderate to severe and intermittent cases of VKC, free ocular examination other than VKC.

Moderate disease is defined as a patient with papillary reaction, corneal involvement in the form of Horner–Trantas dots, and fine punctate erosions.

Severe disease is defined as a patient with large active cobblestones, keratitis, or coarse corneal erosions.

Intermittent disease periodicity is characterized by inflammation-free intervals above two to three months throughout which the case does not take drugs. This means a maximum of three to four episodes annually that remit on treatment.

Exclusion criteria: poor patient compliance, active local infection, any other ocular disease not caused by VKC, and mild cases

Methods:

In group 1, cryotherapy was done in the minor surgery operating room for the tarsal conjunctival papillae and for peri-limbal Horner–Trantas dots. As the patients are almost children and adolescents, cryotherapy was done under general anesthesia in addition to one drop of topical benoxinate 0.4% eye drops followed by subconjunctival and intratarsal injection of 0.5 to 1 ml of mepivacaine or bupivacaine 0.75%. The cryotherapy was done superficially using the double freeze-thaw technique; each freeze would last till a circle of 0.5 to 1 mm developed around the probe tip on the palpebral and limbal conjunctiva. Topical moxifloxacin 0.5% was received two to four times for two weeks, followed by cryotherapy.

In group 2, topical eye drops were administered in the form of topical fluorometholone 0.1 percent suspension eye drops 2-4 times daily for 2 weeks.

In group 3, topical eye drops were administered in the form of topical nepafenac 0.1 percent eye drops four times per day for two weeks. Cases have been monitored at one week, one month, three months, and six months. The follow-up period started from the day of cryotherapy in group 1 and from the last day of topical therapy in groups 2 and 3. Resolution of symptoms and signs, recurrence rates, relapses that require fluorometholone eye drops or a short course of low-dose systemic steroids, and complications were reported.

Statistical methods:

Data are coded, entered, and examined utilizing SPSS (statistical package for social sciences) version twenty and GraphPad Prism 8. Descriptive statistics will be done for the study regarding all gathered parameters. The quantitative parameters will be compared utilizing a paired t-test or one-way ANOVA. The comparison of qualitative parameters will be performed utilizing the chi-square test or Fisher's exact test. P-value level of significance: P above 0.05: non-significant. P below 0.05: significant. P below 0.01: highly significant.

RESULTS

Table 1: Baseline characteristic distribution in all study population

Demographic Data	Group A	Group B	Group C
	Number=20	Number =20	Number =20
Age			
Mean± SD	11.8±1.77	8.3±3.33	11.4±3.49
Range (Min-Max)	9-16	4-15	5-17

The mean age of the studied cases was 11.8 ± 1.77 years in Group A, 8.3 ± 3.33 years in Group B, and 11.4 ± 3.49 years in Group C, with ranges of 9–16, 4–15, and 5–17 years, respectively.

Table 2: Relation between treated groups according 3 month follow up Data

	3 month follow up Data			*P value*	*significant*
	Group A	***Group B***	***Group C***		
	Number =20	***Number =20***	***Number =20***		
tearing, Itching, discharge photophobia, and foreign body sensation					
No symptoms	2(10%)	4(20%)	4(20%)	0.1987	N. S
Mild discomfort	8(40%)	5(25%)	3(15%)		
Moderate discomfort	8(40%)	6(30%)	12(60%)		
Severe symptoms	2(10%)	5(25%)	1(5%)		
Conjunctival hyperaemia					
No hyperaemia	4(20%)	4(20%)	5(25%)	0.7121	N. S
Mild hyperaemia	8(40%)	7(35%)	4(20%)		
Moderate hyperaemia	8(40%)	8(40%)	11(55%)		
Severe hyperaemia	0(0%)	0(0%)	0(0%)		
Palpebral conjunctival papillae					
no papillae	6(30%)	7(35%)	10(50%)	0.6836	N. S
mild	10(50%)	8(40%)	6(30%)		
moderate	4(20%)	5(25%)	4(20%)		
sever	0(0%)	0(0%)	0(0%)		
Punctate keratitis					
no	10(50%)	8(40%)	11(55%)	0.8243	N. S
one quadrant	8(40%)	8(40%)	6(30%)		
two quadrant	2(10%)	4(20%)	3(15%)		
three or more quadrant	0(0%)	0(0%)	0(0%)		
Trantas dots					
no dots	10(50%)	13(65%)	17(85%)	0.0375	Sig.
1-2 dots	10(50%)	5(25%)	3(15%)		
3-4 dots	0(0%)	2(10%)	0(0%)		
more than 4	0(0%)	0(0%)	0(0%)		
Limbal infiltration					
no infiltration	16(80%)	14(70%)	19(95%)	0.2021	N. S
less than 90 degree	4(20%)	3(15%)	1(5%)		
more than 90 and less than 180	0(0%)	2(10%)	0(0%)		
more than 180 degree	0(0%)	1(5%)	0(0%)		
Complication Of Diseases					
no	18(90%)	20(100%)	20(100%)	0.1263	N. S
yes	2(10%)	0(0%)	0(0%)		
Relapse over last 6 months					
no	8(40%)	11(55%)	10(50%)	0.6268	N. S
yes	12(60%)	9(45%)	10(50%)		
Complication of treatment					
no	20(100%)	20(100%)	20(100%)	0.9999	N. S
yes	0(0%)	0(0%)	0(0%)		
Statistical test used: Chi-square test					
p-value not more than 0.05 deemed statistically significant (95% confidence interval).					

After a 3-month follow-up, there was a statistically insignificant variance between the examined groups according to ocular symptoms, conjunctival hyperaemia, palpebral papillae, punctate keratitis, limbal infiltration, complications of disease, relapse, or treatment complications (p above 0.05 for all). However, a statistically significant improvement was found in Trantas dots distribution across groups (p = 0.0375).

Table 3: Relation between treated groups according 6-month monitoring Data

	6 month follow up Data			*P value*	*Statistically significant*
	Group A	*Group B*	*Group C*		
	Number =20	*Number =20*	*Number =20*		
tearing, Itching, discharge, photophobia and foreign body sensation					
No symptoms	2(10%)	3(15%)	5(25%)	0.4637	N. S
Mild discomfort	10(50%)	6(30%)	7(35%)		
Moderate discomfort	4(20%)	8(40%)	7(35%)		
Severe symptoms	4(20%)	3(15%)	1(5%)		
Conjunctival hyperaemia					
No hyperaemia	2(10%)	5(25%)	8(40%)	0.1477	N. S
Mild hyperaemia	10(50%)	7(35%)	8(40%)		
Moderate hyperaemia	8(40%)	6(30%)	4(20%)		
Severe hyperaemia	0(0%)	2(10%)	0(0%)		
Palpebral conjunctival papillae					
no papillae	8(40%)	9(45%)	14(70%)	0.005	Sig.
mild	8(40%)	5(25%)	4(20%)		
moderate	0(0%)	6(30%)	2(10%)		
sever	4(20%)	0(0%)	0(0%)		
Punctate keratitis					
no	12(60%)	10(50%)	12(60%)	0.3268	N. S
one quadrant	8(40%)	6(30%)	6(30%)		
two quadrant	0(0%)	4(20%)	2(10%)		
three or more quadrant	0(0%)	0(0%)	0(0%)		
Trantas dots					
no dots	16(80%)	13(65%)	19(95%)	0.1022	N. S
1-2 dots	4(20%)	5(25%)	1(5%)		
3-4 dots	0(0%)	2(10%)	0(0%)		
more than 4	0(0%)	0(0%)	0(0%)		
Limbal infiltration					
no infiltration	20(100%)	16(80%)	20(100%)	0.0728	N. S
less than 90 degree	0(0%)	3(15%)	0(0%)		
more than 90 and less than 180	0(0%)	1(5%)	0(0%)		
more than 180 degree	0(0%)	0(0%)	0(0%)		
Complication Of Diseases					
no	20(100%)	20(100%)	20(100%)	0.9999	N. S
yes	0(0%)	0(0%)	0(0%)		
Relapse over last 6 months					
no	4(20%)	10(50%)	13(65%)	0.0144	Sig.
yes	16(80%)	10(50%)	7(35%)		
Complication of treatment					
no	20(100%)	20(100%)	20(100%)	0.9999	N. S
yes	0(0%)	0(0%)	0(0%)		

After a 6-month follow-up, a statistically insignificant variance has been observed among the examined groups regarding ocular symptoms, conjunctival hyperaemia, punctate keratitis, Trantas dots, limbal infiltration, or treatment complications ($p > 0.05$ for all). However, there was a statistically significant diminution in palpebral conjunctival papillae (p equal 0.005), with **Group C showing the highest percentage of patients without papillae (70%)**. In addition, relapse rate differed significantly among groups ($p = 0.0144$), with **Group C having the lowest relapse (35%) compared to Group A (80%)**.

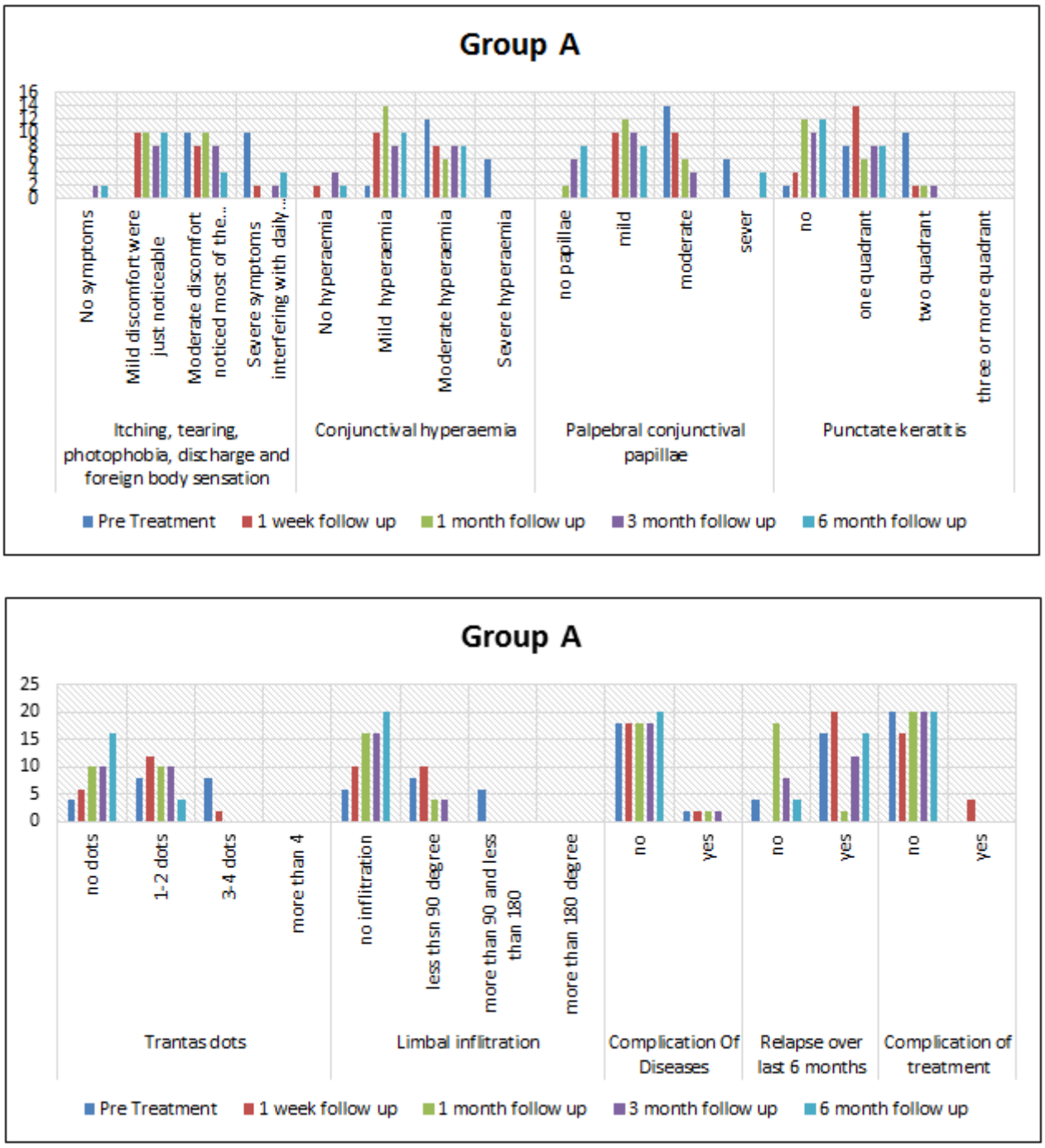

Figure 1: Relation between group A pre-treatment and 6-month follow-up data, in which group A illustrated a statistically significant enhancement in most clinical parameters over six months, with progressive reduction in symptoms and ocular signs ($p < 0.001$). Limbal infiltration resolved completely by 6 months. Complications did not change significantly, except for a transient rise in treatment-related issues at 1 week, which later resolved. The relapse rate decreased significantly after 1 month ($p < 0.0001$).

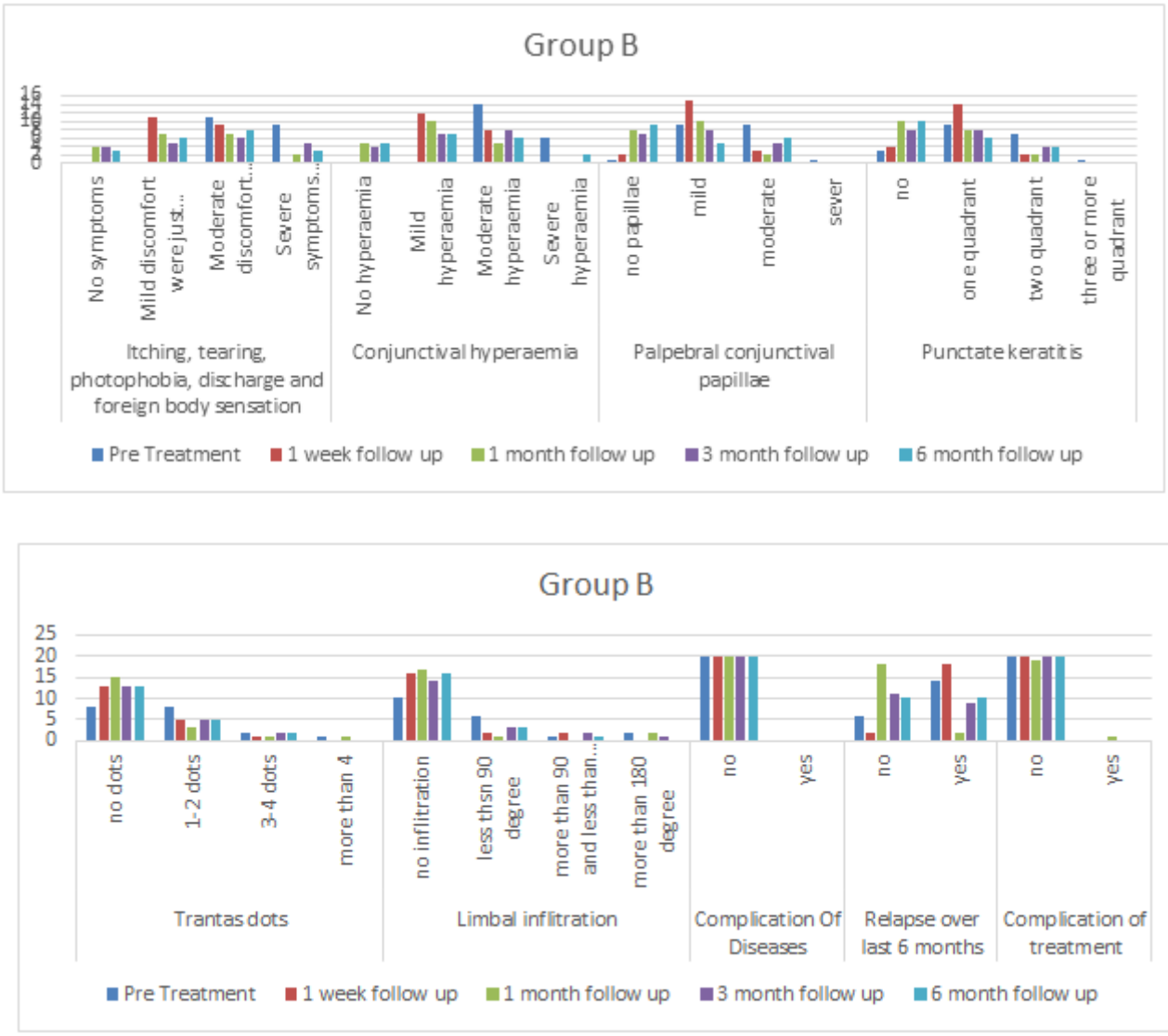

Figure 2: Relation between group B pre-treatment and 6-month follow-up Data, in which In Group B, significant improvement was observed in symptoms (tearing, foreign body sensation, discharge, itching, and photophobia) and conjunctival hyperaemia over the six-month monitoring (p below 0.001). Palpebral papillae also improved at 1 and 6 months. Punctate keratitis and Trantas dots showed gradual but non-significant changes, while limbal infiltration decreased without statistical significance. Disease complications remained absent throughout. A marked reduction in relapse was noted at 1 month (p = 0.0001), and treatment complications were minimal and transient.

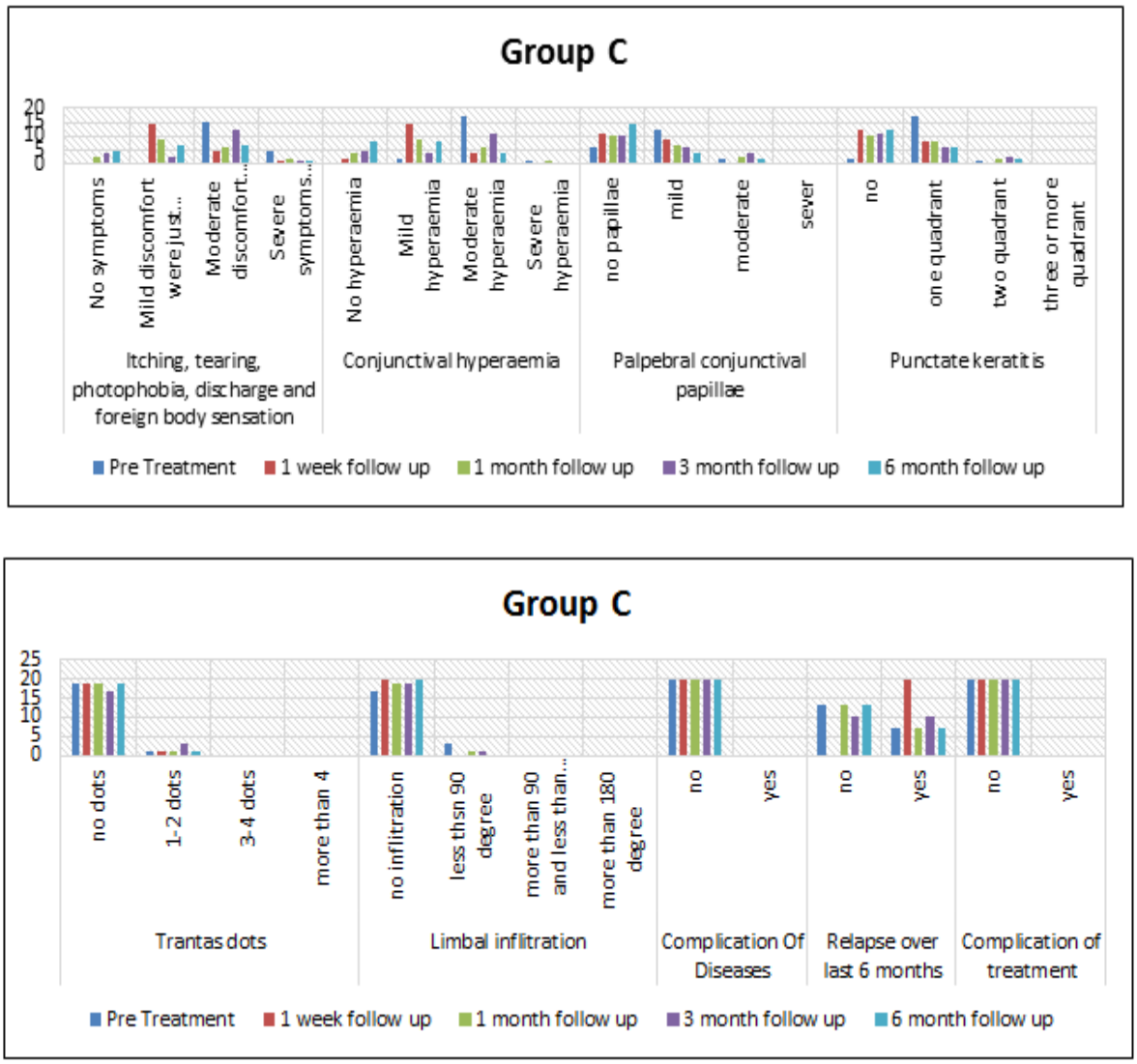

Figure 3: Relation between group C pre-treatment and 6-month follow-up Data in which In Group C, a statistically insignificant improvement in symptoms and conjunctival hyperaemia over 6 months ($p < 0.001$). Palpebral papillae showed gradual improvement, reaching significance at 6 months ($p = 0.027$). Punctate keratitis also improved significantly from 1 week onwards ($p < 0.05$). Limbal infiltration decreased but without statistical significance. Trantas dots and disease complications showed no significant changes. Relapse increased significantly at 1 week ($p < 0.0001$) but returned to baseline levels thereafter. Treatment complications were absent throughout follow-up.

DISCUSSION

Vernal keratoconjunctivitis is marked by the infiltration of the conjunctiva by various inflammatory cell types, particularly eosinophils. The exact pathogenesis of VKC is still unidentified; however, the existence of locally produced immunoglobulins in tears and increased neutrophil chemotactic factors indicates a dual pathology involving mechanical injury and immune mediation. Therapeutic choices for VKC involve surgical and medical interventions [9].

VKC responds well to topical drugs. Topical mast cell stabilizers are the mainstay of management. Oral and topical steroids are greatly efficient; nevertheless, they must be utilized cautiously because of their side effects associated with chronic usage. Histamine antagonists and receptor antagonists have thus far demonstrated limited usefulness [10].

Topical immunomodulators like cyclosporine and tacrolimus serve as acceptable choices for the long-term management of these cases, exhibiting side effects that are typically transient and without rebound influence on discontinuation of the medication [8].

Nevertheless, certain cases have inadequate responses to conservative treatment. These cases require surgical intervention. Supratarsal steroid injection is efficient for acute illness flare-ups but inadequate for complete

remission. The rapid initial relief of symptoms by supratarsal steroid is due to localized inflammation reduction [11].

Complications involve elevated intraocular pressure, skin pigmentation, blepharoptosis, motility disturbance, and infection, as well as conjunctival scarring [8].

Cryotherapy may be a less invasive method for managing refractory cases. The hypothesis suggested that the giant papillae are susceptible to cryotherapy, as the vascular endothelium of the central vascular core is destroyed by freezing [12].

In our study, we treated sixty patients with VKC separated into 3 groups (Group A: Cryotherapy, Group B: Topical Corticosteroid Eye Drops, Group C: Topical Non-Steroidal Anti-Inflammatory Eye Drops), and we followed up on symptoms, signs, recurrence, dependence on treatment, and complications of treatment over a period of six months.

Regarding group (A), there was a notable diminution in the severity of signs and symptoms over the 6-month period.

Severe symptoms interfering with daily activities decreased from 50% to 20%. Also, assessment of conjunctival hyperaemia and conjunctival papillae showed improvement and decreased from 60% to 40% and from 30% to 20%, respectively.

Punctate keratitis, Trantas dots, and limbal infiltration also showed improvement.

Regarding complications and relapse rates, no significant changes were noted over the 6-month period.

But regarding the comparison between the three groups, patients in all groups eventually illustrated long-term relief and a marked decrease in the incidence of exacerbations with non-significant variance between the 3 groups.

Mtanda and Sangawe examined thirty-four cases and suggested cryotherapy as the 1st therapy for vernal keratoconjunctivitis. In their research, ninety-four percent of patients exhibited total symptom relief and papillae flattening.

Research conducted by Singh [13] demonstrated encouraging and dramatic symptomatic improvement in eight of nine cases following cryosurgery.

Abiose and Me examined forty-eight eyes of cases that had bulbar vernal keratoconjunctivitis and eight eyes of cases that had severe giant papillary conjunctivitis that have been managed with cryopexy. Cases demonstrated long-term relief and a significant decrease in their incidence of exacerbations.

Kabra et al., [8] in their case, utilized cryotherapy without excision of papillae with amniotic membrane transplantation in 1 eye and cryotherapy without excision of papillae without amniotic membrane transplantation in the other eye. There was significant enhancement in symptoms of cases, and finally, both eyes illustrated the same result.

Lai et al., [14] in their case report, when comparing the excision of papillae with and without AMT, illustrated the same result in both eyes at the end of two years.

Guo et al., retrospectively examined thirteen eyes of nine cases with refractory giant papillae related to corneal shield's ulcer and/or punctate epithelial erosions who had surgical resection of the papillae combined with amniotic membrane transplantation to cover the tarsal defect. They determined that a smooth tarsal surface was attained in all patients, with no recurrence of the giant papillae in any eye.

More invasive procedures involve surgical excision with mucous membrane grafting.

Iyer et al., [16] studied eleven eyes of six cases with giant papillae and recurrent Shield's ulcer refractory to topical drugs, cryotherapy, and supratarsal steroid injections. The surgical resection of the giant papillae has been performed using MMG.No recurrence of Shield's ulcer occurred in any eye.They determined that surgical excision of refractory giant papillae, followed by mucous membrane grafting, has its benefits in decreasing corneal complications.

CONCLUSION

Cryotherapy might be a simple, efficient, and safe treatment for refractory vernal keratoconjunctivitis cases. Nevertheless, proper care and suitable precautions must be taken throughout the selection of cases and the producer.

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