Artificial tears alone versus 0.45% ketorolac tromethamine with artificial tears for the treatment of acute viral conjunctivitis

Lágrima artificial versus cetorolaco de trometamina 0,45% associado à lagrima artificial no tratamento da conjuntivite viral aguda

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ABSTRACT

Purpose: To evaluate the effects of preservative-free 0.45% ketorolac tromethamine and artificial tears (carboxymethylcellulose) compared with those of preservative-free artificial tears alone on the symptoms and signs of acute viral conjunctivitis.

Methods: This was a randomized, double-masked clinical trial that included 50 patients who were diagnosed with acute viral conjunctivitis and distributed into two groups (Group 0: artificial tears and Group 1: 0.45% ketorolac tromethamine + carboxymethylcellulose). The patients were instructed to use the medication 4 times daily. Signs (conjunctival hyperemia, chemosis, follicles, and secretion) and symptoms (general ocular discomfort, itching, foreign body sensation, tearing, redness, and swelling of the eyelids) were scored at baseline and on the third and seventh days of treatment using a standardized questionnaire and slit-lamp anterior segment examination.

Results: Both groups showed an improvement in the signs and symptoms of conjunctivitis in their follow-up visits. There was no significant difference in symptom and sign scores between Group 0 and Group 1 in the study visits ($p>0.05$). The frequency of side effects during treatment was similar between groups ($p>0.05$).

Conclusions: Our findings indicate that 0.45% ketorolac tromethamine was not superior to the use of artificial tears in relieving the signs and symptoms of viral conjunctivitis.

Keywords: Conjunctivitis, viral/drug therapy; Ketorolac tromethamine/therapeutic use; Ophthalmic solutions

RESUMO

Objetivo: *Avaliar o efeito do colírio de cetorolaco de trometamina 0,45% associado à carboximetilcelulose sem conservante em comparação ao uso isolado de lágrimas artificiais sem conservantes nos sinais e sintomas da conjuntivite viral aguda.*

Métodos: *Ensaio clínico duplo-mascarado randomizado incluindo 50 pacientes com diagnóstico de conjuntivite viral aguda, distribuídos em dois grupos (Grupo 0: lágrimas artificiais e Grupo 1: cetorolaco 0,45% + carboximetilcelulose). Os pacientes foram orientados a utilizar a medicação quatro vezes ao dia. Sinais (hiperemia conjuntival, quemose, folículos e secreção) e sintomas (desconforto ocular geral, prurido, sensação de corpo estranho, lacrimejamento, vermelhidão e inchaço de pálpebras) foram avaliados na consulta inicial, no terceiro e no sétimo dia de tratamento utilizando um questionário padronizado e biomicroscopia de segmento anterior.*

Resultados: *Ambos os grupos apresentaram melhora dos sinais e sintomas de conjuntivite nas visitas de reavaliação. Não foi observado diferença estatística na mudança dos escores dos sinais e sintomas entre o Grupo 0 e o Grupo 1 durante as visitas do estudo ($p>0.05$). A frequência de efeitos colaterais durante o tratamento foi similar entre os dois grupos ($p>0.05$).*

Conclusão: *O uso do cetorolaco de trometamina 0,45% não se mostrou superior ao uso isolado de lágrimas artificiais no alívio dos sinais e sintomas da conjuntivite viral.*

Descritores: *Conjuntivite viral/quimioterapia; Cetorolaco de trometamina/uso terapêutico; Soluções oftálmicas*

INTRODUCTION

Infectious conjunctivitis accounts for approximately 25% consultations in ophthalmology emergency services[1,2] and 1%-2% of family-medicine consultations[3]. Among the types of infectious conjunctivitis, viral etiologies are the most common, and the adenovirus is responsible for approximately 60% cases[4].

Symptoms associated with viral conjunctivitis include redness, tearing, swelling, and irritation that often last from 1 to 3 weeks, and, in general, the management of this condition comprises symptomatic treatment[3]. Despite standard treatment with artificial tears, cold compresses, and topical vasoconstrictors, patients still suffer from great discomfort until the disease resolves completely[5].

Anti-inflammatory drugs, including topical steroids, may be used for the treatment of viral conjunctivitis. Generally, these medications are indicated in severe cases, such as those with appearance of subepithelial corneal opacities and conjunctival membranes. Beneficial effects have been demonstrated with topical steroids[6]; however, side effects such as ocular hypertension, cataract formation, delayed wound healing, and secondary infection limit their use[5]. Some studies have also shown that topical steroids can enhance virus replication and prolong the duration of virus shedding[7].

Ketorolac tromethamine is a topical nonsteroidal anti-inflammatory drug (NSAID) that blocks the cyclooxygenase enzyme, which catalyzes the conversion of arachidonic acid into prostaglandins. Several studies have demonstrated the effectiveness of 0.4% and 0.5% formulations of this drug in relieving inflammation and ocular pain and the prevention and treatment of cystoid macular edema in patients who undergo ocular surgery[8,9]. This topical medication has also been used with good results for the symptomatic treatment of

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seasonal allergic conjunctivitis[10]. In viral conjunctivitis associated with varicella, 0.5% ketorolac was more effective in decreasing conjunctival hyperemia compared with artificial tears[11]. In adenoviral conjunctivitis, 0.5% ketorolac showed results similar to those of artificial tears in terms of providing symptomatic relief, but there were frequent stinging and burning sensations upon eyedrop instillation[5].

Currently, a formulation of 0.45% ketorolac tromethamine associated with carboxymethylcellulose (CMC), with a better tolerability profile and bioavailability, is commercially available and is indicated for the treatment of pain and inflammation in patients undergoing cataract surgery[8,9,12].

This study aimed to evaluate the effects of preservative-free 0.45% ketorolac tromethamine and carboxymethylcellulose compared with those of preservative-free artificial tears alone on the symptoms and signs of acute viral conjunctivitis.

METHODS

This prospective, double-masked, randomized study included 50 patients divided into 2 treatment groups: Group 1, who received the formulation of preservative-free 0.45% ketorolac tromethamine with CMC (Acular CMC®, Allergan, Irvine, USA), and Group 0, who received only preservative-free artificial tears (Optive UD®, Allergan, Irvine, USA). Patients were recruited from the emergency service of Fundação Altino Ventura, Recife, Pernambuco, between June and September 2012. Eligible patients were required to have acute unilateral or bilateral conjunctivitis of less than 2 weeks duration. In addition, they were required to have at least one of the following features compatible with viral conjunctivitis: preauricular lymphadenopathy, upper respiratory tract infection (URTI), or recent contact with individuals with conjunctivitis.

Exclusion criteria included a history of seasonal allergic conjunctivitis, herpetic eye disease, ocular surgery, and/or chronic ocular disease other than refractive error; use of any ocular medication after the beginning of symptoms; contact lens wear; allergy to NSAIDs; pregnancy; age of less than 18 years; presence of a bleeding disorder; corneal epithelial staining with fluorescein; and intraocular inflammation.

Each patient was randomly assigned a sealed envelope containing vials of unidentified 0.45% ketorolac tromethamine with CMC or artificial tears. Both patients and examiners were blinded to the medication. Patients were instructed to place one drop into each symptomatic eye 4 times daily for 7 days and were reassessed after 3-7 days from the first visit. At the end of follow-up for the 50th patient, the randomization code was revealed for data analysis.

In all evaluations, the patients completed a standardized questionnaire where they were asked about the following symptoms: overall discomfort, itching, foreign body sensation, tearing, redness, and lid swelling. Each of the symptoms was rated by the patient at presentation and at follow-up on a 4-point scale: none (0), mild (1), moderate (2), and severe (3). During re-evaluation, the patients were asked about the proper use of medications, side effects, and discomfort with the use of medications. Patients were also asked about the improvement in symptoms after the use of eye drops.

Clinical examination comprised anterior segment slit-lamp biomicroscopy, and all re-evaluations for each patient were performed by the same examiner from the initial consultation. Four signs were assessed on physical examination: conjunctival hyperemia, conjunctival chemosis, conjunctival mucus, and the presence of follicles in the lower tarsal conjunctiva. The signs were classified as none (0), mild (1), moderate (2), and severe (3). For conjunctival hyperemia, grade 0 indicated no detectable hyperemia, grade 1 indicated conjunctival hyperemia that was barely detectable, grade 2 indicated conjunctival hyperemia that was readily detectable, and 3 indicated intense conjunctival hyperemia that could be mistaken for subconjunctival hemorrhage without slit-lamp examination. Only patients with a conjunctival hyperemia score of >1 were included in the study. For the sign of chemosis, grade 0 indicated no detectable conjunctival edema, grade 1 indicated conjunctival edema that was barely detectable, grade 2 indicated conjunctival edema that was readily detectable, and grade 3 indicated conjunctival edema sufficient to cause the protrusion of swollen redundant conjunctiva through closed lids. For the sign of conjunctival mucus, grade 0 indicated no detectable mucus discharge, grade 1 indicated mucus discharge that was barely detectable, grade 2 indicated mucus discharge that was readily detectable, and grade 3 indicated mucus discharge associated with an inflammatory conjunctival pseudomembrane or true membrane. For the sign of follicles, grade 0 indicated no detectable follicles, grade 1 indicated barely detectable follicles, grade 2 indicated readily detectable follicles, and grade 3 indicated an intense follicular reaction.

The study was initiated after approval from the institutional ethics committee. All patients were included in the study after agreement and signature of the study informed consent form, and they were instructed to contact one of the investigators if they were experiencing any significant side effects from the study medication.

The likelihood ratio test was used to evaluate differences in frequencies between categorical variables. Student's t test was used to evaluate differences between means. A p-value of <0.05 was used to indicate statistical significance.

RESULTS

A total of 50 patients met the eligibility criteria and were enrolled in the study. Twenty-six were included in Group 0 (artificial tears) and 24 in Group 1 (0.45% ketorolac tromethamine + CMC). During follow-up, 6 patients missed their re-evaluation appointments (3 in each group; 12% dropout rate during follow-up).

The general characteristics of the patients enrolled in the study are presented in table 1. There were no statistical differences in age, distribution of sex, and symptoms suggestive of viral conjunctivitis between the studied groups (p>0.05).

The patient's perception of general improvement in symptoms after 3 and 7 days of treatment is shown in table 2. There was no statistical difference between groups in relation to the general improvement in symptoms after the use of the medications (p>0.05).

The evolution of conjunctivitis symptoms on the 3rd and 7th days of re-evaluation are shown in tables 3 and 4, respectively. Tables 5 and 6 present the evolution of signs on the 3rd and 7th days of treatment, respectively. As noted in the tables, there was no statistical difference in sign and symptom scores between the 2 groups during follow-up (p>0.05).

Side effects that comprised mild symptoms of burning, itching, and stinging upon eyedrop instillation were reported (64% in Group 0; 57% in Group 1); however, no significant difference was observed (p=0.764).

During follow-up, 6 patients (12%) developed tarsal conjunctival membranes (3 patients from Group 0 and 3 patients from Group 1). These membranes were removed, and a combination of 0.3% ciprofloxacin + 0.1% dexamethasone was added to the initial regimen.

DISCUSSION

Viral conjunctivitis, despite being a self-limiting disease, is associated with high morbidity because of its symptoms and the risk of contagion. Currently, there are no effective treatments to decrease disease duration and contagion, and only symptomatic treatment is indicated[3]. Novel treatment options are being studied, including antiviral drugs such as ganciclovir and povidone-iodine[13-16].

In experimental and *in vitro* studies, ketorolac tromethamine did not lead to prolonged adenoviral replication as opposed to prednisolone, proving a safer alternative when compared with corticos-

Table 1. General characteristics of the studied patients

	Total (n=50)	Group 0 (n=26)	Group 1 (n=24)	*p*
Age (mean ± standard deviation)	31.6 ± 10.7	30.4 ± 8.6	32.8 ± 12.7	0.432[a]
Male [n (%)]	34 (68%)	18 (69%)	16 (67%)	0.999[b]
Unilateral involvement	36 (72%)	21 (81%)	15 (63%)	0.211[b]
Association with URTI[c]	31 (62%)	16 (62%)	15 (63%)	0.999[b]
Preauricular lymphadenopathy	12 (24%)	6 (23%)	6 (25%)	0.999[b]
Recent contact with conjunctivitis	37 (74%)	18 (69%)	19 (79%)	0.526[b]

[a]= Student *t* test; [b]= Fisher exact test; [c]= URTI upper tract respiratory infection.

Table 2. Perception of treatment benefit in the 3rd and 7th follow-up days in patients with viral conjunctivitis

	3th day		7th day	
Evolution of symptoms with treatment	**Group 0 (n=25)**	**Group 1 (n=21)**	**Group 0 (n=23)**	**Group 1 (n=19)**
Considerable improvement	15 (60%)	9 (43%)	20 (87%)	19 (100%)
Slight improvement	7 (28%)	10 (48%)	0 (0%)	0 (0%)
Not helped	3 (12%)	2 (9%)	3 (13%)	0 (0%)
p[a]	0.388		0.239	

[a]= likelihood ratio test.

Table 3. Evolution of symptoms reported by the patient on the 3rd day of treatment compared to the initial consultation

	3th day		
Symptoms on 3th day	**Group 0 (n=25)**	**Group 1 (n=21)**	***p*[a]**
General symptoms			
Worsening	1 (4%)	0 (0%)	0.844
Unchanged	4 (16%)	5 (24%)	
Improvement	20 (80%)	16 (76%)	
Itching			
Worsening	3 (12%)	5 (24%)	0.303
Unchanged	6 (24%)	7 (33%)	
Improvement	16 (64%)	9 (43%)	
Foreign body sensation			
Worsening	2 (8%)	1 (5%)	1.000
Unchanged	9 (36%)	7 (33%)	
Improvement	14 (56%)	13 (62%)	
Tearing			
Worsening	1 (4%)	2 (10%)	0.870
Unchanged	4 (16%)	3 (14%)	
Improvement	20 (80%)	16 (76%)	
Redness			
Worsening	1 (4%)	0 (0%)	0.163
Unchanged	1 (4%)	4 (19%)	
Improvement	23 (92%)	17 (81%)	
Eyelid swelling			
Worsening	2 (8%)	2 (9%)	0.617
Unchanged	3 (12%)	5 (24%)	
Improvement	20 (80%)	14 (67%)	

[a]= likelihood ratio test.

Table 4. Evolution of symptoms reported by the patient on the 7th day of treatment compared to the initial consultation

	7th day		
Symptoms on 7th day	**Group 0 (n=23)**	**Group 1 (n=19)**	***p*[a]**
General symptoms			
Worsening	2 (9%)	0 (0%)	0.495
Unchanged	1 (4%)	0 (0%)	
Improvement	20 (87%)	19 (100%)	
Itching			
Worsening	1 (4%)	0 (0%)	1.000
Unchanged	4 (18%)	4 (21%)	
Improvement	18 (78%)	15 (79%)	
Foreign body sensation			
Worsening	3 (13%)	0 (0%)	0.322
Unchanged	4 (17%)	4 (21%)	
Improvement	16 (70%)	15 (79%)	
Tearing			
Worsening	1 (4%)	0 (0%)	1.000
Unchanged	2 (9%)	2 (11%)	
Improvement	20 (87%)	17 (89%)	
Redness			
Worsening	2 (9%)	0 (0%)	0.495
Unchanged	1 (4%)	2 (11%)	
Improvement	20 (87%)	17 (89%)	
Eyelid swelling			
Worsening	2 (9%)	0 (0%)	0.133
Unchanged	2 (9%)	6 (32%)	
Improvement	19 (82%)	13 (68%)	

[a]= likelihood ratio test.

Table 5. Evolution of signs presented by patients on the 3rd day of treatment compared to the initial consultation

	3th day		
Signs on 3th day	Group 0 (n=25)	Group 1 (n=21)	*p*[a]
Hyperemia			
Worsening	0 (0%)	2 (10%)	0.192
Unchanged	7 (28%)	4 (19%)	
Improvement	18 (72%)	15 (71%)	
Follicles			
Worsening	0 (0%)	2 (9%)	0.175
Unchanged	9 (36%)	5 (24%)	
Improvement	16 (64%)	14 (67%)	
Chemosis			
Worsening	1 (4%)	2 (10%)	1.000
Unchanged	3 (12%)	4 (19%)	
Improvement	21 (84%)	15 (71%)	
Secretion			
Worsening	2 (8%)	3 (14%)	1.000
Unchanged	8 (32%)	8 (38%)	
Improvement	15 (60%)	10 (48%)	

[a]= likelihood ratio test.

Table 6. Evolution of the signs presented by patients on the 7th day of treatment compared to the initial consultation

	7th day		
Signs on 7th day	Group 0 (n=23)	Group 1 (n=19)	*p*-value[a]
Hyperemia			
Worsening	1 (4%)	2 (11%)	0.486
Unchanged	3 (13%)	1 (5%)	
Improvement	19 (83%)	16 (84%)	
Follicles			
Worsening	1 (4%)	0 (0%)	1.000
Unchanged	3 (13%)	2 (11%)	
Improvement	19 (83%)	17 (89%)	
Chemosis			
Worsening	0 (0%)	0 (0%)	1.000
Unchanged	3 (13%)	2 (11%)	
Improvement	20 (87%)	17 (89%)	
Secretion			
Worsening	1 (4%)	3 (16%)	0.206
Unchanged	4 (18%)	1 (5%)	
Improvement	18 (78%)	15 (79%)	

[a]= likelihood ratio test.

teroids[17]. Because of their good response in patients with allergic conjunctivitis[10], 0.5% ketorolac was proposed for the treatment of adenoviral conjunctivitis. However, it was not superior to artificial tears in relieving itching, redness, foreign body sensation, tearing, and eyelid edema and was associated with discomfort (stinging and burning) upon instillation[5]. Such discomfort is associated with the preservative benzalkonium chloride (BAK), the surfactant octoxynol-40, and the metal-chelating agent sodium edetate[8,9]. Therefore, in this study, we evaluated a preservative-free formulation of 0.45% ketorolac with artificial tears (CMC), which presents a better tolerability profile and penetration into ocular tissues[8,9].

Evaluation of a patient's perception of overall improvement on the 3rd and 7th days of treatment showed no significant differences between the 2 studied groups, suggesting that both eye drops had similar effects. This finding was similar to those in previous reports on the use of 0.5% ketorolac tromethamine solution with preservatives[5]. No significant difference was found when the symptoms were individually evaluated or when the signs observed on ophthalmologic examinations were analyzed. In contrast to a previous study evaluating 0.5% ketorolac with preservatives[5], treatment with preservative-free 0.45% ketorolac was not associated with the worsening of ocular hyperemia or stinging upon instillation. The frequency of reported side effects was similar in both groups.

CONCLUSIONS

In conclusion, 0.45% ketorolac tromethamine was not superior to artificial tears in relieving the signs and symptoms of viral conjunctivitis. Further research studies to evaluate safe and effective therapies for this common eye disease are required.

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