Current Eye Research, Early Online, 1–8, 2014

ISSN: 0271-3683 print / 1460-2202 online
DOI: 10.3109/02713683.2014.964419

informa
healthcare

RESEARCH REPORT

Dexamethasone/Povidone Eye Drops versus Artificial Tears for Treatment of Presumed Viral Conjunctivitis: A Randomized Clinical Trial

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ABSTRACT

Purpose: To determine whether topical dexamethasone 0.1%/povidone-iodine 0.4% reduces the duration of presumed viral conjunctivitis better than artificial tears and whether the treatment relieves the symptoms of this disease.

Methods: Randomized, masked and controlled trial. One-hundred twenty-two patients with a clinical diagnosis of presumed viral conjunctivitis were randomized to either the treatment group or the control group. Physicians and patients were masked to the treatment. Swabs were taken from the conjunctival fornix for adenovirus PCR analyses. Patients in the treatment group received topical dexamethasone 0.1%/povidone-iodine 0.4% eye drops four times daily, and patients in the placebo group received artificial tears four times daily, both for seven days. Symptoms were recorded on the day of recruitment and at the time of a follow-up examination 5, 10 and 30 d later. The main outcome was duration of the disease. The others outcomes were overall discomfort, itching, foreign body sensation, tearing, redness, eyelid swelling, side effects of the eye drops, intraocular pressure and the incidence of subepithelial corneal infiltrates.

Results: There was no statistically significant difference between the treatment group and the control group in terms of the patients' symptoms, intraocular pressure and incidence of subepithelial cornea infiltrates during the entire follow-up period. Patients of the treatment group reported more stinging ($p < 0.001$) and a shorter conjunctivitis duration (9.4 ± 4.6 d in the dexamethasone 0.1%/povidone-iodine 0.4% group versus 11.8 ± 4.9 d in the artificial tears group, $p = 0.009$).

Conclusions: The use of topical dexamethasone 0.1%/povidone-iodine 0.4% eye drops four times daily appears to reduce the duration of conjunctivitis, although it causes more stinging than artificial tears.

Keywords: Adenovirus, dexamethasone, povidone-iodine, viral conjunctivitis

INTRODUCTION

Viral conjunctivitis is one of the most common disorders seen in general and ophthalmic primary care practice. It is highly contagious, usually for 10–12 d from onset as long as the eyes are red. It is typically caused by adenovirus. Less common causes include herpes simplex virus, varicella-zoster virus, picornavirus, poxvirus, human immunodeficiency virus, influenza virus, Epstein-Barr virus, paramyxovirus and rubella. An American study on adults and children in an ophthalmic emergency room found that 62% of acute infective conjunctivitis cases had an adenoviral cause.[1–3]

Received 29 June 2014; revised 20 August 2014; accepted 6 September 2014; published online 8 October 2014
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Generally, a diagnosis of viral conjunctivitis is made on the clinical features alone. Patients may give a history of recent exposure to an individual with red eye, or they may have a history of recent symptoms of an upper respiratory tract infection. The eye infection may be unilateral or bilateral. Patients may report ocular itching, foreign body sensation, tearing, redness, discharge, eyelids sticking and photophobia. Signs of acute viral conjunctivitis include inferior palpebral conjunctival follicles, tender palpable preauricular lymph node, epiphora, hyperemia, chemosis, red and edematous eyelids, pinpoint subconjunctival hemorrhages, punctuate keratopathy and occasionally a pseudomembranous. Subepithelial corneal infiltrates may develop 1–2 weeks after the onset of the conjunctivitis.[4] Laboratory tests are typically not necessary. Conventional laboratory identification can be expensive and time-consuming but may be helpful in certain circumstances.[5–9]

Viral conjunctivitis is a self-limiting condition. The infection usually resolves spontaneously within 2–4 weeks. Treatment of adenoviral conjunctivitis is supportive. Patients usually are instructed to use cold compresses and lubricants, such as artificial tears, for comfort. For patients who may be susceptible, a topical antibiotic may be used to prevent bacterial superinfection. Topical steroids may be used for pseudomembranes or when subepithelial infiltrates impair vision, although subepithelial infiltrates may recur after discontinuing the steroids. No evidence exists that demonstrates the efficacy of antiviral agents.[4,10–13] However, many patients still experience substantial discomfort despite standard treatments, and, given the disproportionate morbidity and potential economic impact associated with an outbreak of infective conjunctivitis, a therapeutic agent that reduces clinical symptoms of viral conjunctivitis and minimizes shedding of the infectious virus would be desirable.

Dexamethasone is a potent, well-tolerated steroid[14,15] that has been used extensively as a topical ophthalmic agent both alone and in combination regimens.[10,16–18] While the use of dexamethasone may have some efficacy in the short-term amelioration of symptoms, studies in the New Zealand white rabbit model have suggested that even a short course of relatively low-potency corticosteroids without the addition of a suitable antiviral agent can increase the duration of viral shedding and prolong the infectivity.[10] Povidone-iodine is an antiseptic extensively used in preparation for general surgery, for ophthalmic purposes and for laboratory disinfection.[19–25] Diluted povidone-iodine solutions inhibit numerous viruses, bacteria, fungi and some other parasites.[26] Previously studies have shown that povidone-iodine is a potential option for reducing contagiousness in cases of adenoviral infections.[27] In one Japanese investigation, a number of viruses, including adenovirus and herpes, were found to be very susceptible to povidone-iodine *in vitro*, even in concentrations of 1.0%.[28]

Dexamethasone 0.1%/povidone-iodine 0.4%, an eye drop containing a steroid and an antiseptic, is promising as a suitable therapeutic agent to treat adenoviral keratoconjunctivitis. A small, prospective, open-label, single-arm clinical trial to test dexamethasone 0.1%/povidone-iodine 0.4% on humans with symptoms of acute conjunctivitis who had tested positive for the adenoviral antigen was therapeutically successful.[16] In another study, dexamethasone 0.1%/povidone-iodine 0.4% combination markedly lowered the viral concentration and improved the signs of the disease in rabbits.[29]

Thus, favorable human data in combination with *in vivo* results provide an impetus for a human clinical trial to test the efficacy of this drug on a larger group and to evaluate the safety of the treatment in order to properly establish both the therapeutic benefits and the adverse effects.

The main purposes of this study is to determine whether topical dexamethasone 0.1%/povidone-iodine 0.4% reduces the duration of presumed viral conjunctivitis better than artificial tears and whether the treatment relieves the symptoms of this disease.

METHODS

Study Design

This study was designed as a prospective, masked, controlled study of the efficacy of dexamethasone 0.1%/povidone-iodine 0.4% (pH = 6.7, without preservatives, prepared and provided by Ophthalmos®, São Paulo, Brazil) compared with artificial tears (methylcellulose 0.5% with benzalkonium chloride (BAC) as preservative, pH = 6.6, prepared and provided by Ophthalmos®, São Paulo, Brazil). Patients were recruited from the Eye Emergency Room of the State University of Campinas Teaching Hospital in Brazil, from November 2011 to June 2012. An ethics committee linked to the Institution of origin approved this study, and written informed consent was obtained from all patients. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this study and conducted in accordance with the Declaration of Helsinki. The study was registered at www.clinicaltrials.gov: NCT01481519.

Study Population

Eligible patients were required to have an acute unilateral or bilateral viral conjunctivitis (with the characteristic clinical features such as sudden onset of

acute follicular conjunctivitis, with watery discharge, hyperemia and chemosis) for less than one week. In addition, they were required to have at least one of the following features compatible with viral conjunctivitis: ipsilateral preauricular lymphadenopathy, to be preceded by flulike symptoms (including fever, malaise, respiratory symptoms, nausea, vomiting, diarrhea or myalgia) and/or a recent history of an eye examination or exposure within the family or at work. Exclusion criteria included history of seasonal allergic conjunctivitis, use of ocular medication after the beginning of symptoms, contact lens wear, history of herpetic eye disease, history of ocular surgery, history of chronic ocular disease other than refractive error, allergy to iodine, pregnancy, age younger than 18 years, any bleeding disorder, glaucoma, significant blepharitis or dry eyes according to a slit lamp examination, purulent ocular discharge, corneal epithelial fluorescein staining or intraocular inflammation.

Study Protocol

Patients who met the study criteria and who agreed to participate in the study were randomly assigned to receive either dexamethasone 0.1%/povidone-iodine 0.4% eye drops or artificial tears, by lot. Patients were given sealed, randomly code numbered opaque manila envelopes containing unlabeled bottles of either dexamethasone 0.1%/povidone-iodine 0.4% or artificial tears. Patients were instructed to put one drop into each symptomatic eye four times daily for seven days. The drop identity was masked to both the investigators and patients until the study was completed. At the end of the study, the code for the randomization scheme was obtained.

Ocular swab samples were collected from patients with suspected conjunctivitis by human adenovirus (HAdV), placed in sterile solution of 0.9% NaCl and kept in a freezer at −80 degrees until the time of extraction. These samples were used in the adenovirus PCR analysis. Adenovirus primers were selected from the hexon region DNA sequence of adenovirus types 2 and 5: Hadv1 –5′ GCCGCAGTGGTCTTACATGCACATC 3′ and Hadv2 – 5′ CAGCACGCCGCGGATGTCAAGT 3′ (product size of 300 bp).[30–33] These primers amplify multiple serotypes. Sequencing of 300 bp fragment of the hexon gene allows for the identification of most adenovirus serotypes that are associated with acute conjunctivitis.

Outcome Measures and Follow-Up

Patients were evaluated at baseline and were asked to return 5 (±1), 10 (±1) and 30 (±2) days later for a follow-up evaluation. The main outcome was duration of the disease. The others outcomes were overall discomfort, itching, foreign body sensation, tearing, redness, eyelid swelling, eye drops side effects, intraocular pressure and the incidence of subepithelial corneal infiltrates.

Both at presentation and at follow-up, each patient reported the presence or absence of each symptom and rated the extent of each present symptom. In addition, each patient was asked to report their opinions on the usefulness of the treatment in relieving their symptoms on the following four-point scale: the treatment did not help (0), I'm unsure if the treatment helped (1), I think the treatment helped (2) and the treatment definitely helped (3). Both the questionnaires and the criteria for selecting patients were similar to a previously published conjunctivitis clinical trial.[34]

Subepithelial corneal infiltrates were also investigated, and intra-ocular pressure was measured at every follow-up visit. Patients were also asked about the duration of conjunctivitis on the 30th day. The same doctors examined the same patients at the initial and follow-up evaluations. Patients who did not attend their follow-up appointments were contacted by telephone and asked to attend the next follow-up visit. If that was not possible, the answers to the questionnaire and the information regarding the duration of symptoms were obtained by telephone interview. At each visit, patients were asked whether their use of the medication was consistent, and the importance of its consistent use was reinforced. Patients who were found to have subepithelial corneal infiltrates sometime during the study discontinued the use of the masked eye drops and were treated with corticosteroids (topical prednisolone 0.1% within four weeks).

Patients were instructed to contact one of the principal investigators by telephone if they were experiencing any significant side effects of the eye drops. If the investigator was unavailable, patients were instructed to report to the Ophthalmological Emergency Room of the Hospital of the study, which is open 24 h a day. In addition, patients were asked about any side effects at their 5-, 10- and 30-d follow-up evaluations.

Sample Size and Statistical Analysis

A previous trial found that 78% of patients reported that artificial tears improved their symptoms.[35] This trial was powered to have an 80% chance ($p < 0.05$) of detecting a change from 78% to 97% of patients who felt that their treatment helped. Allowing for a 5% loss from the lack of follow-up, we sought to recruit 112 patients.

We used the SAS System for Windows (Statistical Analysis System) 9.1.3 (SAS software, Institute Inc,

2002–2003, Cary, NC) computer software for the statistical analyses. The data were analyzed according to the group to which the patients were originally assigned. The chi-square or Fisher's exact tests was used for categorical variables; the Mann–Whitney test was used for continuous variables. ANOVA for repeated measures was used to compare the longitudinal measures between groups and time, followed by the profile test. The variables were transformed into ranks due to the lack of normal distribution. p Values < 0.05 were considered statistically significant.

RESULTS

A total of 122 patients met the eligibility criteria and were initially enrolled in the study. Eleven patients did not return on the fifth day of follow-up; eight of these 11 patients were from the artificial tears group, and the other three were from the dexamethasone 0.1%/povidone-iodine 0.4% group. On the 10th day of follow-up, 109 patients were evaluated (56 from the dexamethasone 0.1%/povidone-iodine 0.4% group and 53 from the artificial tears group), and 104 patients were evaluated on the 30th day of follow-up (55 from dexamethasone 0.1%/povidone-iodine 0.4% group and 49 from artificial tears group (Figure 1). There were seven patients in the study who presented early subepithelial corneal infiltrates: two on the fifth day of the follow-up examination (both from the dexamethasone 0.1%/povidone-iodine 0.4% group) and five on the 10th day of the follow-up examination (four from the artificial tears group and one from the dexamethasone 0.1%/povidone-iodine 0.4% group). These patients' use of the study medication was discontinued, and these patients were excluded, because their condition required monitoring and specific treatment with corticosteroids. All patients with subepithelial corneal infiltrates had their problem solved with no long-term consequences after using topical prednisolone 0.1% for four weeks.

The baseline characteristics of the 122 patients included are listed in Table 1. Seventy-two patients' PCR tests were positive for adenovirus, and the incidence was similar in both groups (36 in the dexamethasone 0.1%/povidone-iodine 0.4% group and 36 in the artificial tears group). The two groups were similar at baseline in terms of the patients' demographic and clinical characteristics.

The duration of conjunctivitis reported by the patients was 9.4 (±4.6) d in patients from the dexamethasone 0.1%/povidone-iodine 0.4% group and 11.8 (±4.9) d in patients from the artificial tears group. As seen in Figure 2, this difference was statistically significant ($p = 0.009$). In addition, if we consider only patients with positive PCR in the analysis, the duration of conjunctivitis in patients from the dexamethasone 0.1%/povidone-iodine 0.4% group averaged 9.8 (± 4.1) d, and the artificial tears group averaged 12.2 (±4.1) d. This result was also statistically significant ($p = 0.018$).

The comparisons of symptoms between the groups on the initial evaluations and follow-ups on days 5 and 10 have been summarized as a percentage of

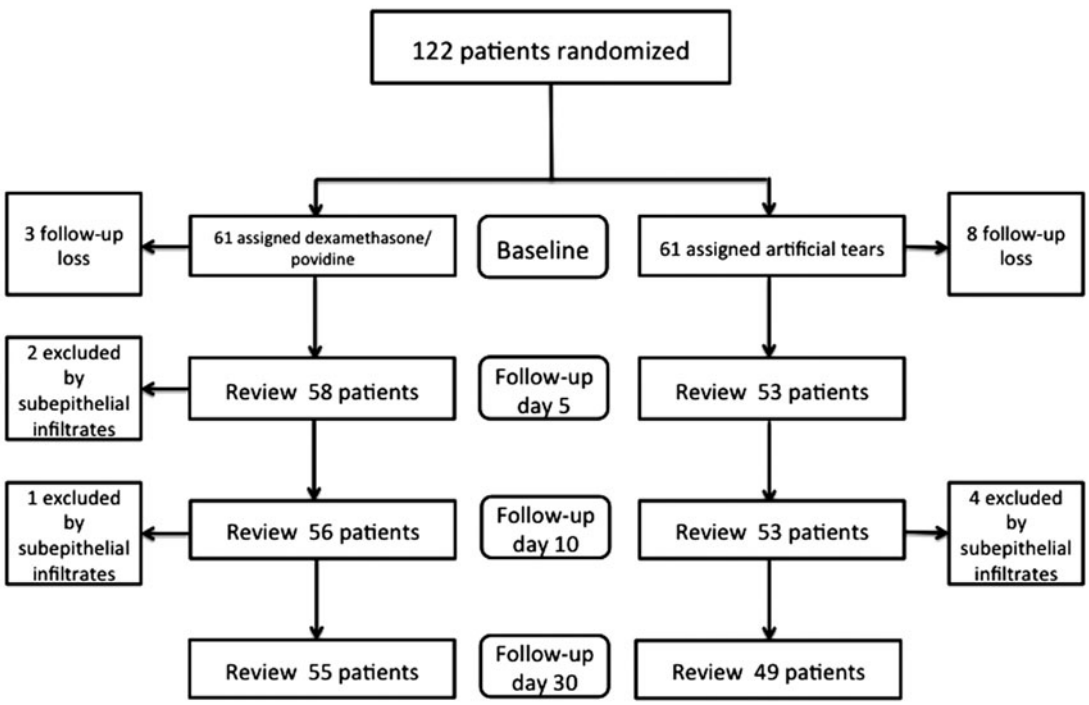

FIGURE 1 Dexamethasone/povidone eye drops versus artificial tears for treatment of presumed viral conjunctivitis: trial profile.

TABLE 1 Dexamethasone/povidone eye drops versus artificial tears for treatment of presumed viral conjunctivitis: demographic and clinical characteristics.

	All patients			Adenovirus PCR +		
	Dexamethasone/ povidone ($n=61$)	Artificial tears ($n=61$)	p Values	Dexamethasone/ povidone ($n=36$)	Artificial tears ($n=36$)	p Values
Median age (years)	36.93 (±12.92)	35.25 (±13.74)	0.38[a]	34.80 (±12.0)	34.80 (±13.70)	0.813[a]
Male (%)	37.7	45.9	0.36[b]	41.6	47.2	0.63[b]
Median days with symptoms	2.23 (±1.45)	1.89 (±1.11)	0.25[a]	2.31 (±1.40)	1.94 (±1.10)	0.312[a]
Associated upper respiratory infection (%)	34.4	22.9	0.14[b]	44.4	16.6	0.01[b]
Follicles on inferior tarsal conjunctiva (%)	93.4	95.0	1.0[c]	97.2	94.4	1.0[c]
Preauricular node (%)	16.3	19.6	0.64[b]	16.6	13.8	0.74[b]
Contact with person with a red eye (%)	52.4	54.0	0.86[b]	58.3	58.3	1.0[b]

[a]Mann–Whitney test.
[b]Pearson chi-square test.
[c]Fisher's exact test.

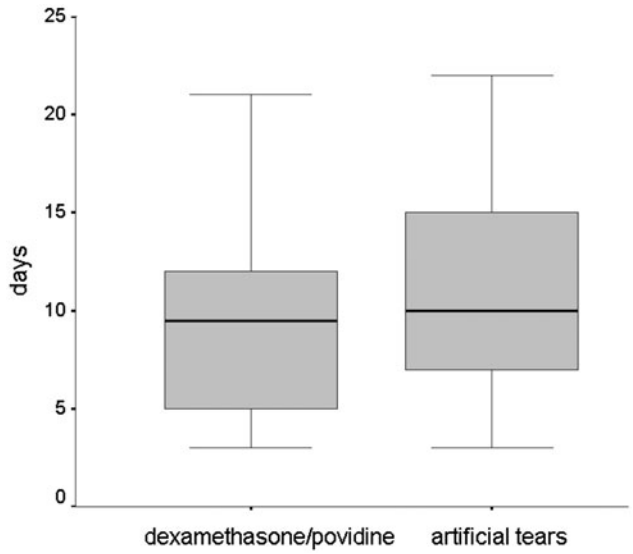

FIGURE 2 Dexamethasone/povidone eye drops versus artificial tears for treatment of presumed viral conjunctivitis: duration of conjunctivitis reported by the patients.

patients in whom the conditions were present (Table 2). We considered only patients with data from all follow-up days for statistical analysis ($n=56$ for treatment group and 53 for control group), where symptoms were reduced. Both medications significantly reduced all symptoms ($p<0.001$), which is expected since it is a self-limiting condition, but there was no statistically significant difference comparing the reduction of any symptoms between the dexamethasone 0.1%/povidone-iodine 0.4% and artificial tears groups.

When asked about the benefits of their treatment, 12 (20.7%) patients in the dexamethasone 0.1%/povidone-iodine 0.4% group answered that the treatment did not help or that they were unsure if the treatment helped, and 46 (79.3%) patients thought it helped or reported that it definitely helped. Meanwhile, 12 (22.6%) patients in the artificial tears group answered that the treatment did not help or that they were unsure if the treatment helped, and 41 (77.4%) patients thought it helped or reported that it definitely helped. There was no statistically significant difference between responses of patients who received artificial tears and those who received dexamethasone 0.1%/povidone-iodine 0.4% ($p=0.800$, Pearson chi-square test).

The incidence of of subepithelial corneal infiltrate at the follow-up examinations 5, 10 and 30 d after the initial examination (baseline) in each group was compared. On day 5, there were 2 (3.4%) cases of subepithelial corneal infiltrate in the dexamethasone 0.1%/povidone-iodine 0.4% group, and there were no cases in the artificial tears group. On day 10, there was one (1.7%) case in the treatment group and four (7.5%) cases in the control group. On day 30, there were eight (14.5%) cases in the treatment group and two (4%) cases in the control group. There was no statistically significant difference in the frequency of the incidence of subepithelial corneal between the two groups on any follow-up day [$p=0.496$ (day 5), $p=0.198$ (day 10), $p=0.098$ (day 30); Fisher's exact test]. These patients with subepithelial corneal infiltrates were successfully treated with topical prednisolone 0.1% within four weeks.

Intraocular pressure was measured at baseline and on follow-up days. Patients from the dexamethasone 0.1%/povidone-iodine 0.4% group had a mean intraocular pressure of 12.1 mmHg (baseline), 12.1 mmHg (day 5), 11.8 mmHg (day 10) and 11.9 mmHg (day 30). The patients receiving artificial tears had intraocular pressure of 12.16 mmHg (baseline), 12.27 mmHg (day 5), 11.8 mmHg (day 10) and 12.33 mmHg (day 30). There was no statistically significant difference between groups.

A comparison of the adverse effects showed that 13 (22.4%) patients who used dexamethasone 0.1%/povidone-iodine 0.4% reported stinging and while only 1 (1.9%) used artificial tears. This was statistically significant, $p=0.001$.

TABLE 2 Dexamethasone/povidone eye drops versus artificial tears for treatment of presumed viral conjunctivitis: comparisons of symptoms between the groups on the initial evaluations and follow-ups on days 5 and 10.

Conjunctivitis Symptom	All patients								Adenovirus PCR +							
	Dexamethasone/ Povidone ($n=56$)				Artificial tears ($n=53$)			Group versus time interaction	Dexamethasone/ Povidone ($n=36$)				Artificial tears ($n=36$)			Group versus time interaction
	Baseline	Day 5	Day 10	p Value*	Baseline	Day 5	Day 10	p Values*	p Values	Baseline	Day 5	Day 10	p Values*	Baseline	Day 5	Day 10	p Values*	p Values
Overall (%)	100	85.7	44.6	<0.001	98.1	84.9	54.7	<0.001	0.316	100	87.8	57.5	<0.001	96.9	93.9	57.5	<0.001	0.658
Itching (%)	96.4	67.8	37.5	<0.001	96.2	75.4	39.6	<0.001	0.672	100	75.7	48.4	<0.001	96.9	78.7	39.3	<0.001	0.573
Foreign body sensation (%)	92.8	57.1	23.2	<0.001	90.5	56.6	28.3	<0.001	0.699	87.8	57.5	27.2	<0.001	90.9	54.5	24.2	<0.001	0.838
Tearing (%)	98.2	60.7	28.5	<0.001	92.4	66.0	32.0	<0.001	0.426	100	66.6	36.3	<0.001	93.9	69.7	33.3	<0.001	0.733
Redness (%)	96.4	69.6	33.9	<0.001	100	77.3	43.4	<0.001	0.799	100	72.7	36.3	<0.001	100	81.8	42.4	<0.001	0.728
Lid swelling (%)	85.7	48.2	25.0	<0.001	86.7	54.7	24.5	<0.001	0.728	93.9	48.4	30.3	<0.001	84.8	51.5	21.2	<0.001	0.501

ANOVA for repeated measures and profile test. Variables transformed in ranks.

DISCUSSION

Topical dexamethasone 0.1%/povidone-iodine 0.4% used four times daily appears to shorten the duration of conjunctivitis, although it causes more stinging than artificial tears.

The open-label pilot human study by Pelletier et al.[16] documented the efficacy of this new formulation of ophthalmic suspension containing povidone-iodine 0.4% dexamethasone 0.1% in the treatment of adenoviral keratoconjunctivitis. This small, open-label human clinical trial was conducted in light of the extensive ophthalmic use of these two drugs: povidone-iodine[19–26] and dexamethasone.[10,16–18]

After the study by Pelletier et al.[16] was published, Clement et al.[29] published results on tests on rabbit corneas and showed that povidone-iodine 0.4% dexamethasone 0.1% was the most effective agent in minimizing the clinical signs of adenovirus infection in rabbit eyes when the treatment was compared to cidofovir 0.5%, tobramycin/dexamethasone ophthalmic suspension and balanced salt solution. The study concludes with a request for a human phase III clinical trial to test the efficacy of this drug on a larger group and also to evaluate the safety of the treatment in order to properly establish both the therapeutic benefit and any negative side effects. With further study, a formula that combines povidone-iodine 0.4% and dexamethasone 0.1% could become a treatment option for adenoviral keratoconjunctivitis in humans. In our randomized clinical trial of viral conjunctivitis, we demonstrated the benefits of povidone-iodine 0.4%/dexamethasone 0.1%. While corticosteroids alone have been shown to increase the duration of viral shedding and viral titers in the adenovirus 5 New Zealand white rabbit model,[10] this trend was not noted in our human study. Our finding is consistent with the results obtained by Pelletier et al.[16] Although the combination of povidone-iodine 0.4% dexamethasone 0.1% contains dexamethasone, the duration of conjunctivitis was lower in the treated group ($p=0.009$), which suggests that the antiviral activities of preparation counteracts the effects of the dexamethasone alone. Thus, the antiseptic effect of povidone-iodine 0.4% dexamethasone 0.1% probably is capable of inhibiting virus replication. It is also important to note that although statistically significant, the dexamethasone 0.1%/povidone-iodine 0.4% formulation decreased the duration of conjunctivitis by only 2.4 d. Given the socio-economic impact of viral conjunctivitis, 2.4 d may be considered important.

Clinical studies in healthy volunteers that compared the ocular tolerance of eye drops with and without BAC have demonstrated that there was an induction of tear film instability or corneal barrier disruption in the subject group administered eye drops with BAC compared with that in the BAC-free group.[36,37]

Both patient's complaints and objective damage to the ocular surface are more frequent among patients treated with eye drops containing a preservative.[38] In addition, it has been shown that povidone-iodine can also be cytotoxic to corneal cells.[39] In our study, more patient discomfort, such as stinging, was observed in the dexamethasone 0.1%/povidone-iodine 0.4% group, although both solutions contain components that produces discomfort. Although there are no studies in the literature evaluating the *in vivo* effects of isolated BAC on patients with viral conjunctivitis, BAC demonstrated potent *in vitro* activity against the majority of microorganisms, including adenovirus.[40,41] Despite that, we observed a reduction of the duration of the disease when the compound with povidone-iodine was used, which may be explained by the antimicrobial activity of povidone-iodine.[24,28]

However, the study was limited in that patients were asked about the duration of their conjunctivitis on the 30th day; there were no objective, pre-defined criteria for this situation. As a result, the duration of conjunctivitis was based on the patients' subjective reporting. This report may have been biased by the anti-inflammatory effect of steroids, and thus may not have resulted from the combination of the steroid with povidone-iodine. The study was also limited in that the symptom questionnaire was based on subjective data (patient response) and lacked an analysis of objective data.

Our study revealed that the PCR tests of 72 patients were positive for adenovirus (59.0% positivity), a finding which is similar to that of a previous study,[1] and the incidence was similar between the two groups (36 in the povidone-iodine 0.4%/dexamethasone 0.1% group and 36 in the group receiving artificial tears). The findings of all variables (overall discomfort, itching, foreign body sensation, tearing, redness, eyelid swelling, intraocular pressure and subepithelial corneal infiltrate incidence) were similar among patients with both negative and positive PCR results.

It was unclear why topical dexamethasone 0.1% as a component of the treatment did not relieve the symptoms of viral conjunctivitis when it was successful in a large randomized placebo-controlled study of the topical steroid alone.[42] A possibility is that patient responses were influenced by the stinging sensation, which was significant in treated group ($p = 0.001$). However, stinging may be reduced through pH normalization or the use of a lower povidone concentration. Additional studies are needed to test this hypothesis. Although a previous study[43] reported a high incidence of permanent ''dry eye'' in the post-infection period of adenovirus with the use of steroids for six weeks, this was not observed in our study or in similar studies with steroids, perhaps because of the short duration of the treatment (seven days). However, no long-term follow-up was performed to evaluate this issue.

Thus, an effective treatment for the symptoms and signs of acute follicular conjunctivitis has yet to be found. An improvement of the side effects and more studies on measurements of viral titers are needed to show whether povidone-iodine 0.4%/dexamethasone 0.1% can be a treatment option.

ACKNOWLEDGEMENTS

We would like to thank the Brazilian company, Ophthalmos S/A, for the materials, the UNICAMP colleagues and professors for their commitment to this study and the Statistical Service of the UNICAMP School of Medical Sciences.

DECLARATION OF INTEREST

No conflicting relationship exists for any author.

Financial Support: Ophthalmos S/A, Sao Paulo, Brazil. The sponsor or funding organization had no role in the design or conduct of this research.

REFERENCES

1. Sambursky RP, Fram N, Cohen EJ. The prevalence of adenoviral conjunctivitis at the Wills Eye Hospital Emergency Room. Optometry 2007;78:236–239.
2. Cooper RJ, Hallett R, Tullo AB, Klapper PE. The epidemiology of adenovirus infections in Greater Manchester, UK 1982-96. Epidemiol Infect 2000;125:333–345.
3. Hussain MA, Costello P, Morris DJ, Bailey AS, Corbitt G, Cooper RJ, et al. Comparison of primer sets for detection of fecal and ocular adenovirus infection using the polymerase chain reaction. J Med Virol 1996;49:187–194.
4. Scott IU. Viral conjunctivitis. 2014 Jun 5. Available from: http://emedicine.medscape.com/article/1191370-overview [last accessed 13 Jun 2014].
5. Park S-W, Lee C-S, Jang H-C, Kim E-C, Oh M, Choe K-W. Rapid identification of the coxsackievirus A24 variant by molecular serotyping in an outbreak of acute hemorrhagic conjunctivitis. J Clin Microbiol 2005;43:1069–1071.
6. Kimura R, Migita H, Kadonosono K, Uchio E. Is it possible to detect the presence of adenovirus in conjunctiva before the onset of conjunctivitis? Acta Ophthalmol 2009;87:44–47.
7. Udeh BL, Schneider JE, Ohsfeldt RL. Cost effectiveness of a point-of-care test for adenoviral conjunctivitis. Am J Med Sci 2008;336:254–264.
8. Kaneko H, Maruko I, Iida T, Ohguchi T, Aoki K, Ohno S, Suzutani T. The possibility of human adenovirus detection from the conjunctiva in asymptomatic cases during nosocomial infection. Cornea 2008;27:527–530.
9. Sambursky R, Trattler W, Tauber S, Starr C, Friedberg M, Boland T, et al. Sensitivity and specificity of the AdenoPlus test for diagnosing adenoviral conjunctivitis. JAMA Ophthalmol 2013;131:17–22.
10. Romanowski EG, Roba LA, Wiley L, Araullo-Cruz T, Gordon YJ. The effects of corticosteroids of adenoviral replication. Arch Ophthalmol 1996;114:581–585.
11. Romanowski EG, Yates KA, Gordon YJ. Antiviral prophylaxis with twice daily topical cidofovir protects against

challenge in the adenovirus type 5/New Zealand rabbit ocular model. Antiviral Res 2001;52:275–280.
12. Hillenkamp J, Reinhard T, Ross RS, Böhringer D, Cartsburg O, Roggendorf M, et al. The effects of cidofovir 1% with and without cyclosporin a 1% as a topical treatment of acute adenoviral keratoconjunctivitis: a controlled clinical pilot study. Ophthalmology 2002;109:845–850.
13. Meyer-Rüsenberg B, Loderstädt U, Richard G, Kaulfers P-M, Gesser C. Epidemic keratoconjunctivitis: the current situation and recommendations for prevention and treatment. Dtsch Arztebl Int 2011;108:475–480.
14. Awan MA, Agarwal PK, Watson DG, McGhee CNJ, Dutton GN. Penetration of topical and subconjunctival corticosteroids into human aqueous humour and its therapeutic significance. Br J Ophthalmol 2009;93:708–713.
15. Weijtens O, Schoemaker RC, Romijn FPHTM, Cohen AF, Lentjes EGWM, van Meurs JC. Intraocular penetration and systemic absorption after topical application of dexamethasone disodium phosphate. Ophthalmology 2002;109: 1887–1891.
16. Pelletier JS, Stewart K, Trattler W, Ritterband DC, Braverman S, Samson CM, et al. A combination povidone-iodine 0.4%/dexamethasone 0.1% ophthalmic suspension in the treatment of adenoviral conjunctivitis. Adv Ther 2009;26:776–783.
17. Holland EJ, Bartlett JD, Paterno MR, Usner DW, Comstock TL. Effects of loteprednol/tobramycin versus dexamethasone/tobramycin on intraocular pressure in healthy volunteers. Cornea 2008;27:50–55.
18. Mohan N, Gupta V, Tandon R, Gupta SK, Vajpayee RB. Topical ciprofloxacin-dexamethasone combination therapy after cataract surgery: randomized controlled clinical trial. J Cataract Refract Surg 2001;27:1975–1978.
19. Kadam SP. Application of betadine (povidone iodine) to infected corneal ulcer. Indian J Ophthalmol 1987;35: 135–136.
20. Isenberg SJ, Apt L, Valenton M, Del Signore M, Cubillan L, Labrador MA, et al. A controlled trial of povidone-iodine to treat infectious conjunctivitis in children. Am J Ophthalmol 2002;134:681–688.
21. Isenberg SJ. The ocular application of povidone-iodine. Community Eye Health 2003;16:30–31.
22. Safar A, Dellimore MC. The effect of povidone iodine flush versus drops on conjunctival colonization before intravitreal injections. Int Ophthalmol 2007;27:307–312.
23. Ferguson AW, Scott JA, McGavigan J, Elton RA, McLean J, Schmidt U, et al. Comparison of 5% povidone-iodine solution against 1% povidone-iodine solution in preoperative cataract surgery antisepsis: a prospective randomised double blind study. Br J Ophthalmol 2003;87:163–167.
24. Benevento WJ, Murray P, Reed CA, Pepose JS. The sensitivity of Neisseria gonorrhoeae, Chlamydia trachomatis, and herpes simplex type II to disinfection with povidone-iodine. Am J Ophthalmol 1990;109:329–333.
25. Melki SA, Safar A, Yaghouti F, Scharper P, Scharper M, Zeligs B, et al. Effect of topical povidone-iodine versus topical ofloxacin on experimental *Staphylococcus keratitis*. Graefes Arch Clin Exp Ophthalmol 2000;238:459–462.
26. Berkelman RL, Holland BW, Anderson RL. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. J Clin Microbiol 1982;15:635–639.
27. Monnerat N, Bossart W, Thiel MA. [Povidone-iodine for treatment of adenoviral conjunctivitis: an in vitro study]. Klin Monbl Augenheilkd 2006;223:349–352.
28. Kawana R, Kitamura T, Nakagomi O, Matsumoto I, Arita M, Yoshihara N, et al. Inactivation of human viruses by povidone-iodine in comparison with other antiseptics. Dermatology (Basel) 1997;195:29–35.
29. Clement C, Capriotti JA, Kumar M, Hobden JA, Foster TP, Bhattacharjee PS, et al. Clinical and antiviral efficacy of an ophthalmic formulation of dexamethasone povidone-iodine in a rabbit model of adenoviral keratoconjunctivitis. Invest Ophthalmol Vis Sci 2011;52:339–344.
30. Kinloch R, Mackay N, Mautner V. Adenovirus hexon. Sequence comparison of subgroup C serotypes 2 and 5. J Biol Chem 1984;259:6431–6436.
31. Turner PC, Bailey AS, Cooper RJ, Morris DJ. The polymerase chain reaction for detecting adenovirus DNA in formalin-fixed, paraffin-embedded tissue obtained post mortem. J Infect 1993;27:43–46.
32. Allard A, Girones R, Juto P, Wadell G. Polymerase chain reaction for detection of adenoviruses in stool samples. J Clin Microbiol 1991;29:2683.
33. Morris DJ, Bailey AS, Cooper RJ, Turner PC, Jackson R, Corbitt G, Tullo AB. Polymerase chain reaction for rapid detection of ocular adenovirus infection. J Med Virol 1995; 46:126–132.
34. Shiuey Y, Ambati BK, Adamis AP. A randomized, double-masked trial of topical ketorolac versus artificial tears for treatment of viral conjunctivitis. Ophthalmology 2000;107: 1512–1517.
35. Ward JB, Siojo LG, Waller SG. A prospective, masked clinical trial of trifluridine, dexamethasone, and artificial tears in the treatment of epidemic keratoconjunctivitis. Cornea 1993;12:216–221.
36. Baudouin C, de Lunardo C. Short-term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. Br J Ophthalmol 1998;82: 39–42.
37. Ishibashi T, Yokoi N, Kinoshita S. Comparison of the short-term effects on the human corneal surface of topical timolol maleate with and without benzalkonium chloride. J Glaucoma 2003;12:486–490.
38. Levrat F, Pisella PJ, Baudouin C. [Clinical tolerance of antiglaucoma eyedrops with and without a preservative. Results of an unpublished survey in Europe]. J Fr Ophtalmol 1999;22:186–191.
39. Chou S-F, Lin C-H, Chang S-W. Povidone-iodine application induces corneal cell death through fixation. Br J Ophthalmol 2011;95:277–283.
40. Bélec L, Tevi-Benissan C, Bianchi A, Cotigny S, Beumont-Mauviel M, Si-Mohamed A, et al. In vitro inactivation of *Chlamydia trachomatis* and of a panel of DNA (HSV-2, CMV, adenovirus, BK virus) and RNA (RSV, enterovirus) viruses by the spermicide benzalkonium chloride. J Antimicrob Chemother 2000;46:685–693.
41. Lazzaro DR, Abulawi K, Hajee ME. In vitro cytotoxic effects of benzalkonium chloride on adenovirus. Eye Contact Lens 2009;35:329–332.
42. Wilkins MR, Khan S, Bunce C, Khawaja A, Siriwardena D, Larkin DFP. A randomised placebo-controlled trial of topical steroid in presumed viral conjunctivitis. Br J Ophthalmol. 2011;95:1299–1303.
43. Trauzettel-Klosinski S, Sundmacher R, Wigand R. [The effects of topical steroids in epidemic kerato-conjunctivitis (author's transl)]. Klin Monbl Augenheilkd 1980;176: 899–906.