Original Article

Comparison between the Efficacy and Tolerability of Polyvinylpyrrolidone-Iodine Eye Drops 0.6% and 1% in Adenoviral Keratoconjunctivitis: A Randomized Clinical Trial

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Abstract

Purpose: To investigate the effect of topical Polyvinylpyrrolidone-iodine (PVP-I) 0.6% on the clinical course of adenoviral keratoconjunctivitis compared with PVP-I 1% and artificial tears.

Methods: We prospectively enrolled all patients over 18 years of age with a polymerase chain reaction (PCR)-confirmed diagnosis of adenoviral keratoconjunctivitis who presented to the hospital between November 2022 and June 2023. Patients were randomized into 3 groups: artificial tears (control), PVP-I 1%, and PVP-I 0.6% eye drops, 4 times daily for 5 days. Clinical signs at presentation and at 6 follow-up visits during the 1st 3 weeks of the acute phase were recorded. Patients were also followed up at 1 and 3 months.

Results: Ninety-four patients completed the study, of which 30, 31, and 33 were in the control, PVP-I 1%, and PVP-I 0.6% groups, respectively. The mean age of the patients was 37.2 years (interquartile range: 25-46). The PCR result was positive in 75.6% of patients with the clinical suspicion. PVP-I, regardless of the concentration, was superior to the artificial tears in terms of time to resolution of lid swelling, discharge, and incidence of subsequent subepithelial infiltrates ($P < 0.05$). However, a concentration of 0.6% was equivalent to 1%. No significant adverse events were reported in any group.

Conclusions: The PVP-I 0.6% topical drops are safe and well tolerated in patients with acute adenoviral keratoconjunctivitis. It can be substituted for the 1% solution as it has comparable effects in improving the clinical course and reducing subsequent complications.

Keywords: Antiviral agents, Epidemic keratoconjunctivitis, Human adenovirus, Povidone-iodine, Subepithelial infiltrates

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Submitted: 04-Nov-2023; **Revised:** 19-Dec-2023; **Accepted:** 25-Dec-2023; **Published:** 10-Aug-2024

Introduction

Infectious conjunctivitis is a common ocular problem worldwide that can be caused by a variety of microorganisms, including viruses and bacteria. Adenovirus accounts for 59%-78% of cases with a clinical diagnosis of infectious conjunctivitis.[1-3] Epidemic keratoconjunctivitis (EKC) is a form of viral conjunctivitis that is highly contagious and is mainly caused by adenovirus. In particular, it may involve the respiratory system and gastrointestinal tract.[4] Adenovirus serotypes 8, 37, 53, 54, 56, and 64 (called adenovirus-D) are associated with EKC, and the clinical course of them is significantly more severe than other serotypes or adenovirus-negative keratoconjunctivitis.[1,5,6]

While the conjunctival manifestations can vary from mild follicular conjunctivitis to hyperacute, exudative conjunctivitis with membranes or pseudomembranes lasting 1-3 weeks, EKC is a unique form of adenovirus conjunctivitis due to

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joco

DOI: 10.4103/joco.joco_251_23

How to cite this article: Makateb A, Soleymanzadeh M, Soleiman-Meigooni S, Asgari A, Etemadi MR, Mafi AR, *et al*. Comparison between the efficacy and tolerability of polyvinylpyrrolidone-iodine eye drops 0.6% and 1% in adenoviral keratoconjunctivitis: A randomized clinical trial. J Curr Ophthalmol 2023;35:337-44.

corneal involvement. Acute EKC is a clinical diagnosis presented by the classic triad of follicular conjunctivitis, preauricular lymphadenopathy, and punctate or geographic epithelial keratitis, although the severity of the disease is highly variable.[7,8] Keratitis usually presents on the 4th day of the disease, which may herald the later development of stromal keratitis, and manifests as subepithelial infiltrates (SEIs). These infiltrates are pathognomonic for EKC and often persist or recur for months to years after the acute infection, occasionally leading to subsequent vision loss.[9,10]

Although adenoviral keratoconjunctivitis is a self-limiting disease, most patients experience severe pain, foreign body sensation, and blurred vision. On the other hand, delayed SEIs can lead to recurrent or permanent vision loss. Although topical corticosteroids can effectively resolve these sight-threatening complications, the recurrence rate after tapering is significant (30%).[11,12] Povidone-iodine (polyvinylpyrrolidone iodine, PVP-I) is a water-soluble complex and has been used in the treatment of conjunctivitis, keratitis, and endophthalmitis.[13] Recent studies have shown that topical use of the PVP-I can be effective in treating acute EKC and reducing the late complications.[14-16] However, this agent is irritating, leading to low compliance. The most commonly studied concentrations are 0.4%-5% of PVP-I.[12,16,17] Recently, a study has compared PVP-I 0.6% with artificial tears and showed promising results.[18]

Here, we aimed to compare the effect of PVP-I 0.6% with 1% on the clinical course of EKC and late complications such as SEIs.

Methods

This study was a randomized, open-labeled, clinical trial that was conducted in a tertiary university hospital (Imam Reza Hospital, affiliated to AJA University of Medical Sciences) from November 2022 to June 2023. It was carried out in compliance with the Declaration of Helsinki and was approved by the Ethical Committee at AJA University of Medical Sciences (IR.AJAUMS.REC.1401.191). The trial was assigned to the Thai Clinical Trials Registry with the identifier code of "TCTR20230825004" and the relevant information is available online through https://www.thaiclinicaltrials.org/show/TCTR20230825004.

Informed consent was obtained from all the patients before enrollment. Due to the infectious nature of the disease and lack of access to all the patients before the start of the study, a covariate adaptive randomization method was used to allocate patients to each study arm.[19] Gender and mean age were considered covariates of randomization, and the study arms included treatment with commercially available artificial tears 4 times daily for 5 days as the control group, treatment with PVP-I 1% eye drops 4 times daily for 5 days as treatment group 1, and treatment with PVP-I 0.6% eye drops 4 times daily for 5 days as treatment group 2.

The study included patients aged 18 years or older with best-corrected visual acuity of 0.60 logMAR or better in each eye, and a clinical diagnosis of acute adenoviral keratoconjunctivitis in at least one eye with symptoms of conjunctivitis lasting up to five days. After informed consent was obtained, cotton swab samples were taken for polymerase chain reaction (PCR) testing and patients were allocated to one of the study arms and treatment was started. If the PCR result was negative, the patient was excluded. Other exclusion criteria were follow-up of <3 months, pregnancy or lactation, presence of ocular inflammation and uveitis, history of elevated intraocular pressure or current glaucoma, history of herpetic keratitis, recurrent corneal erosion, or other types of keratitis, recent ocular surgery in the last 6 months, use of topical or systemic corticosteroids, history of hyperthyroidism, uncontrolled systemic diseases, autoimmune diseases, or debilitating diseases, and known hypersensitivity to iodine.

Contact lenses, corticosteroids, topical or systemic antivirals, or any other topical ophthalmic solutions were not allowed to use in the study.

All patients were examined in the acute phase on days zero (baseline), 3, 5, 7, 10, 15, and 20 after diagnosis of the disease. A complete ophthalmic examination was performed by two ophthalmologists at each visit. Patients were assessed for conjunctival redness, follicular reaction on the inferior palpebral conjunctiva, discharge, eyelid swelling, corneal epitheliopathy, chemosis, and pseudomembrane formation. SEI and symblepharon formation were also evaluated. They were also asked about symptoms such as intermittent blurred vision, eye discomfort, dry eye, and photophobia.

At diagnosis, conjunctival swabs were taken from the lower fornix of the eye using a sterile Virocult swab. The swabs were dissolved in viral transport medium (VTM) and transported on wet ice to the virology laboratory and frozen at -80°C. Viral genome was extracted from the filtered VTM using the MagMAX Viral Ribonucleic Acid Isolation Kit. The quality of the extracts was measured using NanoDrop. HAdV hexon gene hypervariable regions 1-6 were used for detection of HAdV as described by Lu and Erdman.[20] The HAdVhexF1/AdhexR1 primer set was used for the first round of PCR. All samples with negative results with the first primer set were subjected to the second nested PCR using an internal primer including AdhexF2 and AdhexR2. The PCR employed the following settings: a denaturation step at 94°C for 10 minutes. Subsequently, 35 cycles were conducted, each comprising a denaturation step at 94°C for 50 seconds and an annealing step at 44°C for 30 seconds. This was the initial PCR. For the nested PCR, the following temperature and time parameters were employed: 52°C for 30 seconds, 72°C for 45 seconds, and a final extension at 72°C for 10 minutes. The PCR products were separated by electrophoresis in a 2.5% agarose gel and visualized using ethidium bromide under UV light.

Statistical analysis

We used mean, standard deviation, median and range, frequency, and percentage to present data. To compare outcomes between

groups, we used Chi-square test (or Fisher exact test where appropriate) and analysis of variance. To account for type I error inflation based on multiple comparisons, we used the Sidak method. All statistical methods were performed using SPSS (IBM Corp. 2000. IBM SPSS Statistics for Windows, version 27.0. Armonk, NY: IBM Corp). P <0.05 is considered statistically significant.

Results

During the study period, 194 patients with a clinical diagnosis of acute adenoviral keratoconjunctivitis were examined in the emergency department. After exclusion of 38 patients, 156 patients were randomized to each study arm. A total of 94 patients were eligible for the final analysis, of which 30, 31, and 33 were in the control, PVP-I 1%, and PVP-I 0.6% groups, respectively [Figure 1]. There were 56 female participants (59.6%). The mean age of the patients was 37.2 years (interquartile range: 25-46). The PCR result was positive in 75.6% of patients with clinical suspicion.

There was no statistically significant difference in the parameters at presentation (day 0) between the study arms, justifying acceptable randomization. Table 1 shows the number of patients who were free of each sign at presentation and at each follow-up visit. There was no significant difference between 1 and 0.6% concentration in any of the comparisons (P > 0.05), but both treatment arms were superior to the control arm in terms of rapid resolution of eyelid swelling and discharge. Other examination results also showed advantages for the PVP-I treatment groups at some of the follow-up sessions [Table 1 and Figures 2a-d, 3a-c].

Among the mid-term complications, subepithelial infiltration was significantly lower in the PVP-I treatment groups compared to the control group, although there was no difference between each concentration of the PVP-I treatment (P > 0.05). There was no significant difference in symblepharon formation between groups [Table 2].

Patients were also monitored for late-related complications. None of the comparisons of complications were significant between study arms [Table 3].

Discussion

Adenoviruses are the etiological factor in up to 70% of conjunctivitis.[21] There are different serotypes with varying severity of disease.[1] High transmissibility and discomfort

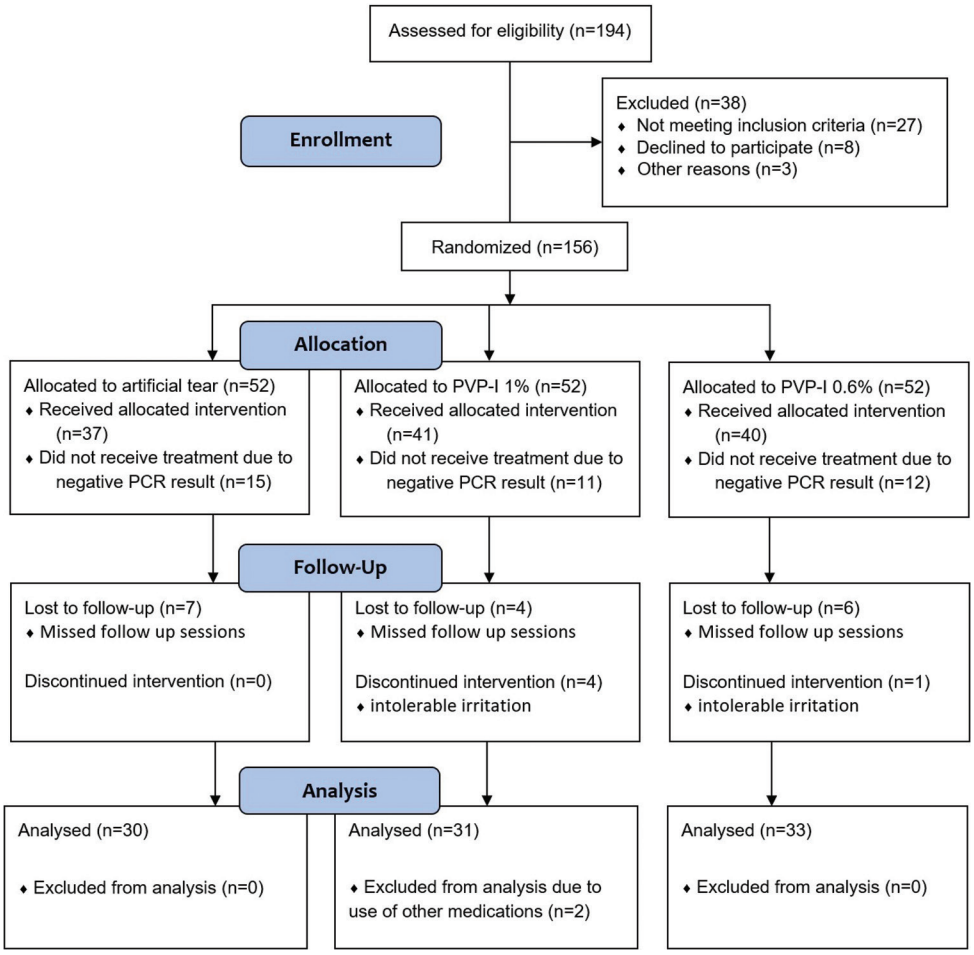

***Figure* 1:** CONSORT *flow* diagram of the progress through the phases of parallel randomized trial of three arms

Table 1: Results of the primary outcome variables in the acute phase of the disease in the study arms

Parameter	Follow-up day	Group			*P* PVP-I 0.6% versus control	*P* PVP-I 0.6% versus PVP-I (1%)
		Control, *n* (%)	PVP-I 1%, *n* (%)	PVP-I 0.6%, *n* (%)		
Conjunctival redness	0	0	0	0	ND	ND
	3	0	0	0	ND	ND
	5	0	0	0	ND	ND
	7	4 (13.3)	3 (9.7)	6 (18.2)	0.613	0.613
	10	11 (36.7)	19 (61.3)	21 (63.6)	0.063	0.846
	15	17 (56.7)	28 (90.3)	30 (90.9)	0.001*	0.936
	20	27 (90.0)	31 (100.0)	32 (97.0)	0.140	ND
Lid swelling	0	11 (36.7)	12 (38.7)	13 (39.4)	0.974	0.974
	3	10 (33.3)	11 (35.5)	14 (42.4)	0.735	0.735
	5	12 (40.0)	17 (54.8)	19 (57.6)	0.332	0.825
	7	14 (46.7)	26 (83.9)	28 (84.8)	<0.001*	0.914
	10	16 (53.3)	27 (87.1)	29 (87.9)	0.001*	0.925
	15	18 (60.0)	29 (93.5)	28 (84.8)	0.003*	0.265
	20	23 (76.7)	30 (96.8)	31 (93.9)	0.022*	0.592
Discharge	0	5 (16.7)	5 (16.1)	8 (24.2)	0.652	0.652
	3	4 (13.3)	12 (38.7)	12 (36.4)	0.057	0.846
	5	6 (20.0)	22 (71.0)	22 (66.7)	<0.001*	0.711
	7	7 (23.3)	26 (83.9)	28 (84.8)	<0.001*	0.914
	10	15 (50.0)	27 (87.1)	30 (90.9)	<0.001*	0.625
	15	17 (56.7)	29 (93.5)	31 (93.9)	<0.001*	0.949
	20	25 (83.3)	30 (96.8)	32 (97.0)	0.066	0.964
Follicular reaction	0	5 (16.7)	1 (3.2)	4 (12.1)	0.607	0.278
	3	3 (10.0)	1 (3.2)	2 (6.1)	0.554	0.554
	5	5 (16.7)	4 (12.9)	5 (15.2)	0.917	0.917
	7	10 (33.3)	16 (51.6)	15 (45.5)	0.343	0.622
	10	10 (33.3)	20 (64.5)	24 (72.7)	0.004*	0.479
	15	18 (60.0)	27 (87.1)	27 (81.8)	0.030*	0.561
	20	27 (90.0)	30 (96.8)	32 (97.0)	0.383	0.964
Chemosis	0	23 (76.7)	24 (77.4)	24 (72.7)	0.895	0.895
	3	22 (73.3)	20 (64.5)	23 (69.7)	0.755	0.755
	5	22 (73.3)	25 (80.6)	26 (78.8)	0.776	0.776
	7	23 (76.7)	29 (93.5)	30 (90.9)	0.104	0.694
	10	23 (76.7)	30 (96.8)	31 (93.9)	0.022*	0.592
	15	25 (83.3)	30 (96.8)	31 (93.9)	0.140	0.592
	20	28 (93.3)	31 (100.0)	33 (100.0)	0.113	ND
Pseudomembrane	0	24 (80.0)	25 (80.6)	25 (75.8)	0.873	0.873
	3	23 (76.7)	23 (74.2)	27 (81.8)	0.756	0.756
	5	23 (76.7)	25 (80.6)	27 (81.8)	0.869	0.869
	7	22 (73.3)	29 (93.5)	31 (93.9)	0.022*	0.949
	10	24 (80.0)	29 (93.5)	31 (93.9)	0.131	0.949
	15	25 (83.3)	29 (93.5)	31 (93.9)	0.278	0.949
	20	29 (96.7)	30 (96.8)	32 (97.0)	0.998	0.998
Corneal epitheliopathy	0	18 (60.0)	20 (64.5)	18 (54.5)	0.718	0.718
	3	17 (56.7)	17 (54.8)	17 (51.5)	0.917	0.917
	5	16 (53.3)	16 (51.6)	19 (57.6)	0.885	0.893
	7	20 (66.7)	21 (67.7)	21 (63.6)	0.937	0.929
	10	19 (63.3)	25 (80.6)	27 (81.8)	0.197	0.904
	15	19 (63.3)	26 (83.9)	29 (87.9)	0.041*	0.645
	20	26 (86.7)	30 (96.8)	30 (93.8)	0.309	0.573

*The values marked with are statistically significant, Numbers indicate patients who did not have the sign at follow-up. PVP-I: Povidone-iodine, ND: Not determined

during the 1 to 3 weeks disease period have made it a major concern. Delayed complications such as SEIs can cause significant ocular morbidity, visual impairment, photophobia, glare, halos, and foreign body sensation. It can persist for months or years and recur many times, requiring appropriate treatment. Currently, there is no approved and effective

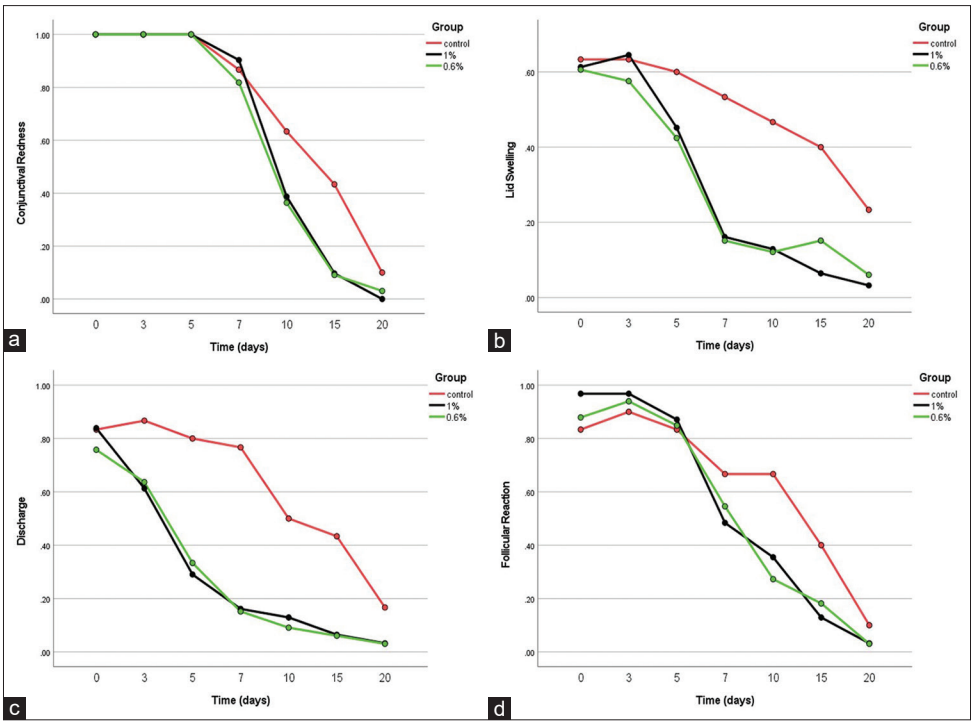

Figure 2: Comparison of resolution of the clinical signs over time in each study arm, including (a) conjunctival redness, (b) lid swelling, (c) discharge, and (d) follicular reaction

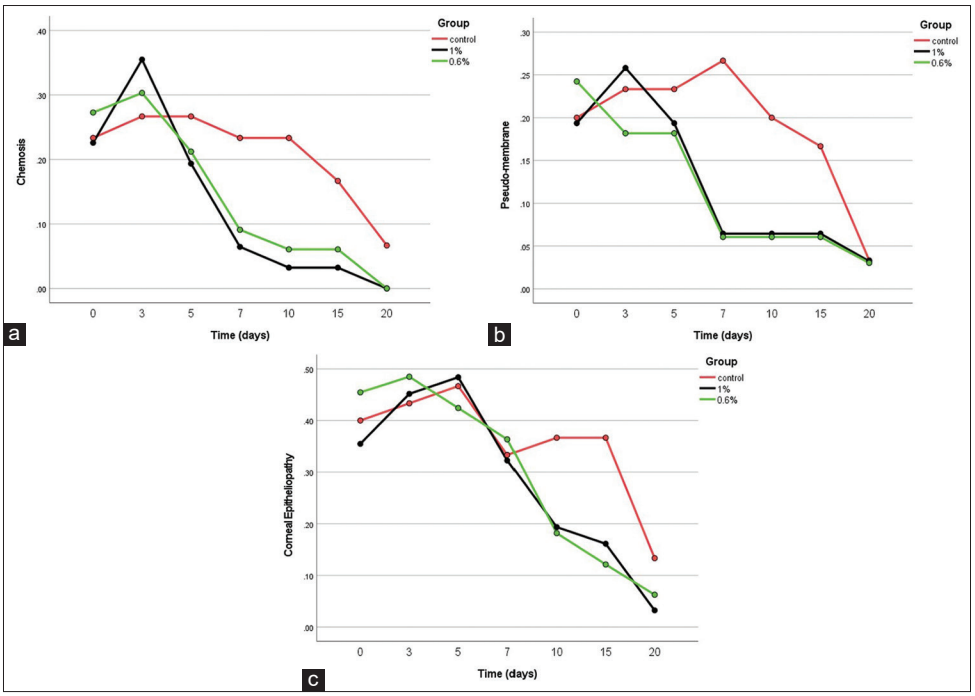

Figure 3: Comparison of resolution of the clinical signs over time in each study arm, including (a) chemosis, (b) pseudomembrane, and (c) corneal epitheliopathy

treatment for adenoviral keratoconjunctivitis. Several antiviral agents such as cidofovir and ganciclovir have been suggested for the 1st week. However, a standard dosage is not known, and significant complications have been reported in comparative studies.[22,23]

PVP-I is a broad-spectrum antiseptic agent used in the preoperative preparation of the skin and mucous membranes.[13] It also inactivates adenoviruses to varying degrees depending on the type,[24,25] which also has a desirable effect on other microorganisms in the case of a misdiagnosis. Povidone is a

Table 2: Comparison of mid-term complications of the disease in the study arms

Parameter	Follow-up (day)	Group			*P* PVP-I 0.6% versus control	*P* PVP-I 0.6% versus PVP-I 1%
		Control, *n* (%)	PVP-I 1%, *n* (%)	PVP-I 0.6%, *n* (%)		
Subepithelial infiltration	15	17 (56.7)	28 (90.3)	28 (84.8)	0.003*	0.508
	30	15 (50.0)	29 (93.5)	28 (84.8)	<0.001*	0.265
Symblepharon	30	27 (90.0)	31 (100.0)	32 (97.0)	0.140	ND

*The values marked with are statistically significant. Numbers indicate patients who did not have the complication at follow-up. PVP-I: Povidone-iodine, ND: Not determined

Table 3: Comparison of long-term complications of the disease in the study arms

Parameter	Follow-up (month)	Group			*P* PVP-I 0.6% versus control	*P* PVP-I 0.6% versus PVP-I 1%
		Control, *n* (%)	PVP-I 1%, *n* (%)	PVP-I 0.6%, *n* (%)		
Discomfort	1	8 (26.7)	3 (10.3)	11 (35.5)	0.073	0.457
	3	12 (40.0)	10 (37.0)	12 (40.0)	0.966	0.846
Dry eye	1	18 (60.0)	23 (79.3)	24 (77.4)	0.185	0.859
	3	24 (80.0)	25 (92.6)	25 (89.3)	0.336	0.670
Blurred vision	1	15 (50.0)	17 (56.7)	16 (51.6)	0.864	0.864
	3	14 (46.7)	14 (48.3)	15 (51.7)	0.925	0.925
Photophobia	1	10 (33.3)	11 (36.7)	13 (41.9)	0.782	0.782
	3	15 (50.0)	16 (57.1)	17 (58.6)	0.776	0.910

Numbers indicate patients who did not have the complication at follow-up. None of the comparisons were statistically significant

synthetic polymer that acts as a carrier for iodine, limiting the amount of free iodine present in solution. Therefore, dilution of the PVP-I would increase the concentration of free iodine. Yates *et al*. evaluated the *in vitro* effect of PVP-I against various human adenovirus serotypes at different concentrations. They showed that the same reduction in virus titers occurred in a shorter time for PVP-I 0.4% than 2%, and to 2% than 5% for serotype 37.[26] This may be due to a higher concentration of free iodine and a faster reaction, suggesting that PVP-I 0.6% may have a more rapid effect rather than PVP-I 1% before clearance from the tear lake.[27]

Different prescription methods have been used up to now. It has been used successfully as a single dose therapy for EKC in infants,[28] three times daily for 2 weeks,[29] and four times daily for 5 days in adults.[17] Burning, stinging, and irritation are problems with administration, necessitating the use of lower concentrations.

In this study, we evaluated the effects of PVP-I 0.6% in comparison to PVP-I 1% and artificial tears in a 5-day regimen once EKC was diagnosed. The results showed a significantly faster improvement in lid swelling and ocular discharge in the acute phase and a decrease in late SEIs compared to the control group. On the other hand, the concentration of 0.6% was not inferior to 1%. These findings, together with less ocular irritation and possibly a more rapid virucidal effect, lead to the conclusion that PVP-I 0.6% drops may be a better choice.

In a recent randomized clinical trial (RCT) in 2022, Ricciardelli *et al*. evaluated the efficacy and tolerability of PVP-I 0.6% treatment for EKC in 59 patients. Participants showed a significantly shorter resolution time and lower incidence of SEI compared to patients in the control group treated with artificial tears. At the final visit, SEIs were present in 8.8% of the treatment group compared to 44% of the control group.[18] Their findings are consistent with our study, as SEIs were present in 50%, 6.5%, and 15.2% of the control, PVP-I 1%, and 0.6% groups, respectively. However, this finding has not been demonstrated in other studies.

In another double-masked RCT in 2019, Shorter *et al*. evaluated the safety and efficacy of a 5% PVP-I solution as a single treatment for the management of EKC in 56 participants. They observed no adverse effects, a transient increase in corneal staining, and concluded that PVP-I 5% was an effective treatment.[30]

Due to the potential chemical irritation of the PVP-I solution and the management of existing inflammation, combination therapy with PVP-I and dexamethasone has gained interest. Pelletier *et al*. in 2009 used the combination of PVP-I 0.4%/dexamethasone 0.1% ophthalmic suspension to treat EKC. They selected cases based on RPS Adeno Detector positivity and did not compare results with placebo. Assessment of clinical resolution 3 days after treatment showed success in eight out of nine cases.[31] We did not use this combination in the current study because some experimental data in rabbits suggest that topical steroids prolong viral shedding time.[32] Furthermore, we only wanted to see if we could use a lower concentration of PVP-I.

In a double-blind RCT in 2017, Kovalyuk *et al*. investigated the effect of a combination of PVP-I 1% and dexamethasone 0.1% drop on EKC in 78 eyes. Eyelid swelling, conjunctival injection, and conjunctival discharge were significantly

reduced. SEIs were observed in 44% of the dexamethasone 0.1% group, 20% of the artificial tear group and 0% of the treatment group. A reduction in viral titer, viral spread, shortening of the clinical course, and preservation of visual function during EKC has been achieved using PVP-I 0.4% in combination with dexamethasone 0.1% four times a day.[33] Pinto *et al*., in a similar study, also concluded that the combination of PVP-I 0.4%/dexamethasone 0.1% was more effective than artificial tears alone in accelerating recovery, but they did not observe a statistically significant difference in the incidence of SEI over the entire follow up period.[34]

Furthermore, in 2018, in a similar RCT, Pepose *et al*. evaluated combination therapy with a higher concentration of PVP-I (PVP-I 0.6%/dexamethasone 0.1%) for a period of 5 days with instillation 4 times daily. They observed a faster resolution of clinical signs and a faster reduction in viral replication than those treated with artificial tears.[12]

To date, only topical corticosteroids and tacrolimus 0.03% appear to alter the course of chronic keratitis and SEI after EKC.[35,36] In this study, the use of PVP-I 0.6% reduced the incidence of SEI formation, presumably by reducing the extracellular viral load and thus the immunological stimuli. However, in a meta-analysis of five studies conducted in 2023, PVP-I in combination with dexamethasone in the acute phase did not influence the risk of developing SEI.[37]

The study was conducted in a single hospital in a single country, which may limit the generalizability of the results. The sample size was relatively small due to the limited time available to conduct the study. Serotype analysis of adenoviruses and assessment of conjunctival viral titers could not be performed due to limited funding for the study, while different serotypes and viral titers may have different disease severity and resolution time.[1,38] Although participants were included if they presented with acute symptoms within 5 days, it is likely that subjects presented at different times during the course of the infection. The follow-up period was relatively short. In order not to miss a follow-up visit, two ophthalmologists took turns to perform the examinations every 2nd day of the week, so interobserver variability could be a source of bias. Another important limitation of the study is the relatively short follow-up period, which makes it difficult to comment on long-term complications of the treatment regimens and the disease itself; in particular, dry eye may be an important side effect due to the destruction of goblet cells with the use of PVP-I. Furthermore, due to the nature of the PVP-I drops, this was an open-label RCT, which may also be a major source of bias.

PVP-I 0.6% ophthalmic solution is safe and well tolerated in patients with acute EKC. The study showed that both 0.6% and 1% concentrations of PVP-I eye drops as a 5-day regimen in the early days of clinically significant adenoviral keratoconjunctivitis were superior to artificial tears in terms of rapid resolution of clinical signs and reduction in later complications such as SEI. PVP-I 0.6% can be safely substituted for the 1% solution due to comparable results. Therefore, as a readily available and inexpensive treatment with broad-spectrum antiseptic priorities, PVP-I 0.6% drops can be used in the management of EKC and, possibly by reducing the viral load, may be effective in reducing the rate of SEI formation and the contagiousness of the disease. Studies with larger samples and longer follow-up are needed to assess long-term complications associated with treatment with PVP-I.

Financial support and sponsorship

The fund for performing PCR tests was provided by the research center of the AJA University of Medical Sciences from budget for research and development.

Conflicts of interest

There are no conflicts of interest.

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