• Clinical Research •

Effect of diluted povidone iodine in adenoviral keratoconjunctivitis on the rate of subepithelial corneal infiltrates

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Abstract

• AIM: To evaluate the clinical characteristics of adenoviral keratoconjunctivitis, the management modalities, as well as the incidence of subepithelial corneal infiltrates (SEI).

• METHODS: Patients with characteristic clinical symptoms and signs, who presented to our clinic within the first week of symptoms and received the diagnosis of adenoviral keratoconjunctivitis between January 2013 and April 2016, were included in the study. A total of 211 patients were included in the study. Patients were evaluated for the incidence of clinical signs, late complications, management preferences, and the effect of diluted povidone-iodine (d-PVP-I) 2%.

• RESULTS: Patients' mean age was 33.03±14.76y. We observed an increase in the number of cases according to the years. At presentation and/or early follow-up, the clinical signs were conjunctival hyperemia (100%), conjunctival follicules (79.1%), edema of the eyelids (39.3%), chemosis (16.1%), pseudomembrane formation (16.6%), and corneal epitheliopathy (29.9%). During late follow-up 13.3% patients developed conjunctival subepithelial fibrosis, and 39.8% developed SEI. A significant decrease in the incidence of SEI development was observed in patients who used d-PVP-I 2% (*P*=0.032; 33.3% *vs* 45.9%, respectively in patients who received d-PVP-I 2% and who did not).

• CONCLUSION: Adenoviral keratoconjunctivitis has a tremendous effect on patient's comfort and abilities in short-term. Additionally, almost half of the patients develop visual problems related to SEI. According to our clinical experience, using d-PVP-I 2% in the first days of adenoviral keratoconjunctivitis might be helpful in reducing the risk of SEI as a complication.

• KEYWORDS: conjunctivitis; corneal opacity; infectious keratoconjunctivitis; keratoconjunctivitis; povidone-iodine; viral conjunctivitis

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INTRODUCTION

Adenoviral keratoconjunctivitis (AKC) is a highly contagious infectious disease, which mainly involves the ocular surface and cornea[1]. It can result in community epidemic infections, and lead to waste in labor productivity. The virus is highly resistant to environmental conditions. The incubation time is between 4 and 24d. Infection usually starts in one eye and in 70% of the cases other eye becomes infected[1].

AKC is a biphasic disease, beginning with the infectious phase, which is followed by the inflammatory phase[2]. During the infectious phase, patients usually complain of foreign body sensation, photophobia, and excessive tearing in one or both eyes. The clinical findings are swelling of the lids, conjunctival hyperemia, follicular conjunctivitis, chemosis, subconjunctival hemorrhage, and pseudomembranes[1]. The infectious phase continues for about two weeks. Then, during the inflammatory phase, approximately 40%-50% of the patients develop subepithelial corneal infiltrates (SEI). When these occur, patients may complain of irritation, photophobia as well as decrease in vision, if the infiltrates obscure the optical axis[3]. The SEI may last from a few months to few years.

There is currently no commercially available casually directed treatment for adenovirus. Considering the morbidity and economic impact of the disease, a therapeutic agent that reduces the clinical symptoms and signs of AKC and minimizing the virus shedding would be desirable. Currently, the treatment usually targets the symptoms and auxiliary effects of the virus. Cold compresses, artificial tears, sometimes anti-inflammatory agents are being added. The use of steroids is controversial[4].

Table 1 The numbers of patients with and without the clinical signs

Clinical signs	Total (*n*=211)			Patients not on d-PVP-I (*n*=109)		Patients on d-PVP-I (*n*=102)		χ	*P*
	With sign	No sign	%	With sign	No sign	With sign	No sign		
Eyelid edema	84	127	40	39	70	45	57	1.53	0.216
Chemosis	35	176	17	16	93	19	83	0.59	0.441
Folicular conjunctivitis	169	42	80	90	19	79	23	0.87	0.352
Pseudomembranes	15	176	7	19	90	16	86	0.12	0.733
Epithelial keratopathy	62	149	29	32	77	30	72	0.00	0.993
Subepithelial infiltrates	84	127	40	51	58	33	69	4.58	0.032[a]
Conjunctival fibrosis	31	180	15	18	91	13	89	0.60	0.440
Symblepharon formation	6	205	3	3	106	3	99	0.01	0.934

The column with title "total" represents the total number of patients with or without clinical signs. The following columns show the numbers of patients who were not on (were not given) diluted povidone iodine (d-PVP-I), and who were given (patients on) diluted povidone iodine (d-PVP-I). Patients who showed the clinical signs were shown as with sign, whereas who lack the particular sign were shown as no sign. The numbers were compared using the Chi-square test, and results were shown with χ (Chi). [a]P<0.05 was accepted statistically significant.

Povidone-iodine is a broad-spectrum antiseptic agent. It is being used in ocular surgeries preoperatively, and in neonatal conjunctivitis. Several studies reported the use of povidone iodine in AKC[5-6]. Recently, some of our authors (Altan-Yaycioglu R and Ulas B) also added diluted povidone iodine (d-PVP-I) in the treatment of AKC cases.

Herein, we aimed to evaluate the clinical features of AKC cases as well as the effect of d-PVP-I 2% on the clinical course and late complications such as SEI.

SUBJECTS AND METHODS

Ethical Approval The study was conducted in accordance with the Declaration of Helsinki. Local ethics committee approval was obtained. Informed consent was waived due to the retrospective nature of the study.

In this retrospectively designed study, the charts of patients who presented to our clinic between January 2013 and April 2016, and received the diagnosis of AKC according to the clinical signs were evaluated. Patients, with the complaints of red eye and pain, and had the clinical signs of conjunctival hyperemia, chemosis, intense serous secretion, and/or eyelid edema and pseudomembrane formation received the diagnosis of AKC. Only patients, who had the symptoms and signs for less than 1wk and had no previous treatment and were followed more than 1mo, were included. Patients with longer history were excluded.

The charts of 285 patients were retrospectively evaluated. Of those, 74 had incomplete follow-up, so they were excluded from further evaluation. A total of 211 patients were included in the assessment. We recorded the age, sex, the incidence of clinical signs at presentation, and late complications. As late complications we noted the data on SEI, conjunctival subepithelial fibrosis, and symblepharon formation, which were observed two to three weeks after the initial symptoms. Additionally, the management and preferred treatment modalities were recorded. Patients were prescribed either one or several of the following: antibiotics, artificial tears, antivirals, steroids, non-steroidal anti-inflammatory drugs (NSAID), d-PVP-I, and cyclosporine A. For preparation of d-PVP-I 2%, povidone iodine 10% was mixed with sterile physiologic serum in 1 to 4 ratios, in order to obtain 2% povidone iodine. Patients were recommended to apply d-PVP-I 2% twice a day for 5d.

The average time frame for SEI formation was 14 to 20d. Topical steroids and cyclosporine A were started if the patient had any SEI resulting in visual disturbances.

We analyzed the incidences of clinical signs, and evaluated their relationship with d-PVP-I 2% use. Also, we compared the incidences of SEI development regarding the use of d-PVP-I 2%, corticosteroid and antiviral during the first week of clinical symptoms. The incidences were compared using the Chi-square test. A probability value less than 0.05 was accepted as statistically significant.

RESULTS

Mean age (±standard deviation, SD) of the patients was 33.03±14.76y. The distribution of patients according to the years was 22 cases in 2013, 41 cases in 2014, 115 cases in 2015, and 41 cases in the first 4mo of 2016. So, we observed an increase in AKC cases during the study period. Although the clinical severity of the disease was similar, a decrease in the SEI formation was observed, as the incidence of SEI formation was 45% (10/22) in 2013, 68.3% (28/41) in 2014, 32.3% (37/115) in 2015, and 22% (9/41) in the first four months of 2016.

The incidences of clinical signs are shown on Table 1. Early clinical signs were conjunctival hyperemia (100%), conjunctival follicles (79.1%), edema of the eyelids (39.3%), chemosis (16.1%), pseudomembrane formation (16.6%), and corneal epitheliopathy (29.9%). In the late phase, we observed

Table 2 The distribution of patients who developed subepithelial infiltrates (SEI+) or not (SEI-)

Medication	SEI+	SEI-	Total	*P*
d-PVP-I				0.032[a]
Patients on d-PVP-I	33[c]	69[b]	102	
Patients not on d-PVP-I	51[b]	58[c]	109	
Total	84	127	211	
Topical corticosteroids				0.314
Patients on topical corticosteroids	20	23	43	
Patients not on topical corticosteroids	64	104	168	
Total	84	127	211	
Antivirals				0.029[a]
Patients on antivirals	14[b]	9[c]	23	
Patients not on antiviral	70[c]	118[b]	188	
Total	84	127	211	

The number of patients and who used diluted povidone iodine (d-PVP-I), topical corticosteroids, and antivirals are given in corresponding cells. Chi-square test was used for statistical comparison. [a]$P<0.05$ was accepted statistically significant; [b]Values higher than expected cases; [c]Values lower than expected cases.

SEI in 39.3%, conjunctival subepithelial fibrosis in 13.3% and mild symblepharon formation in 1.4% of cases.

We included patients who were followed by 5 different ophthalmologists. So there were some differences in the management of patients. All patients were given only topical medication. The prescribed medication were antibiotics in 93.4%, artificial tears in 88.2%, d-PVP-I 2% in 48.3%, corticosteroids in 20.3%, antivirals (ganciclovir) in 10.9%, and NSAID in 5.2% of patients.

A total of 102 patients received 2% d-PVP-I. All patients reported burning and stinging, particularly in the first days. However, all of the managed to use it for the recommended 5d. We observed corneal epithelial defects in two cases, who applied d-PVP-I 2% more than two times a day.

In 35 patients (16.6%) pseudomembrane formation was observed. Of these 22 patients (62.9%) underwent membrane peeling. Of 35 patients with pseudomembrane formation, 21 developed SEI (60%), whereas 14 (40%) had none. In the reverse look of these results, of patients who developed SEI (84 patients), 21 had pseudomembrane (25%), whereas 63 (75%) had none. The occurrence of pseudomembrane formation and SEI development was significantly related (P=0.008).

During the late phase, 60.2% of patients (n=127) received no treatment. The remaining 31.3% were treated for visual disturbances related to SEI. Of patients with SEI (n=84), topical treatment was prescribed in 78.6% (n=66) if the infiltrates resulted in visual disturbances. Of these 40 patients (47.6%) received only steroids, 23 patients (27.4%) used steroids in combination with cyclosporine A, and 3 patients (3.6%) were given only cyclosporine A. On the other hand, 21.4% of patients with SEI (n=18) were followed with artificial tears only, because the opacities did not cause visual disturbances.

When we evaluated the incidence of SEI development according to the used medications during the first-week, we observed a statistically significant difference in d-PVP-I 2% used patients (P=0.032; Table 2). The incidence was 46.8% in patients who did not use d-PVP-I, and 32.3% in patients who were given d-PVP-I 2%. The topical corticosteroid use had no significant effect on SEI development (P=0.314). On the other hand, a significant difference was observed in patients who used antivirals (P=0.029). The incidence of SEI development was 60.1% in patients, who used antivirals and 37.2% in patients who did not.

Furthermore, when we further compared the use of d-PVP-I and antivirals together or alone in different combinations as shown on Table 3. We observed that d-PVP-I 2% decreased the incidence of SEI development (Comparison VI, P=0.023). Additionally, antiviral use did not have any inhibitory effect on SEI development (Combination V, P=0.238). Thus, we have shown that the use of povidone iodine does decrease the incidence of SEI.

DISCUSSION

Adenoviral keratoconjunctivitis is a highly contagious disease, with uncomfortable clinical symptoms, limiting patients' daily activity. Almost 40%-50% of patients with AKC develop SEI, which results in visual disturbances, such as decrease in vision, photophobia, and glare. There is no definite treatment of AKC, so we aimed to investigate the practice patterns in our clinic. In present study on 211 cases with AKC, we observed that almost half of the patients (48.7%) received d-PVP-I 2%, and these patients showed significantly lower incidence of SEI.

Table 3 The distribution of patients who developed subepithelial infiltrates (SEI+) or not (SEI-)

Medication	SEI+	SEI-	Total	*P*
Comparison I				0.378
Patients who used both antivirals and d-PVP-I	7	5	12	
Patients who used neither antivirals nor d-PVP-I	44	54	98	
Total	51	59	110	
Comparison II				0.020[a]
Patients who used antivirals, but not d-PVP-I	7[b]	4[c]	11	
Patients who used d-PVP-I but not antivirals	26[c]	64[b]	90	
Total	33	68	101	
Comparison III				0.794
Patients who used both antivirals and d-PVP-I	7	5	12	
Patients who used antivirals, but not d-PVP-I	7	4	11	
Total	14	9	23	
Comparison IV				0.041
Patients who used both antivirals and d-PVP-I	7[b]	5[c]	12	
Patients who used d-PVP-I but not antivirals	26[c]	64[b]	90	
Total	33	68	101	
Comparison V				0.238
Patients who used antivirals, but not d-PVP-I	7	4	11	
Patients who used neither antivirals nor d-PVP-I	44	54	98	
Total	51	58	109	
Comparison VI				0.023[a]
Patients who used d-PVP-I but not antivirals	26[c]	64[b]	90	
Patients who used neither antivirals nor d-PVP-I	44[b]	54[c]	98	
Total	70	118	178	

The number of patients and who used diluted povidone iodine (d-PVP-I), topical corticosteroids, and antivirals are given in corresponding cells. Chi-square test was used for statistical comparison. [a]$P<0.05$ was accepted statistically significant; [b]Values higher than expected cases; [c]Values lower than expected cases.

The diagnosis of adenoviral conjunctivitis is usually made on the basis of clinical symptoms and signs. Recently, rapid detection testing kits have become available, which provide results in 10min and are highly sensitive and specific[7]. However, they are not easily available in our country. Thus, our current diagnosis still depends on clinical findings. The weakness of this study is that it was entirely dependent on clinical diagnosis only, and no laboratory confirmation of AKC was performed.

AKC usually tends to resolve in three weeks. There is still no accepted treatment, and current management is targeted to relieve patient's discomfort and help with the complications related troubles. In present study, most of our patients were given antibiotics (93.4%) and non-preserved artificial tears (88.2%). In AKC, artificial tears are being used to relieve patient discomfort, and antibiotics are being used to prevent bacterial superinfection, however antibiotic use in AKC is debatable[2].

Currently, no specific antiviral therapy is available to shorten the course of the infection, or stop the viral replication. Several virustatic agents such as cidofovir and ganciclovir are suggested in the first week, although there is a lack in definite dose and comparative studies[2,8]. Cidofovir was reported to have a therapeutic effect in the treatment of AKC in 1% dosage[9]. It was reported to lower the frequency of severe corneal opacities, but 4 to 10 times daily at a 1% concentration resulted local toxicity, such as local toxic effect on the conjunctiva and eyelids, development of pseudomembranes and lacrimal duct stenosis[9]. Ganciclovir is available as a topical antiviral, and 10.9% of our cases were given ganciclovir. Yet, its effect against adenovirus is not definite. Considering the SEI as a late complication, topical ganciclovir resulted in an increase in SEI formation (P=0.029) in our cases. This result might be ambiguous, since relatively small number of patients who used ganciclovir. Still, according to our results, it definitely did not decrease the number of cases with SEI (Table 2). Contrary to our results, one small clinical study showed that ganciclovir shortened the clinical course of AKC and reduced subepithelial infiltrates[10]. Nevertheless, the results of this study should also be confirmed in studies on larger patient numbers.

Particularly in the early phase of AKC, corticosteroids should

be withheld at the time of initiating treatment, since they might increase the replication rate, prolong viral shedding, and increase disabling subepithelial opacities[4,11]. Thus, many clinicians believe that steroid treatment should be spared for complicated cases[11]. Though, in cases with severe inflammation or vision-threatening complications, steroids might be useful to relieve patient discomfort. In present study, 20.3% of patients received topical corticosteroids in the early phase, and no significant effect on SEI was observed (P=0.314). In 2015, there was an obvious increase in the numbers of AKC cases. During these epidemic two out of five authors started to use d-PVP-I. If started in the first 3d of symptoms, we observed a more rapid recovery (personal experience). Even if started later than 3d, we believed that it still might have an effect. So, we used d-PVP-I 2% two times a day for 5d. Care should be taken to use only one or maximum two drops at each time. If more is given, the epithelial cells on the ocular surface might be damaged, as we observed epithelial defects in two cases.

Povidone iodine is a potent disinfectant that kills extracellular organisms. In a study comparing the effectiveness of multiple antiseptics, only povidone iodine with a concentration higher than 0.5% was shown to inactivate the adenoviruses within 1-minute of exposure[6]. In adenoviral conjunctivitis, it has been shown to reduce the viral load[12]. It is highly effective against free adenovirus, but less effective against intracellular adenoviral particles. And, if started in the first week, it might decrease the severity of clinical signs, and result in decrease in complications. A study reported that conjunctival irrigation with 2.5% d-PVP-I was effective in the treatment of adenoviral conjunctivitis in infants[13]. Also, in a study including 150 epidemic keratoconjunctivitis cases, Hutter[5] reported better clinical results in patients treated with povidone iodine. In present study, 48% of our patients were given d-PVP-I 2%. The incidence of SEI was 32% in patients, who used d-PVP-I 2%, and 46% in patients who did not. The difference was statistically significant (P=0.032).

A new treatment of dexamethasone and povidone iodine has been proposed. Topical PI 0.4% and dexamethasone 1% combination was shown to decrease the secretion of virus and reduce disease progression[14]. The authors believed that topical dexamethasone relieves the symptoms, and povidone iodine kills the virus in tears reducing risk of spread and disease progression.

These SEI lesions are believed to represent a cellular immune reaction against viral antigens, deposited in the corneal stroma under the Bowman's membrane[15]. Patients may complain of irritation, photophobia as well as decrease in vision, if the infiltrates obscure the optical axis[3]. The infiltrates may last from a few months to few years. *In vivo* confocal microscopic evaluation of infiltrations revealed hyperreflective inflammatory cells in the basal epithelium and the anterior stroma together with subepithelial infiltrations of dendritic cells[16]. Histopathologic evaluation of SEI have shown that they are composed of lymphocytes, histiocytes and fibroblasts accompanied by a disruption of the collagen Ia, and are thought to be the result of delayed immune response to viral antigens in the corneal stroma[17]. SEI may resolve spontaneously or with topical steroid treatment, without leaving permanent scarring. In the treatment of existing corneal opacities only topical steroids and cyclosporine A have been shown to be effective[18]. They probably suppress the immunologic response directed against viral antigens that persists in the cornea[18].

Topical steroids are being used to decrease the corneal opacities, as 75% of our patients with SEI. Although they may help in short-term, they do not have any effect on long-term outcome[19]. The opacities may recur following cessation, thus a subset of patients may need prolonged use of topical steroids. It was reported that in cases who were resistant to steroid tapering or discontinuation, cyclosporine A 0.05% seemed to be effective[20]. Also, Levinger *et al*[21] reported on 12 eyes of 9 patients with SEI related to AKC, who were unresponsive to topical corticosteroids or developed complications to their use. Switching to topical 1% cyclosporine A in aqueous vehicle and carboxymethyl cellulose gel drops provided improvement in symptom score and visual acuity of those patients. Topical cyclosporine was reported to reduce the formation of subepithelial infiltrates[22-23]. In our cases with SEI, we prescribed cyclosporine A in 31% of cases. Cyclosporine eye-drops are recommended as steroid sparing agents, but they are not effective in acute disease symptoms, and they have no proven effect on the course of the disease[9].

In conclusion, AKC has a very contagious potential, and is difficult to treat. It is a very distressing disease that limits the patient's comfort and daily activities for almost two weeks. And, almost half of these patients develop decrease in vision related to SEI. According to our results, using d-PVP-I 2% in the first few days of clinically significant AKC might help to reduce the risk of SEI as a complication. Diluted povidone iodine should be started as soon as possible when we suspect AKC. Although we couldn't show this in present study, our personal observation is that the disease does not show the severe clinical sings if we start it in the first few days. After 3d, it does not have much effect on clinical signs, however it does decrease the incidence of SEI, possibly by decreasing the virus load. It's possible mechanism of action is probably decreasing the virus load in the first week. Thus, we believe that it might be a very useful, inexpensive, and easy to access aid in the management of AKC.

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