

THE EFFICACY OF OCULAR 2.5% POVIDONE IODINE SOLUTION IN THE TREATMENT OF ADENOVIRAL KERATOCONJUNCTIVITIS

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ABSTRACT

Aim: To evaluate the efficacy of combined topical povidone iodine 2.5% and fluorometholone (FML) in the treatment of adeno viral conjunctivitis.

Method

A prospective study conducted at King Hussein Medical Center, ophthalmology department between January 2018 and October 2019. Sixty two patients with clinical presentation of adenoviral keratoconjunctivitis who did not respond to a 3-day treatment with a combination of topical antibiotic and antihistamine eye drops were randomly divided into 2 groups. Group 1 (31 patients/39 eyes) received combined artificial tears and fluorometholone eye drops and group 2 (31 patients/41 eyes) received topical 2.5% povidone iodine solution, one drop 2 times daily in addition to combined artificial tears and fluorometholone eye drops for a duration of 2 weeks. The patients were evaluated continuously for 1 month (day 0,1,3; 1st and 2nd week) and then after 6 months post treatment for visual acuity, conjunctival congestion, eye discharge, lacrimation, integrity of corneal epithelium, burning sensation, pain, pseudo membrane and sub epithelial corneal infiltrate formation.

Results: Sixty two patients aged between 10 and 68 years (mean 37 ± 12 years) were involved in the study. The disease was bilateral in 18 patients. The duration of the disease presentation ranged between 3 to 15 days (mean 4 days). In both groups, the most common presentations were redness, burning sensation and watery discharge. Povidone iodine significantly resulted in earlier improvement of symptoms and was able to shorten the duration of the disease. The severity of itching, redness, burning sensation, watery discharge, eye lid swelling and the subsequent membrane, pseudo membrane and sub-epithelial infiltrate formation significantly (p value < 0.05) improved in the 2nd group by 3rd day, 1 week, 2 weeks, 1 month and 6 months of treatment. At 1 month, the rate of subsequent sub epithelial infiltrates formation had decreased significantly. Also, the incidence of pseudo membrane formation decreased in addition to eradication of an already formed one without the need for surgical removal.

Conclusion: Combined treatment with povidone iodine, topical steroid and artificial tears was able to significantly shorten the duration of disease, led to faster relief of symptoms and decreased the rate of subsequent sub epithelial infiltrate formation. Povidone iodine solution was shown to be effective in decreasing the incidence, as well as eradication of pseudo membrane formation.

Key words: Adenovirus, keratoconjunctivitis, povidone iodine.

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INTRODUCTION

Adenovirus is considered to be the most common cause of infectious conjunctivitis (1). In addition to the eyes, respiratory, intestinal and genitourinary tracts are targets for this virus (2). Watery discharge, hyperemia, pseudo membrane formation, chemosis, follicular conjunctival reaction, subconjunctival hemorrhage and lymphadenopathy are highly suggestive of adenoviral keratoconjunctivitis (3,4). Group D adenoviruses of type 8, 19, or 37 are the most.

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The diagnosis is usually established through clinical findings; cell culture, antigen detection, and PCR methods are rarely used (6).

Although the disease is self-limiting in most of the cases, treatment may be needed to relieve symptoms, shorten the course of disease and to prevent complications like pseudo membrane and corneal sub epithelial infiltrate formation. Anti-viral medications, such as Ganciclovir and Cidofovir were tried with promising results (7). Irrigation with Povidone–iodine 5% solution has proven broad-spectrum antimicrobial, including antiviral benefits (8). Topical corticosteroids were reported to be helpful in relieving symptoms and clearance of sub epithelial infiltrates (9,10). Cyclosporine and Tacrolimus were sometimes effectively used to avoid unfavorable side effect of steroids (11).

The aim of this study is to evaluate the efficacy of combined topical povidone iodine 2.5% and fluorometholone (FML) in the treatment of adeno viral conjunctivitis and its efficacy in eradication of already formed pseudo membranes and decreasing the formation of pseudo membranes and sub epithelial infiltrates.

METHOD

A prospective study conducted at King Hussein Medical Center between January 2018 and October 2019. All patients in the ophthalmology department with clinical presentation suggestive of adenoviral keratoconjunctivitis received a combination of topical antibiotic and anti-histamine (Ofloxacin and Naphthazoline) eye drops. Sixty two patients (after excluding one patient with allergic signs to povidone iodine) who did not improve after 3 days were included in the study. They were randomly divided into two groups: the 1st group (31 patients/39 eyes) received combined artificial tears and fluorometholone eye drops, and the 2nd group (31 patients/41 eyes) received topical 2.5% povidone iodine solution, one drop 2 times daily in addition to the combined artificial tears and fluorometholone eye drops for a duration of 2 weeks. Topical 2.5% povidone iodine solution was prepared by diluting 2 ml of 10% povidone iodine solution in 8 ml normal saline or balanced salt solution (BSS) then packing it in a sterile eye drop. The patients were evaluated continuously for 1 month (day 0, 1 and 3; 1st and 2nd week) and then after 6 months post treatment for visual acuity, conjunctival congestion, eye discharge, lacrimation, integrity of corneal epithelium, burning sensation, pain, pseudo membrane and sub epithelial corneal infiltrates formation. Results of the two groups were compared and analyzed using chi-square test.

The severity of ocular signs and symptoms was variable among patients, but there was no statistical difference between the two groups at presentation. Itching, redness, burning sensation and discharge were scored from 0 to 5, where 0 stands for complete absence of symptom and 5 for the most severe form. Eye lid swelling was given scores of 0, 1, 2 and 3 representing absence, mild, moderate and severe swelling, respectively. The sub epithelial infiltrates were assessed by slit lamp examination; severity score was related to the area of corneal

involvement, where a score of 0,1, 2, 3, 4 and 5 indicate 0, 20%, 40%, 60%, 80% and 100% involvement, respectively. The severity of ocular signs and symptoms are summarized in table 4.

RESULTS

Sixty two patients aged between 10 and 68 years (mean 37 ± 12 years) were involved in the study. The disease was bilateral in 18 patients. The duration of the disease presentation ranged between 3 to 15 days (mean 4 days). One patient developed allergic reaction to povidone iodine solution and was excluded from the data analysis at an early stage of the study (N.B this patient was from group 2, with 32 patients in this group at the beginning of the study, and after excluding this patient we continue the study and the data analysis with 31 patients in this group). Itching, redness, burning sensation, watery discharge and lid swelling improved in both groups. However, the improvement was significantly higher in the 2nd group (P value <0.05) and was evident from the 1st day after initiation of treatment, figure (1) and (2). At one month, the symptoms were almost gone from the 2nd group, except for a burning sensation which was present only in one eye. On the other hand, itching, redness, burning sensation and watery discharge were present in -10%, 3%, 31% and 5% of eyes, respectively in the 1st group.



Figure (1): before and after treatment



Figure (2): before and after treatment

Table 1 Demographic features of the patients

	1 st group (31 patients/ 39 eyes)	2nd group (31patients / 41 eyes)	Total (62 patients)
Mean age (years)	38	36	37
Male to female ratio	1.1:1	1.2:1	1.1:1
Bilaterality	8 (26%)	10 (32%)	29%
Duration of symptoms in each eye (days)	3.1	2.9	3.0

In both groups the most common presentations were redness, burning sensation and watery discharge. The frequency of subjective and objective clinical findings for 1st and 2nd groups is summarized in tables 2 and 3, respectively.

Table 2 Represents the subjective and objective clinical findings among eyes in the 1st group before and after treatment.

	Immediately before treatment	1st day	3 rd day	1 week	2 weeks	1 month	6 months
itching	32 (82%)	28 (72%)	24 (62%)	19 (49%)	15 (38%)	4 (10%)	4 (10%)
redness	39 (100%)	38 (97%)	34 (87%)	28 (72%)	18 (46%)	1 (3%)	2 (5%)
Burning sensation	39 (100%)	36 (92%)	33 (85%)	29 (74%)	24 (62%)	12 (31%)	4 (10%)
Watery discharge	39 (100%)	35 (90%)	35 (90%)	29 (74%)	17 (44%)	2 (5%)	1 (3%)
Eye lid swelling	28 (72%)	28 (72%)	26 (67%)	19 (19%)	10	0 (0%)	0 (0%)
Pseudo membranes	20 (51%)	20 (51%)	20 (51%)	12 (31%)	4 (10%)	0 (0%)	0 (0%)
Follicular reaction	24 (62%)	24 (62%)	18 (46%)	9 (23%)	2 (5%)	0 (0%)	0 (0%)
Corneal Superficial punctate stain	1 (3%)	1 (3%)	3 (8%)	2 (5%)	1 (3%)	1 (3%)	1 (5%)
Sub epithelial infiltrates	16 (41%)	16 (41%)	20 (51%)	22 (56%)	14 (36%)	12 (31%)	6 (15%)

Table 3 Represents the subjective and objective clinical findings among eyes in the 2nd group before and after treatment.

	Immediately before treatment	1st day	3 rd day	1 week	2 weeks	1 month	6 months
Itching	35 (85%)	26 (67%)	18 (44%)	2	1 (3%)	0 (0%)	0 (0%)
Redness	41 (100%)	33 (80%)	24 (59%)	12 (29%)	2 (5%)	0 (0%)	0 (0%)
Burning sensation	41 (100%)	32 (78%)	26 (63%)	13 (32%)	4 (10%)	1 (3%)	0 (0%)
Watery discharge	41 (100%)	30 (73%)	19 (46%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)
Eye lid swelling	30 (73%)	26 (63%)	18 (44%)	8 (20%)	1 (3%)	0 (0%)	0 (0%)
Pseudo membranes	19 (46%)	15 (37%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Follicular reaction	26 (63%)	24 (58%)	14 (34%)	6 (15%)	1 (3%)	0 (0%)	0 (0%)
Corneal Superficial punctate stain	2 (5%)	2 (5%)	2 (5%)	1 (3%)	1 (3%)	1 (3%)	0 (0%)
Sub epithelial infiltrates	18 (44%)	16 (39%)	10 (24%)	4 (10%)	1 (3%)	1 (3%)	0 (0%)

Table 4 Represents the mean values of the score severity for the most frequent ocular signs and symptoms in both groups before and after treatment.

Time	Immediately before treatment		1st day		3 rd day		1 week		2 weeks		1 month		6 months	
	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd
groups														
Itching	4.5	4.3	4.4	4.1	4.2	3.1	2.6	1.1	2.4	0.2	0.9	0	0.8	0
redness	4.1	4.2	4.1	4.0	4.0	3.9	3.8	2.4	2.4	0.9	1.2	0	0.9	0
Burning sensation	3.7	3.9	3.7	3.8	3.6	3.1	3.2	2.2	2.2	0.6	1.3	0	0.8	0
Watery discharge	4.7	4.5	4.6	4.4	4.1	3.3	3.3	2.0	3.2	1.0	0.5	0	0.9	0
Eye lid swelling	2.4	2.3	2.3	2.1	1.8	0.9	0.5	0.1	0.5	0	0	0	0	0
Sub epithelial infiltrates	3.5	3.5	3.5	3.5	3.4	3.0	2.9	1.5	2.6	0.8	2.1	0.2	1.6	0

Higher scores of signs and symptoms were significantly related to the time of presentation (>1 week) but not related to age and gender.

DISCUSSION

The exact incidence of adenoviral conjunctivitis is not well studied in Jordan though it is routinely seen in our practice, constituting up to 75% of infectious conjunctivitis cases (12). Cell cultures, polymerase chain reaction or immuno-chromatography methods which are used to confirm the diagnosis is not performed at our hospital for epidemic adeno-keratoconjunctivitis. Therefore, the diagnosis is established only through clinical assessment.

In the present study, there was no statistically significant difference in age, gender and duration of the disease between the two groups. The frequency of each signs and symptoms in both groups were comparable at presentation. Itching, redness, burning sensation, watery discharge and lid swelling improved in both groups. However, the improvement was significantly higher in the 2nd group (P value <0.05) and was evident from the 1st day after initiation of treatment. At one month, the symptoms were almost gone in the 2nd group, except for a burning sensation which was present only in one eye. On the other hand, itching, redness, burning sensation and

watery discharge were present in 10%, 3%, 31% and 5% of eyes, respectively in the 1st group. These results suggest that povidone iodine significantly resulted in earlier improvement of symptoms and was able to shorten the duration of the disease. The explanation for this is that the extracellular viruses that cause the symptoms are effectively disinfected and killed by povidone iodine solution. Yacyioglu et al presented data with better clinical outcome in patients treated with povidone iodine for adeno- keratoconjunctivitis (13).

In both groups, pseudo membrane formation was strongly associated with follicular reaction (P value<0.05). Acute inflammation induced by innate immune response in the conjunctiva release pro-inflammatory cytokines leading to vasodilation and capillary leakage. Pseudo membranes occur as a result of exudation of serum, fibrin, and leukocytes from dilated capillaries (14). Improvement in pseudo membranes formation and follicular reaction was observed in both groups due to the use of topical steroids which suppress the immune response to the infection. However, improvement was significantly (P value <0.05) better in the 2nd group as a result of virus eradication induced by povidone iodine. Eradication of already formed pseudo membranes in the second group was an important finding, especially in pediatric patients avoiding the need for any surgical intervention, figure (3) and (4). Gilmore reported low rate of peritoneal adhesions with the use of povidone iodine solution which suggests an additional fibrinolytic effect (15).



Figure (3): before and after treatment



Figure (4): before and after treatment

It is estimated that 40% to 50% of patients with adenoviral conjunctivitis develop sub epithelial infiltrates which may last for months to years and result in impaired vision (16). In the present study 43% of eyes had sub epithelial infiltrates. The 1st group did not show any improvement in the already formed sub epithelial infiltrates at day 1 or 3. Moreover, in this group 4 and 2 eyes which did not have SEI before, developed the infiltrates by 3rd day and 1st week, respectively. Nevertheless, improvement did occur, at 1 month 31% of eyes showed SEI compared to the 41% at presentation. On the other hand, the use of povidone iodine resulted in a decrease in the incidence of sub epithelial infiltrates formation during the course of the disease in addition to a significant elimination of already formed sub epithelial infiltrates (94% of eyes) at one month figure (5). In addition, the infiltrates did not develop in any eye which did not have them at presentation. This study showed that povidone iodine was effective in preventing the development of infiltrates and resolving of already existing ones. Rana et al. reported lower rates of sub epithelial infiltrates among eyes which used povidone iodine but not in those already having the infiltrates at presentation (17).



Figure 5 (a) at presentation

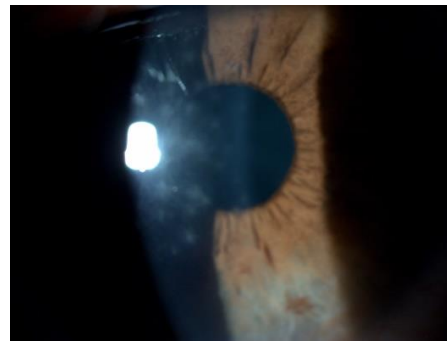


figure 5 (b) after 1 week

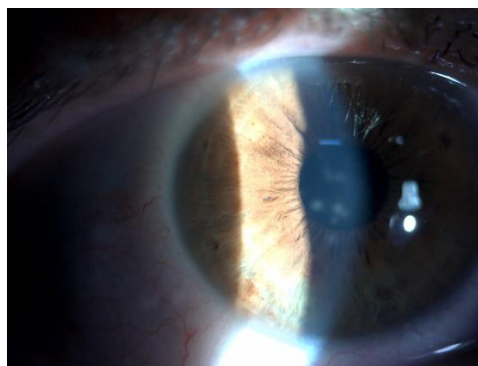


figure 5 (c) after 5 weeks

Sub epithelial infiltrates are deposits of lymphocytes, histiocytes and fibroblasts within the corneal stroma beneath Bowman's membrane, resulting from delayed immune response to the viral antigens (18). Topical steroids,

cyclosporine and tacrolimus have been effectively used to treat the sub epithelial infiltrates (19,20). However, opacities may recur again after halting the treatment (21). Darougar et al reported that the virus was being shed from the patient's eyes after 12 months of the illness (22), explaining the recurrence of corneal opacities and the chronic nature of the disease in some cases. Therefore, eradicating the virus from the infected eye by using povidone iodine solution will greatly help in reducing the possibility for developing corneal opacities while facilitating the topical steroid to deal with already existing infiltrates. The long term effect of treatment with povidone iodine on the sub epithelial infiltrates and its recurrence was markedly pronounced after 6 months as well. The use of topical steroid may result in suppression of local immunity and give the chance for more viral replication; this effect can be counteracted by the addition of povidone iodine. Superficial punctate keratitis was reported to be a rare manifestation of adeno- keratoconjunctivitis (5). It occurs as a result of virus replication within the corneal epithelium (23) but also as a result of chemical injury induced by the medication (24,25). The rate of punctate stain of the cornea was relatively low in the present study. There was better improvement of the epithelial stain in the 2nd group, but it was not statistically significant. However, an important illation from these results is that povidone iodine was not toxic to the corneal epithelium. Most of the studies have used lower concentrations of povidone iodine, like 0.6%,1% and 2% (9,17,26). The present study has used a higher concentration of 2.5% which was safe and well tolerated. Using a higher concentration may help in decreasing the viral load within the eye.

Another aspect which was uniquely explored in the present study is the severity of ocular manifestations of adenoviral keratoconjunctivitis. The severity of itching, redness, burning sensation, watery discharge, eye lid swelling and sub epithelial infiltrates were significantly (p value <0.05) lower in the 2nd group.

It is worthy to mention that patients in the 2nd group who started treatment within one week from the onset of symptoms responded better and faster than those who presented later. This may be related to the viral load within the eye which is expected to be higher triggering a heightened immune response.

In contrast to other studies, the present investigation has explored new elements related to adenoviral keratoconjunctivitis. It presented data regarding the efficacy of povidone iodine solution in eliminating already formed sub epithelial infiltrates and pseudo membranes and also protecting against the risk of their formation. In addition, the severity of ocular manifestations was shown to be significantly alleviated with the use of povidone iodine solution particularly at earlier stages of the disease. The limitation of the study is that definite diagnosis of adeno virus and its subtype was not confirmed by laboratory tests, clinical examination was the mainstay of diagnosis for suspected cases. However, combined treatment with povidone iodine, topical steroid and artificial tears was able to shorten the duration of the disease, decrease the rate to corneal opacity and led to faster relief of symptoms.

CONCLUSION

Combined treatment with povidone iodine, topical steroid and artificial tears was able to significantly shorten the duration of disease, led to faster relief of symptoms and decreased the rate of subsequent sub epithelial infiltrate formation. Povidone iodine solution also was shown to be effective in decreasing the incidence of pseudo membrane formation and in the eradication of already formed pseudo membrane and sub epithelial infiltrates. So we recommend using povidone iodine solution -2.5% along with topical steroid and artificial tears as early as possible in the treatment of adenoviral keratoconjunctivitis.

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