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Is Povidone-iodine Safe and Effective in the Treatment of Children and Adults with Viral Conjunctivitis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not, "Is povidone-iodine safe and effective in the treatment of children and adults with viral conjunctivitis?"

STUDY DESIGN: Review of three English language primary studies, published between 2002 and 2015.

DATA SOURCES: Two randomized controlled trials (RCTs) and one non-randomized, prospective, interventional pilot study were found using PubMed and the Cochrane database.

OUTCOMES MEASURED: Each study evaluated the efficacy of povidone-iodine for the treatment of viral conjunctivitis measured by days until cured as determined by patient rating of symptom strength and ophthalmological grading of ocular signs. Drug tolerability was defined as the proportion of participants sustaining povidone-iodine application until 7 days or recovery.

RESULTS: Tunay, Ozdemir & Petricili (2015) found that a one-time irrigation with povidone-iodine 2.5% and Netilmisin drops resulted in a significant reduction in symptom severity (p<0.05) and decreased time to recovery (p=0.001) as compared to instillation of Netilmisin alone. Isenberg et al. (2002) found no significant difference (p =.133-.824) in the overall number of days until cured or proportion cured at week 1 between subjects receiving neomycin-polymyxin-B-gramicidin and povidone-iodine 1.25% ophthalmic solutions 4 times daily. Trinavarat and Atchaneeyasakul (2012) found the recovery rate within a week of treatment with povidone-iodine 2% 4 times daily to be 77% (95%CI=65.1%-85.8%). No severe adverse effects were found to be associated with povidone-iodine treatment in any of the three studies.

CONCLUSION: Results of all 3 studies demonstrated that povidone-iodine is safe in the treatment of adenoviral conjunctivitis in infants, children, and adults. Results also indicated that povidone-iodine may be an effective treatment for viral conjunctivitis by reducing the symptom severity and illness duration. Further comparative studies are needed in order to prove the efficacy of povidone-iodine in viral conjunctivitis treatment.

KEY WORDS: Povidone-iodine, Betadine, Conjunctivitis, Adenoviral conjunctivitis

INTRODUCTION

Acute viral conjunctivitis is a highly infectious, self-limited ocular disease spread via respiratory droplets, ocular secretions, and hand-to-eye contact. It is most commonly caused by adenovirus.[1] The condition typically presents with unilateral or bilateral corneal injection, watery discharge, foreign body sensation, ocular irritation, and crusted eyelids. Signs of adenoviral conjunctivitis may include preauricular lymphadenopathy, chemosis, small conjunctival hemorrhages, and a follicular conjunctival reaction.[1,2]

Viral conjunctivitis is extremely common, however, accurate epidemiological statistics for the isolated condition are unavailable.[3] Laboratory isolation, via polymerase chain reaction assay (PCR) as a diagnostic tool is rarely utilized due to financial cost and time.[4-6] Although time-sparing, user-friendly, with high sensitivity and specificity, rapid antigen immunoassay is also infrequently used in the clinical setting.[7,8] Consequently, viral conjunctivitis is typically diagnosed clinically, and can be difficult to distinguish from bacterial conjunctivitis on clinical grounds alone. As a result, healthcare providers usually treat all presenting cases of conjunctivitis empirically.[3]

Research indicates that 6 million people annually in the United States suffer from conjunctivitis, with viral conjunctivitis being the most common cause of all infectious conjunctivitis cases.[9] In addition, it is estimated that at least 1% of all primary healthcare visits in the U.S. are due to cases of conjunctivitis.[10] Although viral conjunctivitis is a considerable economic burden, an accurate estimate of its specific healthcare costs has not yet been determined.[11] An outbreak affecting 41 individuals in a U.S. hospital was found to cost the hospital $29, 527 ($1,085 in medical costs, $8,210 for investigatory measures, $3,084 for preventative measures, and $17,184 in productivity loss).[1]

Although viral conjunctivitis is usually self-limited with resolution in 1-4 weeks, reasonable cause for concern exists due to its high rate of infectivity and possible complications. Keratitis is a severe complication which can manifest as epidemic keratoconjunctivitis (EKC). EKC occurs worldwide in the general population, hospitals, neonatal ICUs, and nursing homes.[13] The condition remains infectious for 10-14 days after onset of symptoms.[14] Diagnosed patients are advised to limit personal contact, resulting in several missed work or school days. In severe cases, pseudomembrane formation and multifocal subepitheliel infiltrates can lead to the development of subepitheliel fibrosis, symblepharon, and permanent vision loss.[15,16]

Currently, no specific curative treatment exists for viral conjunctivitis and standard therapy is thus supportive. Topical antibiotics such as ofloxacin and neomycin are used in order to treat or prevent bacterial infection.[17] For symptomatic relief, cool compresses, artificial tears, topical antihistamines, and vasoconstrictors are commonly employed.[18] Topical steroids such as prednisolone acetate 1% are typically reserved for severe cases as they can result in prolongation of the disease course.[19,20]

Povidone-iodine (Betadine; PVP-I) is an antimicrobial antiseptic agent that is highly effective against multiple microorganisms, including adenovirus. It has been successfully utilized pre and post operatively in ophthalmological surgery, and in ophthalmia neonatorum prophylaxis.[21-24] PVP-I may serve as a cost-effective alternative in shortening the duration and intensity of symptoms in viral conjunctivitis in both developing countries and the U.S. PVP-I is also an attractive alternative due to increasing rates of antibiotic resistance in the U.S.[25]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not povidone-iodine is safe and effective in the treatment of children and adults with viral conjunctivitis.

METHODS

Two double blind, randomized controlled trials, and one non-randomized, prospective, interventional pilot study were included in this systemic review. The populations of interest for this review included individuals of any age, gender, or race suffering from viral conjunctivitis. The outcomes of interest used in selection of studies included efficacy and tolerability of povidone-iodine. Studies were selected if they compared interventional treatment with PVP-I to a commonly utilized ocular antibiotic or placebo control. Uncontrolled studies that assessed the efficacy and tolerability of PVP-I with a course of treatment were also considered for review.

All studies selected were published in the English language in peer-reviewed journals. The author utilized the Cochrane Systemic Reviews and PubMed databases for articles published after the year 2000 with the keywords, "Povidone-iodine, "Betadine," "viral conjunctivitis," and "adenoviral conjunctivitis." Studies were included if they were POEM based and if they evaluated the safety and efficacy of povidone-iodine in patients diagnosed with viral conjunctivitis. Exclusion criteria included studies solely investigating subjects with diagnosed bacterial conjunctivitis. After extensive review of the literature, 2 randomized controlled trials and one uncontrolled, interventional pilot study, all published between the years 2002 and 2014, were selected for the current review. Refer to Table 1 for individual demographics of each study. Statistics reported in the 3 studies included means, standard deviations, percent change from baseline, confidence intervals, and p-values.

Table 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Tunay, 2015[26]	RCT	35	1-4mos	Infants with ophtho exam demonstrating + ocular symptoms or a + Rapid	Bacterial growth in conjunctival swab culture; use of ophthalmic drops in past 2 wks.	0	Single dose PVP-I 2.5% solution followed by artificial tears and

				Pathogen Screening-Adeno Detector Test result			Netilmisin 0.3% VS artificial tears and Netilmisin
Trinavarat, 2012[14]	Interventional, uncontrolled pilot study	61	10-84yrs	Pts with clinical diagnosis of EKC	<6yrs; pregnant/lactating; PVP-I allergy; prior ocular surgery; contact lens use; chronic eye disease; current use of eye medication	13	PVP-I 2% solution applied to affected eye 4x a day for 1 week or until recovery
Isenberg, 2002[17]	RCT	221	7mos-21yrs	1mo-21yrs with history of untreated red inflamed eye with discharge ≤14 days with 2+ findings of viral conjunctivitis on exam	+ bacterial cultures, no eye discharge; ocular antibiotic use ≤14 days, pruritic eyes with giant papillae of tarsal conjunctivae; allergy to PVP-I, neomycin, polymyxin, or bacitracin; perforated sclera/cornea; hypopyon	84*	PVP-I 1.25% solution in affected eye 4 times daily VS neomycin-polymyxin B-gramicidin in affected eye 4 times daily

*In Isenberg et al., 43 pts in the PVP-I group dropped out and 41 in the Abx group dropped out. This study investigated both bacterial and viral conjunctivitis and did not specify drop-out rates based on infectious origin.

OUTCOMES MEASURED

Tunay et al.[26] randomly divided 35 infants with EKC into two groups during an outbreak in a neonatal ICU. Diagnosis was based upon ophthalmologic exam and negative bacterial cultures. The affected eyes of Group 1 (n=15) were irrigated with a single dose of PVP-I 2.5% solution, followed by artificial tears (sodium hyaluronate 0.15%, 6X1) and antibiotic drops (Netilmisin 0.3%, 4X1). Group 2 infants (n=20) were treated with artificial tears and Netilmisin alone. The eyes were anesthetized prior to treatment. The outcome of PVP-I efficacy was measured by days until recovery and strength of symptoms. Patients were examined twice

weekly until recovery, which was defined as the absence of ocular findings on ophthalmological exam. Findings of lid edema, conjunctival chemosis, and fragility of conjunctival vasculature were scored on a 0 to 3 scale (0=none, 1=mild, 2=moderate, 3=severe). Presence or absence of pseudomembrane formation was also recorded.

In an interventional, uncontrolled pilot study, Trinavarat and Atchaneeyasakul[14] treated 61 patients during 2 episodes of EKC ($\overline{x}$ age=41.7yrs) with PVP-I 2% in each affected eye 4 times daily for one week. Diagnosis was based upon ophthalmological exam at an outpatient ophthalmic clinic. The main outcomes were recovery rate within one week of treatment, and drug tolerability. Drug tolerability was defined as the proportion of subjects sustaining treatment until recovery or after 7 days of treatment. Participants graded symptoms of lid swelling, injection, irritation, foreign body sensation, tearing, light sensitivity, and general discomfort as none, mild, moderate, or severe at baseline and at day 7. Investigator measures included ratings at baseline and day 7 of blepharedema, conjunctival congestion/ chemosis, subconjunctival hemorrhage, follicular reactions, eye discharge, corneal involvement, anterior chamber reaction, and preauricular lymphadenopathy. Recovery was defined as absence of ocular discomfort.

In a double-blind RCT, Isenberg et al.[17] treated 221 individuals ($\overline{x}$=6.6yrs) with viral conjunctivitis in an outpatient ophthalmology clinic with either PVP-I 1.25% or neomycin-polymyxin-B-gramicidin ophthalmic solution one drop 4 times daily in each affected eye (administered by the patient). Diagnosis was based upon clinical exam findings and negative bacterial cultures. Efficacy was measured as days until cured and proportion cured after 1 week of treatment. Patients graded the degree of eye inflammation as none, mild, moderate, or severe utilizing colored illustrations of eyes on a daily basis while also recording any adverse effects. Weekly ophthalmological grading was performed in categories of conjunctival redness, eyelid

swelling, and discharge, rated on a 0 (none) to 5 (severe) scale, with a total score of 0 being indicative of a cured infection.

RESULTS

Two studies compared PVP-I solution with antibiotic solution 4 times daily and one with single-dose PVP-I followed by Netilmisin drops in the treatment of viral conjunctivitis. A third uncontrolled study investigated tolerability and recovery rate of PVP-I 4 times daily. One study involved infants diagnosed with EKC in a neonatal ICU as participants, while the other two included both children and adults in an outpatient setting.

Tunay et al.[26] treated 15 infants with a single dose of PVP-I 2.5% followed by artificial tears and antibiotic drops (Group 1), and 20 infants with artificial tears and antibiotic drops (Group 2). Median clinical scores of ocular findings (Table 2) were found to be significantly lower in Group 1 than in Group 2 ($p < 0.05$) at day 7 of treatment.

Table 2: Ocular findings and recovery times between Group 1 and Group 2 (Tunay et al.)

Ocular Findings	Group 1 ($n=15$) (min-max)	Group 2 ($n=20$) (min-max)	p* Value
Lid edema	1 (0-2)	2 (1-3)	0.0001
Conjunctival chemosis	1 (1-2)	2 (2-3)	0.0001
Fragility of conjunctival vasculature	1 (0-2)	3 (2-3)	0.0001
Recovery time (day)	7 (6-9)	12 (9-18)	0.0001
Pseudomembrane formation (%)	% 6 ($n=1$)	% 45 ($n=9$)	0.021**

Min, minimum; max, maximum
*Mann-Whitney U test
**Fisher's exact test

Median recovery rate was also significantly lower in Group 1 (7d) than in Group 2 (12d) (p=0.001).[26] Total recovery in 7 days occurred in 60% of infants in Group 1 (EER), and 5% of infants in Group 2 (CER). The relative benefit increase (RBI) and absolute benefit increase

(ABI) were calculated to be 11% and 55%, respectively. The number needed to treat (NNT) in

this study was calculated to be 2 (Table 3). A NNT of 2 indicates that for one patient to benefit

from treatment with PVP-I, 2 patients must be treated.

Table 3: Efficacy of PVP-I 2.5% on recovery time: NNT (Tunay et al.)

Proportion of patients with total recovery in 7 days on antibiotic drops alone (CER)	Proportion of patients with total recovery in 7 days on PVP-I and antibiotic drops (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
.05	.60	11	.55	2

Trinavarat et al.[14] found the recovery rate within 7 days of treatment with PVP-I 2% to be

77% (95% CI=65.1%-85.8%) as demonstrated by the absence of general ocular discomfort in 47

participants (Table 4). Significant reduction in severity of the majority of eye findings and

symptoms occurred between comparison at baseline and at day 7 (p=0.000), with complete

disappearance of preauricular lymphadenopathy. At baseline, superficial punctate keratitis

occurred in 5 (8.2%) eyes, while subepitheliel infiltration occurred in 1 (1.6%) eye. At day 7,

superficial punctate keratitis was found in 7 (11.5%) eyes, and subepitheliel infiltration in 2

(3.3%) eyes. Thus, PVP-I 2% could not completely prevent corneal involvement.

Table 4: Recovery rate within 7 days of PVP-I 2% treatment (Trinavarat et al.)

Pts with ocular discomfort, Baseline	Pts with ocular discomfort, Day 7	P-value	Recovery rate within 7 days	95% CI
N=61(100%)	N=14 (22.9%)	0.000	77.0%	65.1%-85.8%

Isenberg et al.[17] treated a total of 459 children diagnosed with either bacterial, viral

(n=221), or chlamydial conjunctivitis with PVP-I 1.25% or neomycin-polymyxin-B-gramicidin

ophthalmic solution. Eighty-four participants dropped out of the study without returning to the

treatment facility for follow-up. The authors do not specify the drop-out rate in terms of

infectious etiology, but rather by treatment group, with 43 drop-outs in the PVP-I group and 41

in the antibiotic group (p=.74). Due to the similarity of drop-out rates across treatment groups,

these cases were not considered in the final analysis as statistical outcomes would not have been altered even if they were included as treatment failures.

The number of days until cured as rated by the ophthalmologist was 8.8 (SD=2.8) for the PVP-I group, and 9.0 (SD=3.0) for the antibiotic group[17]. As rated by the patient, days until cure was 5.8 (SD=3.0) for the PVP-I group, and 5.7 (SD=2.8) for the antibiotic group. The authors found no significant difference in days until recovery between the PVP-I and the antibiotic groups (p=.150).

The proportion cured by day 7 was also not found to be significant between the 2 groups (p=.133).[17] As rated by the ophthalmologist, the percent cured was 56.3% in the PVP-I group (EER), and 52.0% in the antibiotic group (CER). The RBI was calculated to be 8.27%, while the ABI was 4.3%. The numbers needed to treat (NNT) was determined to be 24 (Table 5).

Table 5: Efficacy of PVP-I 1.25% on ophthal rated recovery time: NNT (Isenberg et al.)

Proportion of patients with total recovery in 7 days, antibiotic drops alone (CER)	Proportion of patients with total recovery in 7 days on PPV-I alone (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
.52	.563	.0827	.043	24

The percent cured by day 7 as rated by the patient was 77.2% in the PVP-I group (EER), and 78.6% in the antibiotic group (CER). The resulting RBI was calculated to be 2.69%, while the ABI was 1.4%. The NNT was determined to be 72 (Table 6).

Table 6: Efficacy of PVP-I 1.25% on patient rated recovery time: NNT (Isenberg et al.)

Proportion of patients with total recovery in 7 days, antibiotic drops alone (CER)	Proportion of patients with total recovery in 7 days on PPV-I alone (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
.786	.772	.0269	.014	72

Trinavarat et al.[14] assessed drug tolerability, defined as the proportion of participants able to sustain PVP-I 2% for 7 days or until complete recovery. The tolerability rate was calculated

to be 78.7% (95% CI=66.9%-87.1%). Thirteen participants dropped out of the study prior to

recovery or 7 days of treatment due to reported stinging in the treated eye (Table 7). Neither

Tunay et al.[26], nor Isenberg et al.[17] found any significant adverse or toxic effects of PVP-I 2.5%

and PVP-I 1.25% treatment, respectively.

Table 7: Tolerability of PVP-I (Trinavarat et al.)

Study	Adverse effect	# of participants with stinging	Tolerability rate	95% CI
Trinavarat et al.[14]	Stinging	13 (21.3%)	78.7%	66.9%-87.1%

DISCUSSION

Although viral conjunctivitis is typically a self-limited condition, its high rate of

infectivity, epidemic outbreaks, social and economic burden, and rare but severe complications

warrant investigation of a safe and effective treatment. Antibiotics may help to prevent rare

opportunistic bacterial infections, but they are unsuccessful at reducing rate of recovery or

symptom strength,[17] while antiviral agents actually prolong the course of infection.[19,20]

Povidone-iodine is a commonly utilized antiseptic agent that is both cost-effective and

readily available in the U.S. and abroad. It has been successfully utilized in the prophylaxis of

neonatal conjunctivitis, as well as pre-surgical and post-cataract surgery endopthalmititis.[21-24]

PVP-I is pregnancy Category C due to its poorly understood effects on the neonatal thyroid

gland.[27] The only absolute contraindication is iodine hypersensitivity, which is extremely rare.

Severe ocular or systemic side effects have not been reported in the literature. Although local

side effects such as a stinging sensation (as reported in Trinavarat et al.[14]) may occur, this effect

can be easily avoided by topical anesthesia, followed by irrigation and swabbing of the lids.[14]

This side effect has not been found to result in any long-term sequelae.[28]

The most effective method of treatment delivery with PVP-I has yet to be determined. Each study in this review utilized different solution potencies and dosing regimens. Regardless of the potency used, all studies found PVP-I to be safe and tolerable. The Trinavarat et al.[14] study is limited by the absence of a comparison control group. While Tunay et al.[26] concluded that PVP-I 2.5% was significantly effective in reduction of symptom severity and recovery time, Isenberg et al.[17] demonstrated PVP-I 1.25% to be as ineffective as antibiotic treatment. The differing results could be due to several factors such a PVP-I potency, dosing regime, or patient age.

In Trinavarat et al.[14], reliability could have been improved with laboratory confirmation of a viral causative agent. However, this methodology itself is a reflection of standard clinical procedure, with confirmatory diagnostics rarely indicated and often unavailable. Patient compliance in Trinavarat et al.[14] and Isenberg et al.[17] also could not be guaranteed, as PVP-I was self-administered by patients outside of the treatment facility.

Determination of a "cured" case is subject to both ophthalmological and patient subjectivity. Aside from the effects of personal clinical judgement, the diagnostic criteria itself varied across studies. Lastly, this review itself is limited by the minimal number of RCT trials available in the literature, each with varying methodology.

CONCLUSION

Based upon evaluation of these 3 studies, it can be concluded that povidone-iodine ophthalmic solution is safe in the treatment of viral conjunctivitis of infants, children, and adults. However, it remains inconclusive as to whether or not povidone-iodine is any more effective than antibiotics or symptomatic treatment alone. Future studies conducted in a controlled environment comparing the efficacy of povidone-iodine solution versus symptomatic treatment

alone are warranted. Additionally, the use of a quick diagnostic screening tool such as the RPS

Adeno Detector in future studies will aid in strengthening the reliability and validity of research

outcomes.

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