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The effect of povidone iodine flush versus drops on conjunctival colonization before intravitreal injections

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Abstract
Background To determine the most effective method of applying povidone iodine 5% to decrease conjunctival colonization before intravitreal injections.
Methods Twenty-eight patients from two tertiary care centers undergoing intravitreal injection for diffuse diabetic macular edema, exudative age-related macular degeneration, venous occlusive disease, or refractory pseudophakic cystoid macular edema were prospectively randomized to two study arms. One arm received 2–3 drops of 5% povidone iodine (drops group) and the second received a 10 ml flush of the same solution (flush group). The inferior conjunctival fornix was cultured before and after antiseptic technique was performed in all patients. Three culture media, thioglycollate broth, chocolate agar and blood agar, were used for each sample.
Results Each study group had 14 patients. Prior to antisepsis, 22 of the 28 (78.6%) subjects had positive conjunctival cultures. 16 and 14 bacterial organisms were isolated in the first and second groups, respectively. After using 2–3 drops of 5% povidone iodine in the first study arm of patients, three of 16 (18.7% reduction) bacterial organisms were no longer isolated in thioglycollate broth media. With flush irrigation of 10 ml of 5% povidone iodine, seven of 14 (50% reduction) bacterial organisms were no longer isolated (*P*-value 0.07) in broth media. No difference in reduction of bacterial colonization was found on plated media (chocolate agar and blood agar).
Conclusions Irrigating the conjunctival fornix with 5% povidone iodine results in greater reduction of bacterial colonization compared with drop application of the same solution. Flush irrigation may provide better protection against the risk of endophthalmitis with intravitreal injections.

Keywords Conjunctival colonization · Intravitreal injections · Povidone iodine

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Introduction

While the risk of endophthalmitis following intraocular surgery is estimated at less than 0.1%, the intravitreal injection of triamcinolone acetonide (Kenalog®; New York, USA) has a

reported rate of endophthalmitis of 0.87% [1, 14, 17]. The higher incidence of endophthalmitis following intravitreal injections may result from directly tracking virulent bacteria into the vitreous cavity. An association between developing endophthalmitis and iatrogenic communication with the vitreous cavity intraoperatively has also been found in a large prospective study [19].

Intravitreal injection of triamcinolone acetonide has been reported as a useful treatment for diabetic macular edema, venous occlusive disease, uveitis, pseudophakic cystoid macular edema, and age-related macular degeneration [3, 8, 11–13]. With the expanding uses of intravitreal injections, Aiello et al. published a set of guidelines for performing intravitreal injections, which included the application of 5% povidone iodine (Betadine®, Connecticut, USA) [2]. The recommended technique included the application of povidone iodine to the eyelid margins, eyelashes, and conjunctival surface without specific instructions on how to apply it to the conjunctival surface (i.e., placing drops versus flushing the surface).

Several studies have shown that 1–2 drops of 5% povidone iodine to the ocular surface can significantly reduce bacterial colonization and the risk of endophthalmitis [4, 10, 19]. On the other hand, a large prospective randomized study and two other separate studies indicated that flush irrigation of 10 ml of 5% povidone iodine can effectively reduce bacterial colonization [5, 7, 16]. Our study evaluated bacterial reduction on the ocular surface between flush irrigation of 5% povidone iodine and droplet application prior to intravitreal injection of triamcinolone acetonide.

Materials and methods

Twenty-eight patients undergoing intravitreal triamcinolone acetonide injection for diffuse diabetic macular edema, age-related macular degeneration, venous occlusive disease, or refractory pseudophakic cystoid macular edema were enrolled in our study. The study was approved by the institutional review board at the University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System. Informed consent was obtained from each study participant. No participant had a known allergy to povidone iodine at the time of study enrollment. Patients were randomized to receive 2–3 drops or a 10 ml flush of 5% povidone iodine. Randomization was accomplished by having the patient select one of fifty index cards labelled ''drops'' or ''flush'' from an enclosed box.

Patients were taken to the minor operating room and placed supine on the operating table. 1–2 drops of topical anesthetic solution was placed on the bulbar conjunctival surface. We obtained the initial specimens from the temporal or nasal quadrant of the inferior conjunctival fornix with a sterile cotton-tipped applicator. The specimen was inoculated on chocolate agar plates, blood agar plates, and in thioglycollate broth. Chocolate agar plates were immediately placed in an anaerobic bag. A 5% povidone iodine prep was then performed to the eyelids and lashes with a sterile gauze. Patients randomized to the first study arm received 2–3 drops of 5% povidone iodine to the bulbar conjunctiva and for the second study arm, a flush irrigation of 10 ml of the same solution was used to irrigate the conjunctival surface. Special care was taken to thoroughly irrigate the inferior fornix by pulling the lower eyelid down with a sterile gloved hand. Sterile gauze was positioned temporally to catch any overflow of povidone iodine. Two minutes after povidone iodine application, cultures were obtained from the nasal or temporal quadrant of the inferior conjunctival fornix with a new sterile cotton-tipped applicator. If the nasal quadrant was cultured before the povidone iodine application then the temporal quadrant was cultured afterwards, and vice versa. An eyelid speculum was placed, and the intravitreal injection was carried out in the usual manner.

After completion of the procedure, the culture media were taken to the microbiology laboratory for incubation at 37°C for seven days. The presence or absence of bacterial growth was recorded for all culture media. The microbiologist obtaining the results was not informed of group assignments. Statistical analysis was performed with the Fisher probability test.

Results

Twenty-eight patients were enrolled in the study. Twenty-six of the 28 patients were men. The average age of the enrolled subjects was 71 years. Twelve were being treated for diffuse diabetic macular edema, four for venous occlusive disease, nine for age-related macular degeneration, and three for refractory pseudophakic cystoid macular edema.

Among the 28 patients, 14 patients were randomized to each group. In the drops group, 12 of 14 (85.7%) patients had pretreatment bacterial growth. In the flush group, 10 of 14 (71.4%) patients had pretreatment bacterial growth, yielding a total pretreatment bacterial growth of 22 of 28 subjects (78.6%). Baseline conjunctival cultures (including all media types) grew 16 isolates in the drops group and 14 isolates in the flush group. The most common isolate was coagulase—negative staphylococci (66.6%). Tables 1 and 2 summarize the results.

In the drops group, eight bacterial organisms (from six subjects) were isolated from pre-treatment plated cultures (blood agar and chocolate agar plates). Five of the eight isolates were no longer detected after povidone iodine treatment (62.5% reduction). In thioglycollate broth media, 16 bacterial organisms (from 12 subjects) were isolated from pre-treatment cultures. three of 16 isolates were no longer detected (18.8% reduction).

In the flush group, four bacterial organisms (from four subjects) were isolated from pre-treatment cultures on plated media. Three of the four isolates were no longer detected after treatment (75% reduction). In thioglycollate broth media, 14 bacterial organisms (from 10 subjects) were isolated from pre-treatment cultures. Seven of 14 isolates were no longer detected in after treatment (50% reduction).

When comparing reduction rates between the two groups using both types of culture media, statistical significance was found for the broth media (P value = 0.07) while the difference was not statistically significant in plated media. Tables 3 and 4 summarize results of thioglycollate broth media.

No povidone iodine-related or study-related complications occurred in either group.

Discussion

Povidone iodine is broadly accepted as an effective antiseptic agent for ophthalmic surgery. A recent survey found that 92% of retinal specialists use a povidone iodine preparation before intravitreal steroid injections [18]. Kiffney et al. showed that reducing full strength 10% povidone iodine by half

Table 1 Pre-treatment bacterial growth in the drops group

Subject	Bacteria
1	*Staphylococcus epidermidis*
Diphtheroids	
2	*Staphylococcus epidermidis*
3	*Staphylococcus epidermidis*
Proteus Mirabilis	
4	*Staphylococcus epidermidis*
5	*Staphylococcus epidermidis*
6	*Staphylococcus epidermidis*
7	*Staphylococcus aureus*
8	None
9	*Staphylococcus epidermidis*
Staphylococcus aureus	
10	None
11	*Staphylococcus epidermidis*
12	*Staphylococcus epidermidis*
13	*Gram var bacilli*
Staphylococcus epidermidis	
14	*Staphylococcus epidermidis*

Table 2 Pre-treatment bacterial growth in the flush group

Subject	Bacteria
1	*Staphylococcus epidermidis*
2	None
3	*Staphylococcus epidermidis*
4	*Staphylococcus epidermidis*
5	*Proteus Mirabilis*
Staphylococcus epidermidis	
6	*Staphylococcus epidermidis*
7	None
8	None
9	*Bacillus* sp.
Staphylococcus epidermidis	
10	*Bacillus* sp.
Staphylococcus epidermidis	
11	*Staphylococcus epidermidis*
12	*Streptococcus viridans*
Staphylococcus epidermidis	
13	None
14	*Bacillus* sp.

Table 3 Post-treatment bacterial growth in thioglycollate broth media: drops group

Subject	Bacteria	Before drops	After drops
1	*Staphylococcus epidermidis*	Yes	Yes
	Diptheroids	Yes	Yes
2	*Staphylococcus epidermidis*	Yes	Yes
3	*Staphylococcus epidermidis*	Yes	Yes
	Proteus mirabilis	Yes	Yes
4	*Staphylococcus epidermidis*	Yes	Yes
5	*Staphylococcus epidermidis*	Yes	Yes
6	*Staphylococcus epidermidis*	Yes	Yes
7	*Staphlyococcus aureus*	Yes	None
8	None		
9	*Staphlyococcus aureus*	Yes	Yes
	Staphylococcus epidermidis	Yes	Yes
10	None		
11	*Staphylococcus epidermidis*	Yes	Yes
12	*Staphylococcus epidermidis*	Yes	None
13	*gram var bacilli*	Yes	None
	Staphylococcus epidermidis	Yes	Yes
14	*Staphylococcus epidermidis*	Yes	Yes

greatly reduced ocular irritation while maintaining bactericidal efficacy [15]. Diluting the strength of povidone iodine any further results in less bactericidal efficacy [6]. With the recent increase in the number of intravitreal injections performed for different retinal disorders, identifying the most effective application technique of povidone iodine is of significant importance.

Flush irrigation of the conjunctiva with saline has been shown to increase isolated bacterial flora. Isenberg et al. compared the number of isolated bacterial species before and after a normal saline irrigation of the conjunctival fornix and documented a statistically significant increase in the number of species isolated [9]. This is likely a result of displacing organisms from within the conjunctival crypts onto the conjunctival surface. Consequently, the sole use of a saline irrigation plays no role in ophthalmic surgery preparation today.

Several studies have demonstrated that 1–2 drops of 5% povidone iodine reduces bacterial colonization of the conjunctiva [4, 10]. Speaker et al. showed a lower incidence of endophthalm-

Table 4 Post-treatment bacterial growth in thioglycollate broth media: flush group

Subject	Bacteria	Before flush	After flush
1	*Staphylococcus epidermidis*	Yes	Yes
2	None		
3	*Staphylococcus epidermidis*	Yes	Yes
4	*Staphylococcus epidermidis*	Yes	None
5	*Proteus Mirabilis*	Yes	None
	Staphylococcus epidermidis	Yes	Yes
6	*Staphylococcus epidermidis*	Yes	Yes
7	None		
8	None		
9	Bacillus sp.	Yes	None
	Staphylococcus epidermidis	Yes	Yes
10	*Bacillus* sp.	Yes	None
	Staphylococcus epidermidis	Yes	None
11	*Staphylococcus epidermidis*	Yes	Yes
12	*Streptococcus viridans*	Yes	None
	Staphylococcus epidermidis	Yes	Yes
13	None		
14	*Bacillus* sp.	Yes	None

itis with patients treated with two drops of povidone iodine [19]. Of note, in the Speaker et al. study, drops of povidone iodine were applied to the conjunctival surface after irrigating the surface with a balanced salt solution.

Miño de Kaspar et al. compared reduction of bacterial growth using a 10 ml flush irrigation of 5% povidone iodine to two drops of the same solution before anterior segment surgery [16]. They found a statistically significant advantage to using a flush irrigation based on results from blood culture liquid media. As with our study, they were unable to document any difference in flora reduction using plated media.

Our study lends additional credence to the suggestion that a 10 ml flush irrigation of 5% povidone iodine is more effective at reducing ocular flora than 2–3 drops. Whereas no significant difference in reduction of conjunctival colonization was found between the two study arms, thioglycollate broth medium results suggest that a greater reduction in ocular flora can be obtained with a flush irrigation.

A flush irrigation of povidone iodine appears to be a more effective antiseptic technique than droplet administration secondary to two mechanisms. The irrigation serves to dislodge hidden bacteria from the fornix of the conjunctiva and the povidone iodine serves to provide the bactericidal component. Utilizing one technique without the other may result in less-optimal surgical preparation.

Our study attempts to compare two methods in a standardized setting with very little bias. Stringent criteria for achieving success were applied to this investigation. Previous studies that addressed the effect of povidone iodine on conjunctival colonization reported on overall reduction in colony and/or species count. We defined success as complete sterility of the conjunctival surface based on the premise that we do not know how many colonies of bacteria it takes to create an endophthalmitis. Since sterility is more difficult to accomplish, we would need a larger number of subjects to reach statistical significance. Consequently, results of this study should be interpreted with care secondary to limitations associated with study design.

We add this study to the literature to further support the use of a 10 ml flush irrigation of 5% povidone iodine to the conjunctival surface as a preoperative antiseptic technique.

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