

DILUTE POVIDONE-IODINE PROPHYLAXIS MAINTAINS SAFETY WHILE IMPROVING PATIENT COMFORT AFTER INTRAVITREAL INJECTIONS

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Purpose: To report the rates of postintraocular injection (IVI) endophthalmitis with topical conjunctival application of various concentrations of povidone-iodine (PI), including no PI.

Methods: Retrospective chart review of patients receiving IVTs performed in a single practice between January 2011 and June 2016. Concentration of PI for all injections was recorded and cases of endophthalmitis identified and reviewed.

Results: A total of 35,060 IVTs in 1854 patients were included from the 5.5-year period. 29,281 injections were performed with standard 5% PI, 5,460 injections with diluted PI (3,731 with 2.5%, 1,673 with 1.25%, 56 with 0.625%), and 319 IVTs with no PI. Incidence of patient-reported PI sensitivity occurred in 15.9% of patients. Fourteen cases of endophthalmitis were identified: 12 in eyes that received 5% PI, one in an eye that received 1.25% PI, and one in an eye receiving no PI. The incidence of endophthalmitis was 0.04% for 5% PI, 0.02% for dilute PI, and 0.31% for no PI prophylaxis. All cases underwent prompt vitrectomy and had positive cultures for coagulase-negative *Staphylococcus*.

Conclusion: Application of dilute PI solution to the conjunctiva at the time of IVT is an effective alternative to 5% PI for endophthalmitis prophylaxis in betadine-sensitive patients.
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The advent of anti-vascular endothelial growth factor agents resulted in rapid proliferation of intravitreal injections (IVI) as a method for drug delivery. Today, IVI is one of the most commonly performed medical procedures in the United States with 2.6 million being performed in Medicare recipients alone in 2014 (<https://cms.data.gov>). Expert panels have published and updated guidelines for IVTs in an effort to improve outcomes and minimize procedure-related complications.^{1–3}

Perhaps, the most devastating of complications, endophthalmitis has been reported with varied rates; yet overall, the incidence seems to be low at around 0.019% to 0.083% of IVTs.^{4–10} Previous reports have demonstrated the significant benefit of topical povidone-iodine (PI) in prophylaxis of endophthalmitis after intra-

ocular surgery, which led to the extrapolation of PI use in IVTs for prophylaxis of endophthalmitis and its wide acceptance among retina specialists.^{11,12}

Infrequently, retina specialists are faced with the dilemma of withholding treatment versus treating without PI prophylaxis in patients with a self-reported betadine allergy or sensitivity. Recent reports have demonstrated that rates of post-IVI endophthalmitis increase dramatically in the absence of preinjection antisepsis with PI.^{9,10} An alternative option to this dilemma may include applying a diluted PI solution at a concentration that is tolerated more favorably by the individual patient, rather than withholding PI or IVI. This study reports endophthalmitis rates among patients receiving standard PI, serial dilutions of PI, and no PI in an office-based clinical setting.

Methods

A retrospective chart review was conducted at a single practice, identifying all patients who had

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undergone intravitreal injection for retinal vascular diseases between January 1, 2011, and June 30, 2016, by querying the billing database. All injection procedures were reviewed for concentration of PI used.

Injections were performed by four different physicians according to practice injection protocols. Over the course of the study, anesthetic protocols included an initial tetracaine drop followed 1 minute later by a viscous tetracaine drop, which was left in place for approximately 15 minutes. An additional drop of tetracaine was placed before placement of a sterile bladed lid speculum. Gloves were worn by all physicians and no masks were used.

Regarding antisepsis, up until March 2011, patients routinely received lid scrubs with 10% PI swabs before placement of the sterile eyelid speculum, and antibiotic prophylaxis with a fourth generation fluoroquinolone was used for 3 days before and 3 days after injection. Between March 2011 and March 2012, PI lid scrubs were abandoned; however, peri-injection antibiotic drops were continued. Between March 2012 and March 2013, antibiotic prophylaxis was changed to less expensive first and second generation antibiotics administered 1 day before injection and for the week following. Finally, in March 2013, antibiotic prophylaxis was abandoned.

Throughout the course of this series, PI was delivered to the conjunctival surface using a disposable pipette. No predetermined amount of contact time was specified. After IVT, the conjunctiva was irrigated with sterile buffered saline solution before removal of the speculum.

Unless the patient specifically expressed previous sensitivity or allergy to PI, 5% solution was standardly used. Patients were queried as to their level of comfort with their previous injection. If the patient expressed significant discomfort, burning, irritation, or foreign body sensation, a more dilute concentration was applied for the present injection. Stock solutions of 5% PI were diluted with buffered saline solution to 2.5%, 1.25%, and 0.625% concentrations.

All cases of endophthalmitis were recorded and patients were treated within 24 hours of presentation with prompt pars plana vitrectomy and intravitreal injection of vancomycin 1 mg, ceftazidime 2.25 mg, and dexamethasone 400 μ g. Mean time to endophthalmitis presentation and maximal visual recovery were calculated. Mean change in vision was also calculated and compared with baseline using Excel (Microsoft, Redmond, WA) to perform a paired 2-sample, 2-tailed *t*-test.

Results

A total of 35,060 eligible IVTs were performed for retinal vascular diseases in 1,854 patients in the 5.5-year time span of the study.

Overall, 29,281 IVTs were performed with 5% PI, 5,460 IVTs with diluted PI ($n = 3,731$ with 2.5% PI, $n = 1,672$ with 1.25% PI, and $n = 56$ with 0.625% PI), and 319 IVTs with no PI (Table 1). Indications for administration of diluted PI or no PI included reported betadine allergy or hypersensitivity to 5% PI with previous IVT. A total of 295 (15.9%) patients received at least one IVT with either diluted PI or no PI. Overall, 1.0% ($n = 18$) had at least one injection with no PI, 0.3% ($n = 6$) with 0.625% PI, 4.3% ($n = 80$) with 1.25% PI, and 13.7% ($n = 253$) with 2.5% PI. Standard 5% PI was used exclusively in 84.1% ($n = 1,559$) of patients during the course of the study.

Fourteen cases of endophthalmitis occurred for an overall incidence of 0.04%. Standard 5% PI preinjection prophylaxis was used in 12 cases (85.7%), 1.25% PI in one case (7.1%), and no betadine in the final case (7.1%). Incidence of endophthalmitis after IVT with 5% PI, dilute PI, and no PI were 0.04%, 0.02%, and 0.31%, respectively (Table 1). Withholding PI, therefore, conferred a higher incidence of endophthalmitis when compared with 5% PI (odds ratio [OR] = 7.652, 95% confidence interval 0.99–59.03, $P = 0.0509$) or dilute PI (OR = 17.167, 95% confidence interval 1.071–275.1, $P = 0.0446$) (Figure 1). Rates of endophthalmitis were also lower in IVTs with dilute PI when compared with 5% PI (OR = 0.4457, 95% confidence interval 0.058–3.429, $P = 0.4367$). Mean time from injection to presentation with endophthalmitis was 4 days and maximal visual improvement was obtained, on average, at 23.02 weeks. Change in vision from baseline to maximal visual recovery decreased a mean 2.66 letters, which was not a statistically significant difference among the 14 cases (Table 2; $P = 0.193$).

Multivariate regression analysis demonstrated no significant interaction in the change in Early Treatment Diabetic Retinopathy Study letter score from baseline to presentation by PI concentration ($R^2 = 0.0024$, $P = 0.82$), use of peri-injection topical antibiotics ($R^2 = 0.1404$, $P = 0.26$), elapsed time between injection and presentation ($R^2 = 0.1467$, $P = 0.45$), or anti-vascular endothelial growth factor agent ($R^2 = 0.0673$, $P = 0.26$) with overall adjusted $R^2 = 0.0205$. Simple linear regression similarly demonstrated poor correlation between PI concentration and the change in Early Treatment Diabetic Retinopathy Study letters from baseline to maximal recovery ($R^2 = 0.0235$, $P = 0.601$), and the elapsed time to presentation ($R^2 = 0.0016$, $P = 0.995$).

Discussion

Intravitreal injections account for the majority of procedures performed in the typical retina

Table 1. Subgroup Analysis Evaluating the Incidence of Endophthalmitis After Intravitreal Injection With and Without Povidone-Iodine

	Concentration of Povidone-Iodine				No PI	Total
	5% PI	2.5% PI	1.25% PI	0.625% PI		
Total # injections	29,281	3,731	1,673	56	319	35,060
Total # of patients	1805	253	80	6	18	1854
Cases of endophthalmitis	12	0	1	0	1	14
Incidence of infection	0.041%		0.018%		0.314%	0.04%

specialist’s office because they are used to deliver drugs for a myriad of retinal vascular conditions. Although some conditions may be ameliorated with a single treatment, other conditions, such as exudative age-related macular degeneration, have shown optimal visual outcomes with sustained, long-term therapy.¹³ This repeated exposure subjects patients to a higher cumulative risk of complications, most notably, endophthalmitis.

Iodine has been recognized as a potent antiseptic agent for over a century and its use continues in the form of PI. Povidone-iodine is well known to be a potent germicidal agent against bacteria, viruses, and fungi with no reported cases of resistance, making it an ideal antiseptic choice. Although the mechanism by which PI sterilizes is not fully understood, it is believed that diatomic iodine is released as free iodine from the polyvinylpyrrolidone coating carrier agent to disrupt normal cell protein synthesis.¹⁴ Perioperative PI antiseptics became the gold standard for cataract surgery after a large prospective study that demonstrated a 4-fold decrease in incidence of endophthalmitis when compared with silver protein solution. Its use has been adapted to nearly all invasive ophthalmic procedures including intravitreal injections.¹¹ Interestingly, previous in vitro studies demonstrated a paradoxical increase in germicidal activity at decreased contact times with diluted 10% PI solutions up to a 1:1,000 solution.¹⁵

Despite no evidence to suggest the presence of true anaphylaxis to PI in patients with previous reactions to iodinated contrast media, many physicians and patients are reluctant to use topical PI in patients who report such an allergy.¹⁶ Modjtahedi et al⁹ recently demonstrated that patients undergoing intravitreal injections without PI prophylaxis experienced a nearly 500-fold increase in the incidence of endophthalmitis at 9.4% compared with 0.019% in those receiving PI. Similarly, a report from the Diabetic Retinopathy Clinical Research Network demonstrated a rate of endophthalmitis of 15% when PI was withheld, compared with 0.031% in patients treated per protocol with appropriate prophylaxis.¹⁰ Although the incidence was slightly lower in our cohort, the odds of endophthalmitis were still 7.65x and 17.17x greater in patients not receiving PI compared with those receiving 5% and dilute PI, respectively. Although dilute PI seemed to corroborate the paradoxical increase in germicidal activity with decreased PI concentration as demonstrated by the OR of 0.44, this was not statistically significant ($P = 0.4367$). However, reduced strength PI did show a statistically significant protective effect compared with no PI as demonstrated by the OR of 17.167 ($P = 0.0446$), again suggesting increased efficacy with decreased PI concentrations (Figure 1). The rationale for increased germicidal activity with decreased contact time stems from the increased availability of free iodine. However, at concentrations of

Odds of developing endophthalmitis after IVT with differing concentrations of povidone iodine

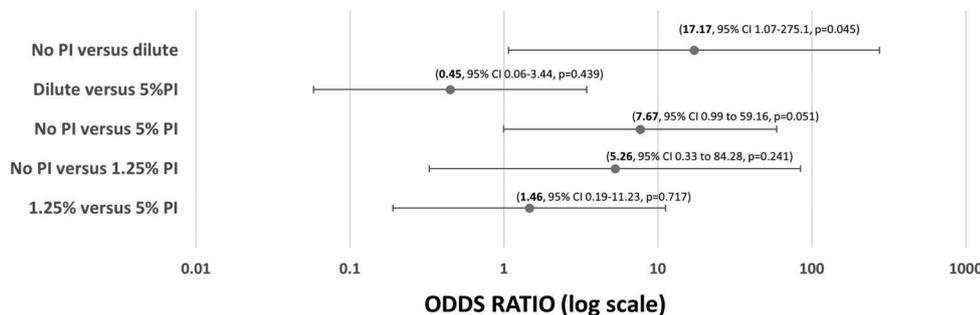


Fig. 1. Forest plot of OR and 95% confidence intervals for endophthalmitis after intravitreal injection with differing PI concentrations, plotted on a logarithmic scale.

Table 2. Cases of Endophthalmitis in a Single Practice Over 5.5 Years

Case	Agent	year	Culture Result	[PI]	Topical Antibiotic	Visual Acuity at Injection	Days to Present	Visual Acuity at Presentation	Maximum Recovered Visual Acuity	Weeks to Maximum Recovered Visual Acuity
1	Ranibizumab	2011	<i>Staphylococcus epidermidis</i>	5%	Yes	20/40	3	CF 3'	20/100	6.0
2	Ranibizumab	2011	<i>Staphylococcus epidermidis</i>	5%	Yes	20/30	3	HM	20/25	66.0
3	Ranibizumab	2011	<i>Staphylococcus epidermidis</i>	5%	Yes	20/80	3	HM	20/80	12.6
4	Bevacizumab	2012	<i>Staphylococcus epidermidis</i>	5%	Yes	20/200	4	CF 2'	20/200	1.1
5	Ranibizumab	2012	<i>Staphylococcus epidermidis</i>	5%	Yes	20/25	3	HM	20/25	2.0
6	Ranibizumab	2012	<i>Staphylococcus epidermidis</i>	5%	Yes	20/25	4	HM	20/25	86.7
7	Ranibizumab	2012	<i>Staphylococcus epidermidis</i>	1.25%	Yes	20/40	3	HM	20/40	24.0
8	Ranibizumab	2013	<i>Staphylococcus epidermidis</i>	5%	Yes	20/25	5	20/200	20/25	41.3
9	Ranibizumab	2013	<i>Staphylococcus epidermidis</i> / <i>Staphylococcus warneri</i>	5%	No	20/25	2	CF 6'	20/20	26.6
10	Ranibizumab	2013	<i>Staphylococcus hominis</i>	5%	No	20/25	5	CF 1'	20/25	29.4
11	Ranibizumab	2013	<i>Staphylococcus capitis</i>	5%	No	20/400	8	HM	20/400	4.7
12	Ranibizumab	2013	<i>Staphylococcus capitis</i>	5%	No	20/30	5	20/100	20/50	8.4
13	Ranibizumab	2014	<i>Staphylococcus epidermidis</i>	None	No	20/200	5	CF 1'	20/200	12.3
14	Ranibizumab	2016	Mixed Gram-positives	5%	No	20/30	3	CF 3'	20/60	1.1
							Mean = 4 days	Δ baseline to max recovered vision = -2.66 letters (P = 0.193)	Mean = 23.02 weeks	

CF, counting fingers; HM, hand motion.

less than 1:1,000, free iodine stores may be depleted, thereby limiting the germicidal effect.

In our patient population, we found 15.9% of patients expressing sensitivity to PI. This number may greatly underestimate the true prevalence, given that patients may not report their discomfort to physicians. Reluctance to report their discomfort may stem from a preconceived expectation that an injection is supposed to be uncomfortable. Furthermore, some patients may simply not return for follow-up due to the discomfort experienced. The latter condition highlights the importance of minimizing pain with treatment to facilitate compliance to therapy and patient retention. Yet, although accommodating patient comfort is important, minimizing risk of endophthalmitis through the use of PI is paramount. Two additional studies have looked at the efficacy of dilute PI for endophthalmitis prevention with IVT with 1.25% versus 5%

PI in conjunction with topical levofloxacin, and 0.25% PI with peri-injection topical levofloxacin.^{17,18} Impressively, Shimada et al had no cases of endophthalmitis in 15,144 consecutive injections using 0.25% PI, clearly superior to the incidence seen in other reports with standard 5% PI. Although these other authors reported low endophthalmitis rates after IVT with PI dilutions, other comparative studies have not been able to reproduce this protective effect of reduced PI concentrations in vivo. Conjunctival fornical swabs before and after instillation with either 1% or 5% PI in patients undergoing cataract surgery demonstrated a statistically significant reduction in bacterial colony-forming units in those receiving 5% PI compared with 1%, especially when higher bacteria concentration is present at baseline.¹⁹ In this study of 100 patients, however, it is important to note that no patient developed endophthalmitis.

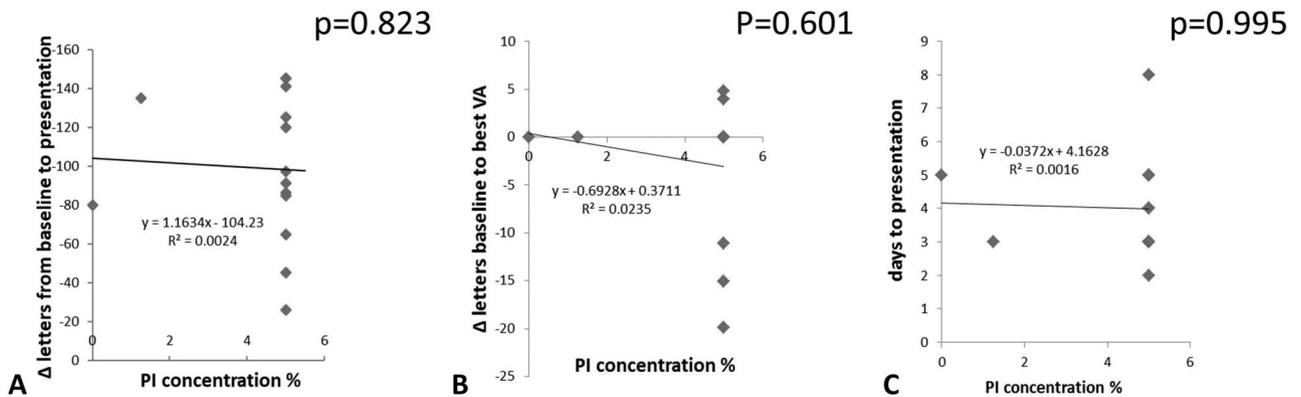


Fig. 2. Line fit plot from individual simple linear regressions analyzing PI concentration impact on cases of endophthalmitis regarding (A). severity of vision loss at presentation, (B). Severity of vision loss from baseline at maximal visual recovery, and (C). Days until presentation.

Overall, endophthalmitis rates in our study were consistent with other published data. Interestingly, all cases of endophthalmitis were culture-positive for coagulase-negative *Staphylococcus* species, and patients did well with prompt vitrectomy and intravitreal antibiotics. Mean time to presentation was 4 days and patients lost on average 2.7 letters from their baseline vision. Maximal visual recovery occurred, on average, at 23 weeks (Table 2).

Although an overall reduction in incidence of endophthalmitis was noted with dilute PI, we further evaluated whether the severity of endophthalmitis or outcomes was different among the 3 groups receiving either 5%, dilute, or no PI. Change in vision at presentation compared with baseline, change in vision from baseline to maximal visual recovery, and time to presentation were used as surrogate values for infection severity with the assumption that more severe cases may have a more significant effect on vision or present sooner. Simple linear regression comparing these three surrogate variables with concentration of PI did not confer any significant correlation (Figure 2). Likewise, multivariate regression did not show any relationship between anti-vascular endothelial growth factor agent, use of prophylactic topical anti-

biotics, or concentration of PI on the severity of presenting vision decrease (adjusted $R^2 = 2.05\%$; Figure 3).

Although this study includes a fairly robust total number of injection procedures, it is nonetheless limited by its retrospective nature and unequal distribution between 5%, dilute, and no PI. Our practice has standardized many aspects of the procedure for all treating physicians including anesthesia, application method, use of speculum, use of gloves, postinjection irrigation, and previous prophylactic antibiotic use. The standard use of viscous tetracaine for anesthesia has been more recently abandoned in our practice due to reports of increased endophthalmitis risk with such anesthetics, especially if PI is not first applied to the conjunctival surface. One of the more significant variables we did not control for was PI contact time. Friedman et al²⁰ demonstrated that at least 30 seconds of PI contact time was warranted to adequately decrease conjunctival bacterial counts. However, decreased PI contact times may still be effective with dilute PI based on previous in vitro data.¹⁵

In conclusion, although endophthalmitis is one of the more feared complications of intravitreal injections, its incidence remains low when antisepsis with PI is used. Our report demonstrates that dilute PI

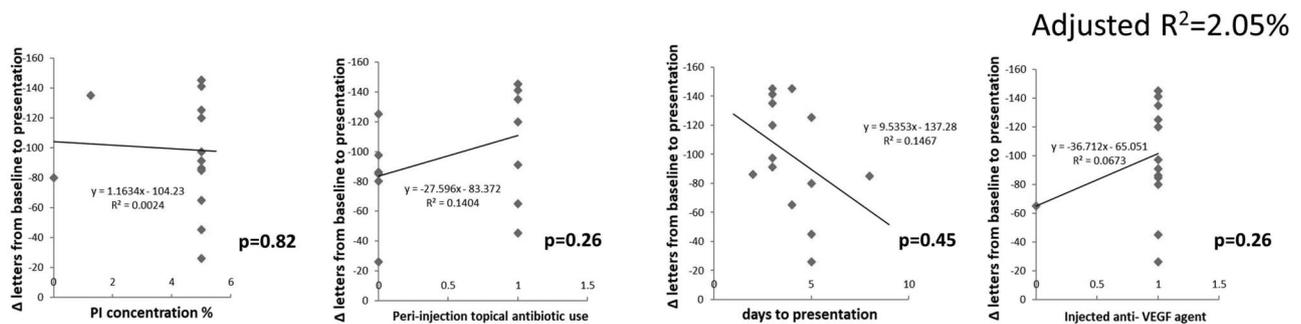


Fig. 3. Line fit plot from multivariate regression analysis of the influence of factors on severity of vision loss at presentation with endophthalmitis. VEGF, vascular endothelial growth factor.

provides effective prophylaxis while enhancing patient comfort. This is especially critical in patients with sensitivity to the standard PI concentration who may otherwise refuse PI prophylaxis or abandon treatment. Further prospective investigation is warranted to confirm the efficacy in prophylaxis for endophthalmitis and increased patient tolerability.

Key words: endophthalmitis, prophylaxis, povidone-iodine, betadine, allergy, sensitivity, dilution, incidence, intravitreal injection.

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