

## Hypochlorous acid antiseptic washout improves patient comfort after intravitreal injection: A patient reported outcomes study

Anthony Fam, Paul T Finger, Ankit S Tomar, Gaurav Garg, Kimberly J Chin

**Purpose:** Current ocular antiseptic practice for intravitreal injection (IVI) employs 5% povidone-iodine (Betadine®) drops which frequently cause ocular discomfort and prolonged irritation. In an effort to improve comfort while maintaining efficacy, we studied a hypochlorous acid (HOCL 0.01%) spray washout prior to injection. **Methods:** Patients had received a minimum of 3 IVIs prepared with Betadine® antiseptics prior to entry in this study. Their subsequent IVIs were prepared with Betadine® followed by HOCL 0.01% washout. Facets of comfort were measured by a Likert-scaled questionnaire to compare their experiences after IVI. **Results:** Thirty-seven participants were enrolled. Addition of HOCL 0.01% spray after Betadine® reduced the duration of discomfort ( $P = 0.001$ ) and need for artificial tears postinjection ( $P = 0.003$ ). It improved their reported quality of life ( $P = 0.04$ ) and sleep ( $P = 0.01$ ). There were neither HOCL-related side effects nor endophthalmitis during this study. **Conclusion:** Topical HOCL 0.01% spray after topical Betadine® antiseptics significantly improved patient comfort following IVIs.

**Key words:** Antisepsis, Betadine®, comfort, HOCL, hypochlorous acid, intravitreal, PRO, prophylaxis, quality of life

Intraocular vasculopathies such as age-related macular degeneration, diabetic macular edema, retinal vein occlusions, radiation retinopathy, radiation optic neuropathy, and other such pathologies utilize intravitreal antivascular endothelial growth factor and steroids in their treatment.<sup>[1-5]</sup> Thus, intravitreal injections (IVIs) have become the most frequently performed procedure in ophthalmology.<sup>[6]</sup> One of the most feared complications of IVI is endophthalmitis because it risks loss of vision, loss of eye, and mental health.<sup>[7]</sup> Studies have revealed the likelihood of endophthalmitis to be 0.019–0.09% per IVI.<sup>[6]</sup> To prevent this complication, disinfection of the conjunctival surface is typically performed prior to injection.

Povidone-iodine (Betadine®, Alcon, Fort Worth, Texas, USA) (Betadine®) is the most commonly used antiseptic solution prior to IVI.<sup>[6]</sup> Conjunctival surface disinfection guidelines recommend 5–10% Betadine®.<sup>[8]</sup> Studies have supported this practice, showing that the risk of endophthalmitis is higher in patients who are not pretreated.<sup>[9]</sup> For prophylaxis, one drop of Betadine® 5% aqueous solution has been applied to the conjunctival surface 30 seconds prior to IVI through the pars plana. However, many studies report that patients can experience allergic reactions, pain, edema, and significant discomfort after Betadine®.<sup>[10]</sup> Patients have reported that the most uncomfortable part of the IVI procedure is the Betadine® antiseptics and that anesthetics are not sufficient in preventing this discomfort.<sup>[11]</sup> Since IVIs have been administered routinely on a monthly basis, this poses a considerable problem for patients and clinicians, as pain has been shown to negatively impact treatment compliance.<sup>[12]</sup>

The New York Eye Cancer Center, New York, New York, USA

**Correspondence to:** Paul T. Finger, MD, The New York Eye Cancer Center, Fifth Floor, 115 East 61<sup>st</sup> Street, New York, NY 10065, USA. E-mail: pfinger@eyecancer.com

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Hypochlorous acid (HOCL) 0.01% (Avenova®, NovaBay Pharmaceuticals, Inc., Emeryville, California, USA) is a potent oxidizing agent effective against a wide spectrum of organisms, including the most common bacteria implicated in postinjection endophthalmitis [Table 1].<sup>[13-16]</sup> This form of HOCL 0.01% is commercially formulated free of sodium hypochlorite and at a pH of 6.5-7.0. It simultaneously possesses anti-inflammatory properties and has been used safely cutaneously on the eyelids as an antimicrobial and in wound healing, making it a viable alternative or addition to the current standard of care for IVI prophylaxis, Betadine®.<sup>[17-19]</sup> Herein, we present a patient reported outcomes (PRO) study that seeks to evaluate comfort after Betadine® 5% antiseptics, followed by HOCL 0.01% washout prior to IVI.

## Methods

Institutional Review Board (IRB) approval for this prospective cohort PRO analysis was obtained from the The New York Eye Cancer Center IRB and Ethics committees. This study was conducted at a single practice between November 2019 and January 2020. Every consecutive patient since November 2019 receiving IVIs at this single center was eligible for enrollment. Inclusion criterion was that every patient must have received ocular surface antiseptic preparation for IVIs with Betadine® 5% alone for more than three prior injections. Exclusion criteria

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**Table 1: Antimicrobial spectrum coverage for Betadine 5% and HOCL 0.01%**

Microbial species	Betadine 5%		HOCL 0.01%	
	Coverage	Duration of exposure	Coverage	Duration of exposure
<b>Gram Positive</b>				
<i>Staphylococcus aureus</i> (SA)	+++	1 min	+++	1 min
Methicillin-resistant SA	+++	1 min	+++	1 min
<i>Staphylococcus epidermidis</i>	+++	1 min	+++	<1 min
<i>Staphylococcus haemolyticus</i>	+++	<1 min	+++	<1 min
<i>Staphylococcus saprophyticus</i>	+++	<1 min	+++	<1 min
<i>Staphylococcus pyogenes</i>	+++	<1 min	+++	<1 min
<i>Corynebacterium diphtheriae</i>	+++	<1 min	+++	<1 min
<i>Enterococcus faecalis</i>	+++	<1 min	+++	<1 min
<i>Bacillus oleronius</i>	+++	<1 min	+++	<1 min
<i>Clostridium perfringens</i>	+++	<1 min	+++	<1 min
<i>Propionibacterium acnes</i>	+++	<1 min	+++	<1 min
Diphtheroids	+++	<1 min	+++	<1 min
<b>Gram negative</b>				
<i>Acinetobacter baumannii</i>	+++	<1 min	+++	<1 min
<i>Escherichia coli</i>	+++	<1 min	+++	<1 min
<i>Enterobacter aerogenes</i>	+++	<1 min	+++	<1 min
<i>Haemophilus influenzae</i>	+++	<1 min	+++	<1 min
<i>Klebsiella pneumoniae</i>	+++	<1 min	+++	<1 min
<i>Moraxella catarrhalis</i>	+++	<1 min	+++	<1 min
<i>Proteus mirabilis</i>	+++	<1 min	+++	<1 min
<i>Pseudomonas aeruginosa</i>	+++	<1 min	+++	<1 min
<i>Serratia marcescens</i>	+++	<1 min	+++	<1 min
<i>Vibrio vulnificus</i>	+++	<1 min	+++	<1 min
<i>Bacteroides fragilis</i>	+++	<1 min	+++	<1 min
<b>Other bacteria</b>				
Actinobacteria	++	<1 min	+++	<1 min
Spores	++	<1 min	+++	<1 min
<b>Parasites</b>				
Acanthamoeba	+++	<1 min	+++	<1 min
<b>Fungi</b>				
<i>Candida albicans</i>	+++	<1 min	+++	<1 min
<i>Aspergillus niger</i>	+++	<1 min	+	1 min
<i>Malassezia furfur</i>	+++	<1 min	+++	<1 min
<b>Viruses</b>				
Adenovirus	++	<1 min	+++	<1 min
Rotavirus	+++	<1 min	+++	<1 min
Rhinovirus	++	<1 min	+++	<1 min
Coxsackievirus	++	<1 min	+++	<1 min
Influenza virus	+++	<1 min	+++	<1 min
SARS-CoV2 (COVID-19)	+++	<1 min	+++	<1 min

+: Weak Coverage; ++: Medium Coverage; +++: Strong Coverage. Data from references<sup>[14-16,20-22,25,32-38]</sup>. Betadine: povidone-iodine, HOCL: hypochlorous acid

included patients below the age of 18 and patients unable to comprehend or answer the questions asked in the questionnaire. These patients were then eligible to begin receiving antiseptic preparation with 1 drop of Betadine® 5%, followed by six or more sprays of epibulbar HOCL 0.01% prior to the injection. This number of sprays was utilized so that the brown of the Betadine no longer appeared visible on the ocular surface. This ensured that a majority of the Betadine was effectively washed out by the HOCL 0.01%. PROs comparing each patient's experiences were then collected following three IVIs, which

utilized the new antiseptic technique. All subjects therefore received a minimum total of 6 IVIs: 3 with Betadine alone, and 3 with Betadine followed by HOCL 0.01%. They then answered the questionnaire and provided written informed consent for participation, use of Avenova®, and publication of their results.

#### Comparative antibiotic coverage

Betadine® 5% and HOCL 0.01% are both characterized by their broad-spectrum antibacterial, antifungal, and antiviral activity.<sup>[14-16,20-22]</sup> However, most commonly used prior to

ophthalmic surgeries and IVI, Betadine® 5% was selected for its proven efficacy in significantly reducing the rate of endophthalmitis in patients receiving IVI.<sup>[9]</sup> In contrast, HOCL 0.01% has been used to treat blepharitis and meibomian gland dysfunction and thus dry eye.<sup>[14]</sup> However, in our comparative review of the literature, HOCL 0.01% was found to offer even wider antibiotic coverage for actinobacteria replace with for actinobacteria, bacterial spores, and viruses [Table 1].

### Injection technique

The anesthetic protocol used for all patients included: one drop of viscous ophthalmic lidocaine gel (Akten, Akorn, Lake Forest, Illinois, USA), followed again by a second drop after 4 min. After an additional 4 min, all patients received one drop of Betadine® 5% preparation onto the inferior fornix 30 seconds prior to HOCL 0.01%. Then, the eyelids are manually opened and a minimum of six sprays of HOCL 0.01% was used to prepare the eye and eyelids. A single physician administered all drops, sprays, and injections. IVIs utilized a 1 cc syringe and a 30-gauge needle. Manual eyelid retraction allowed access to the inferior bulbar conjunctiva. There, angled self-sealing transscleral injections were placed through the pars plana into the vitreous.<sup>[23]</sup>

### Patient reported outcomes measures

A unique Likert-style patient survey was designed based on the Ocular Surface Disease Index patient questionnaire for dry eyes. However, our PRO survey measured ocular surface discomfort and quality of life in association with either Betadine® only or Betadine® followed by HOCL 0.01%. The questionnaire was comprised of 10 items to evaluate five measures of patient comfort for each of the two arms of the study [Table 2]. The five measures included: duration of discomfort after injection, the frequency of use of pain medication, the frequency of use of postinjection artificial tears, the frequency of disturbance of quality of life and vision, and the frequency of sleep disturbance. There are four options for answering each question. This format was based on a Likert-scale questionnaire with scores of 1–4 given to answers “Never,” “Once in a While,” “Often,” and “Always,” respectively. The questions addressing duration of discomfort after injection were also in Likert-scale format, with scores of 1–4 given to answers “Seconds,” “Minutes,” “Hours,” and “Days,” respectively. A four-point Likert scale was used as there is no neutral response that a patient could report on an even scaling. Furthermore, given the patient population and the average age at which they completed the survey, a four-point scale was determined to be easier for comprehension purposes and faster to complete. The reliability of the questionnaire and its answers was determined using Cronbach’s Alpha. Finally, background information such as age, sex, race, past medical history, and pre-existing ocular surface disease were collected separately.

Both the questionnaire and our medical staff informed patients that their participation was voluntary, that they can withdraw their responses from the study if they felt uncomfortable being included. Patients were also informed that their responses will be kept confidential and their personal health information would be both encrypted and password protected. In addition, patients were randomly assigned a number which was linked to each of their names, which corresponded with the patient’s questionnaire submission. Additionally, no patient identifiers are present in any of the remainder of the data collected.

**Table 2: Patient questionnaire with Likert item and scored answers**

#### Part 1: Patient Experience: Betadine 5% Preparation Alone

##### Question/Likert Item

How long did you have discomfort/irritation after your injection with the use of Betadine alone?

**(1) Seconds (2) Minutes (3) Hours (4) Days**

Did you use to take any pain medications after your injection prepared with the use of Betadine alone?

**(1) Never (2) Once in a While (3) Often (4) Always**

Did you use artificial tears for relief from irritation after your injections, when your eye was prepared with Betadine alone?

**(1) Never (2) Once in a While (3) Often (4) Always**

After the use of Betadine alone, did you experience any change in your quality of life (e.g., while watching television, driving, reading, or looking at a screen)?

**(1) Never (2) Once in a While (3) Often (4) Always**

Did the discomfort from the use of Betadine alone interfere with your sleep habits that same evening?

**(1) Never (2) Once in a While (3) Often (4) Always**

#### Part 2: Patient Experience: Betadine 5% Followed by Avenova® Washout

##### Question/Likert Item

How long do you have discomfort/irritation after your injection with the use of Betadine followed by Avenova?

**(1) Seconds (2) Minutes (3) Hours (4) Days**

Do you use to take any pain medications after your injection prepared with the use of Betadine followed by Avenova?

**(1) Never (2) Once in a While (3) Often (4) Always**

Do you use artificial tears for relief from irritation after your injections, when your eye is prepared with Betadine followed by Avenova?

**(1) Never (2) Once in a While (3) Often (4) Always**

After the use of Betadine followed by Avenova, do you experience any change in your quality of life (e.g., while watching television, driving, reading, or looking at a screen)?

**(1) Never (2) Once in a While (3) Often (4) Always**

Does the discomfort from the use of Betadine followed by Avenova interfere with your sleep habits that same evening?

**(1) Never (2) Once in a While (3) Often (4) Always**

### Statistical analysis

The Cronbach’s Alpha test was employed to determine the internal consistency between the scaled items in the test. This determines if the questionnaire employed is a reliable test. A value greater than 0.700 was considered to indicate high test reliability.<sup>[24]</sup> Wilcoxon’s signed-rank test was performed to estimate the change in comfort scores before and after the addition of HOCL 0.01% to the conventional Betadine® antiseptic prophylaxis. A *P*-value less than 0.05 was considered statistically significant. The data were analyzed using commercially available software (SPSS version 18.0; SPSS, Inc., Chicago, IL).

### Results

Thirty-nine patients from a single clinical center enrolled in the study. Two subjects did not participate due to an inability to comprehend and answer the questions, resulting in a total of 37 study participants. There were no patients less than 18 years of age or pregnant females. Of these patients, 15 were female (40.5%). The average age of the cohort was 62.4 years (range 29–83 years). Thirty-one of the patients (83.8%) identified

as "Caucasian," 5 (13.5%) identified as "African American or black," and 1 (2.7%) identified as "other." Underlying illnesses in the cohort include hypertension (24/37, 64.9%), diabetes (5/37, 13.5%), and prior cardiac illness (5/37, 13.5%).

Furthermore, the Cronbach's Alpha scores for measuring the employed questionnaire's reliability showed scores of 0.723 for the Betadine alone question set, and 0.704 for the Betadine with Avenova question set. These numbers indicate high reliability of the questionnaire administered in this study. Finally, a Wilcoxon signed-rank test was performed to compare and analyze the five measures of patient comfort between both antiseptic preparations [Table 3].

#### Duration of patient comfort

For the question assessing the duration of patient comfort, a small number of participants (5/37, 13.5%) responded that they experienced discomfort/irritation for seconds after the procedure when Betadine® 5% was used alone. In contrast, the addition of HOCL 0.01% caused a large shift, where the majority (20/37, 54.1%) responded that they experienced discomfort/irritation for only seconds after the procedure. The shift from Betadine® alone to Betadine® followed by HOCL 0.01% resulted in a statistically significant reduction in duration of postinjection discomfort ( $P = 0.001$ ).

#### Use of pain medication

For the question assessing patients' use of pain medication following IVIs, the majority (26/37, 70.3%) responded that they never used pain medication after the use of Betadine® 5% alone. However, with HOCL 0.01%, the majority (28/37, 75.5%) responded that they never used pain medication after

the procedure. The change in use of pain medication was not statistically significant ( $P = 0.20$ ).

#### Use of artificial tears

For the question assessing patients' use of artificial tears following IVIs, a large number of patients (18/37, 48.6%) responded that they require artificial tears following Betadine® 5% alone. With the addition of HOCL 0.01% spray washout, a majority of patients (27/37, 73%) responded that they did not require artificial tears. The decrease in usage of artificial tears was found to be statistically significant ( $P = 0.003$ ).

#### Quality of life

For the question assessing patients' quality of life following IVIs, the majority (20/37, 54.1%) responded that they experienced a decrease in their quality of life after Betadine® 5% alone. In contrast, with the addition of HOCL 0.01% spray washout, a larger majority of patients (24/37, 64.9%) responded that they never experienced a change in their quality of life after the procedure. The addition of HOCL 0.01% spray washout resulted in a statistically significant increase in patients' reported quality of life ( $P = 0.04$ ).

#### Quality of sleep

For the question assessing patients' quality of sleep following IVIs, a large number of patients (15/37, 40.5%) responded that they experienced a change in quality of sleep following Betadine® 5% prophylaxis. However, with the addition of HOCL 0.01% spray washout, a majority of patients (32/37, 86.5%) responded that they never experienced a change in their quality of sleep after their injection. This study found that the shift from Betadine® 5% alone to Betadine® followed by HOCL

**Table 3: Results of Wilcoxon signed-rank test in evaluation of questionnaire**

Likert Item	Scoring	Betadine® 5% Alone		Betadine® 5% With HOCL 0.01% Washout		Z-Score	P
		n (out of 37)	%	n (out of 37)	%		
Length of discomfort experienced after Injection	1	5	13.5	20	54.1	-3.43	0.001
	2	11	29.7	7	18.9		
	3	17	45.9	9	24.3		
	4	4	10.8	1	2.7		
Frequency of need of pain medication after injection	1	26	70.3	28	75.7	-1.29	0.20
	2	5	13.5	6	16.2		
	3	4	10.8	2	5.4		
	4	2	5.4	1	2.7		
Frequency of need of artificial tears after injection	1	19	51.4	27	73	-3.00	0.003
	2	4	10.8	5	13.5		
	3	4	10.8	2	5.4		
	4	10	27	3	8.1		
Frequency of experience in change of quality of life after injection	1	17	45.9	24	64.9	-2.01	0.04
	2	9	24.3	7	18.9		
	3	6	16.2	3	8.1		
	4	5	13.5	3	8.1		
Frequency of interference in sleep habits after injection	1	22	59.5	32	86.5	-2.41	0.01
	2	9	24.3	3	8.1		
	3	4	10.8	1	2.7		
	4	2	5.4	1	2.7		

0.01% spray washout resulted in a statistically significant improvement in patients' quality of sleep ( $P = 0.01$ ).

## Discussion

Herein, we present the first PRO study assessing patient comfort with the use of HOCL 0.01% spray washout antiseptics following Betadine<sup>®</sup> prophylaxis for IVI. The questionnaire developed and employed in this study evaluated five distinct aspects of patient comfort. We found that the use of HOCL 0.01% significantly reduced patients' experience of discomfort following the procedure. Specifically, the duration of discomfort was reduced from hours to mere seconds, the need for artificial tears was halved, and a significant improvement in the quality of life and sleep were reported.

Traditionally, Betadine<sup>®</sup> has been used for antiseptic prophylaxis and has demonstrated efficacy in diminishing the incidence of postinjection ocular infections.<sup>[6,9]</sup> The microbial spectrum covered by Betadine<sup>®</sup> 5% provides strong coverage against a majority of the microorganisms implicated in endophthalmitis.<sup>[16,20,22,25]</sup> However, because of the associated discomfort with ocular surface Betadine<sup>®</sup>, patients may be disinclined towards frequently administered IVIs, which may result in poor follow-up in a large number of patients.<sup>[6]</sup> Betadine<sup>®</sup> causes this discomfort due to its composition and its associated chemical constituents, which are known to be ocular irritants.<sup>[26]</sup> Prior studies have attempted to resolve the discomfort associated with Betadine<sup>®</sup> by utilizing dilutions of Betadine<sup>®</sup>,<sup>[27]</sup> as well as by utilizing saline irrigation postinjection.<sup>[28]</sup> In these studies, Betadine<sup>®</sup> diluted to 2.5, 1.25, and 0.5% provided improvement in postinjection patient comfort, but did not consistently demonstrate a protective effect in-vivo.<sup>[27]</sup> In contrast, postinjection saline irrigation has been associated with significantly fewer corneal epithelial defects but did not significantly improve patient discomfort.<sup>[28]</sup>

HOCL 0.01% has been shown in a number of studies to have comparable antimicrobial activity to Betadine and may cover additional viruses and bacterial species more effectively [Table 1].<sup>[16,29-38]</sup> A number of studies have demonstrated that HOCL is a naturally occurring anti-inflammatory agent that functions well as an antiseptic preparation.<sup>[18,19]</sup> Gold *et al.* found that HOCL 0.01% significantly reduced inflammation and was effective in killing >99.9% of tested microbes.<sup>[18]</sup> Likewise, Ngo *et al.* evaluated the comfort levels of several eyelid cleansing products in the treatment of blepharitis associated with *Demodex folliculorum* and found HOCL 0.01% to have the highest levels of patient comfort following treatment.<sup>[17]</sup> This may in part be explained by the ability of HOCL to mediate inflammatory cytokines, such as reducing the activity of leukotriene B4, histamine and interleukin-2, all of which are involved in the development of pruritus and irritation.<sup>[31]</sup> Finally, when HOCL is employed as a washout, it serves to remove residual irritant particles of Betadine, without diluting its antimicrobial effect, since it is a comparable antimicrobial.

The results of the present study concurred with the above literature in that HOCL 0.01% spray washout demonstrated a significant reduction in discomfort while increasing the patients' quality of life. This study hypothesizes, but did not prove, that the use of HOCL 0.01% spray following Betadine<sup>®</sup> not only reduced the irritation following IVIs but did so without diminishing the antimicrobial effect [Table 1]. Clearly,

our study only addresses HOCL's ability to improve patient comfort after IVIs. This study did not show that HOCL 0.01% can replace Betadine 5% for antibiotic prophylaxis. That would best be proven utilizing a randomized control trial comparing HOCL 0.01% spray to Betadine<sup>®</sup>, which is beyond the scope of this study.

Our study provided medical evidence that HOCL 0.01% spray washout improved patient comfort after Betadine 5% prophylaxis. Our patients responded to a 10-question survey to compare their past to their current experience, making recall bias a potential weakness of the study. However, recall bias would not change the overall consensus that patients had a significant preference for the use of HOCL 0.01% spray after Betadine<sup>®</sup> versus Betadine<sup>®</sup> alone. Another weakness of this study is its sample size. More patients were not included as this was a pilot study, and a larger sample size is being recruited, given the positive findings exhibited in the present study. Despite this, the results showed a statistically significant patient preference for the inclusion of HOCL 0.01% spray and improved the quality of life, even in the relatively small cohort. Future studies will be needed to evaluate the efficacy and patient satisfaction of HOCL 0.01% spray as a monotherapy prophylaxis. Finally, the use of Betadine<sup>®</sup> before the HOCL 0.01% spray may have reduced the comfort that might be found after monotherapy with HOCL 0.01% spray. Even with this limitation, the addition of HOCL 0.01% spray still reduced irritation and increased the quality of life as compared to Betadine<sup>®</sup> alone.

The strengths to this study are that it is the first to evaluate HOCL 0.01% spray as a means to improve comfort related to ocular IVI prophylaxis. All of the patients experienced both arms of the study. They were therefore able to directly compare their experience with Betadine<sup>®</sup> alone to their experience with Betadine<sup>®</sup> with HOCL 0.01% spray. This thereby eliminated any confounding factors inherent to subjective pain reporting, since pain would expectedly have high interpatient variability. Additionally, given its demonstrated prophylactic efficacy, the standard 5% Betadine<sup>®</sup> was employed throughout this study. The HOCL 0.01% spray washout was a potent antimicrobial which ensured that, compared to saline washout, the antibiotic effect was not diminished. This is an additional strength over the use of saline or saline-lubricant postinjection, which may dilute the antibiotic effect of Betadine<sup>®</sup>.

## Conclusion

This study suggests that the use of HOCL 0.01% spray after Betadine<sup>®</sup> 5% for IVI prophylaxis will offer improved patient comfort as a rinse for Betadine<sup>®</sup>. The known spectrum of antiseptic coverage provided by HOCL 0.01% spray was equal to or better than Betadine<sup>®</sup>, and affects the majority of the pathogens commonly implicated in endophthalmitis. This research reports on the novel use of HOCL 0.01% as an ocular surface anti-septic. Clearly, a larger study will be required to evaluate its safety profile at preventing endophthalmitis when used as prophylaxis prior to IVIs.

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W02008060491A2 "Anti-VEGF treatment for radiation induced vasculopathy." However, no conflicting relationship exists for any author.

### Conflicts of interest

There are no conflicts of interest.

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