Topical Proparacaine Eye Drops to Improve the Experience of Patients Undergoing Intravitreal Injections

NCT# 02951351

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MAYO CLINIC

Protocol IRB#16-004063

STUDY NAME

INTRODUCTORY STATEMENT

The specific aims of this study are to compare patient experience with and without a proparacaine drop after povidone iodine. To ensure the extra drop does not interfere with antisepsis, conjunctival cultures will be obtained from patients undergoing intravitreal injection before and after the application of the extra eye drop.

A. Background information:

1. Intravitreal injections

Intravitreal injections are used to treat patients with many ocular conditions including: exudative age related macular degeneration, endophthalmitis, CMV retinitis, forms of choroidal neovascularization, e.g. diabetic retinopathy, and macular edema.

2. A feared complication, endophthalmitis

Endophthalmitis is a post-injection complication with great morbidity. A comprehensive review published in 2004 outlining the risk of endophthalmitis after intravitreous injection found a 0.2% prevalence per injection, which increased to 0.6% prevalence for injection with triamcinolone acetonide. All other injected medications had a risk of 0.1% per injection.[1] A 2011 study published in *Retina* reported that 1 out of every 4000 to 8000 injections of anti-VEGF medications results in endophthalmitis.[2] Finally, a study using a Medicare database found that of 41,000 injections, the rate of post-injection endophthalmitis was about 0.09% per injection.[3]

The specific bacteria that cause post-injection endophthalmitis have been reported in a study by McCannel as most commonly coagulase-negative *Staphylococcus* species in 65.4% of cases where a bacterium was identified. *Streptococcus* species were identified in 30.8% of endophthalmitis cases; most commonly viridans group streptococci (VGS), *S. salivarius*, and *S. mitis*. [4]

3. Preventative measures

To prevent endophthalmitis, sterilization is attempted before injections using 5% povidone-iodine (PI), Betadine, which has been demonstrated to be as effective as topical antibiotics. [5] Povidone iodine's use prior to IVI is supported by a number of studies.[6, 7] Apt *et al.* demonstrated that one drop of povidone iodine administered preoperatively reduced bacterial colonies in conjunctival cultures by 91% versus 33% for control eyes.[8] Isenberg demonstrated that preoperative administration of povidone iodine was as effective as neomycin, polymyxin B, and gramicidin (Neosporin, Johnson & Johnson, New Brunswick, NJ) ophthalmic solution given three consecutive days prior to surgery in reducing conjunctival cultures.

Neosporin plus povidone iodine was more effective than either alone, leading to a 99.9% decreased colony count.[6] Overall, povidone iodine is nontoxic to the eye in the appropriate concentrations, has a broad antimicrobial spectrum (including bacteria, fungi, protozoa, and viruses), has a low propensity to select for bacterial resistance, is inexpensive, and is widely available.[9]

4. Antimicrobial properties of proparacaine

The antibacterial properties of proparacaine have been previously reported. A study on the effects of topical anesthetics on bacteria using a disk diffusion technique studied proparacaine and 0.5, 0.25, and 0.125% concentrations found that proparacaine inhibited the growth of *Staphylococcus aureus* at 1,250 µg/mL, and inhibited *Pseudomonas aeruginosa* growth at 2,500 µg/mL. [10] Proparacaine has also been demonstrated to have antimicrobial properties against *Staphylococcus epidermidis* and viridans group streptococci (VGS). It has been shown to reduce the number of culture-positive eyes, with 4 of 40 eyes being culture-positive after proparacaine, versus 12 of 36 eyes being culture-positive after receiving control solution, containing only preservative.[11] The mechanism by which proparacaine acts as an antimicrobial has been studied; it is thought to disrupt bacterial cell membranes causing permeability and lysis.[12, 13] Finally, benzalkonium chloride, the preservative component of proparacaine, has been demonstrated to have antimicrobial effects, with an *in vitro* study showing that benzalkonium chloride inhibits *S. aureus* growth.[14]

5. Background research (see attachment):

We have previously conducted a study comparing the minimum inhibitory concentrations (MICs) of topical anesthetics utilized prior to intravitreal injection (proparacaine, tetracaine, lidocaine), preservative benzalkonium chloride, and antiseptic povidone iodine for bacteria causing endophthalmitis. Lidocaine (8.53×10^{-5} mol/mL) had MICs of 4.27×10^{-5}-8.53×10^{-5} mol/mL, and tetracaine (1.89×10^{-5} mol/mL) had MICs of 9.45×10^{-6} mol/mL for all isolates. Proparacaine (1.7×10^{-5} mol/mL) had MICs of 1.32 to 5.3×10^{-7} mol/mL, 4.25×10^{-6} mol/mL for *S. epidermidis,* VGS, respectively). Benzalkonium chloride (3.52×10^{-7} mol/mL) had MICs of 1.86×10^{-9}-1.1×10^{-8} mol/mL, 4.40×10^{-8} mol/mL for *S. epidermidis,* VGS, respectively. Povidone iodine (1.37×10^{-4} mol/mL) had MICs of 2.14×10^{-6}-4.28×10^{-6} mol/mL, 8.56×10^{-6} mol/mL for *S. epidermidis,* VGS, respectively.

Proparacaine was the anesthetic with lowest MICs, lower than that of povidone iodine. Benzalkonium chloride had a lower MIC than proparacaine. All tested topical anesthetics and

povidone iodine inhibited growth of *S. epidermidis* and VGS at commercially available concentrations.

We also previously studied synergy and antagonism for all isolates using povidone iodine at 25% and 50% of its MIC. Proparacaine with povidone iodine demonstrated synergy against all VGS studied and additivity or indifference against all strains of *S. epidermidis*. Benzalkonium chloride with povidone iodine demonstrated synergy against 80% of *S. epidermidis* isolates studied and additivity or indifference against all VGS.

6. Significance

Intravitreal injections are one of the most common procedures performed by ophthalmologists. As its indications expand and the population with conditions treated with intravitreal injections grows, it is beneficial to know how to prevent complications such as endophthalmitis. It is often the case that patients will have a painful injection and refuse additional vision-saving treatment. A study to compare the timing of eye drops could help improve patient experience. It will also be important to compare conjunctival cultures of patients treated with proparacaine alone and with povidone iodine may be informative from an antimicrobial standpoint.

From the perspective of patient experience, recent studies have demonstrated great patient dissatisfaction with the application of povidone iodine. In a study by van Asten *et al.,* more patients (26%) reported povidone iodine application than intravitreal injection (10%) to be the most bothersome part of the intravitreal injection process. [15] The current expert guidelines for IVI stress the importance of 5.0% povidone iodine use. The guidelines recommend that povidone iodine should be the last agent applied before performing injections, and physicians should be careful as the anesthetic may interfere with the contact of povidone iodine to the conjunctival surface. Therefore, the guidelines recommend applying povidone iodine before and after topical anesthetic. It is possible, though, that the antimicrobial effects of proparacaine allow it to be applied following the povidone iodine in patients who find PI unpleasant.

It would also be useful to determine the impact of proparacaine and povidone iodine on each other. In our preliminary studies, proparacaine with povidone iodine demonstrated synergy against all VGS studied. Benzalkonium chloride with povidone iodine demonstrated synergy against 80% of *S. epidermidis* isolates studied. These results may influence choice of topical anesthetic.

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Proparacaine (http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch#) is a topical anesthetic commonly used prior to intravitreal injections. This proposal recommends deviating from the usual protocol of one drop of proparacaine prior to povidone iodine to adding an addition drop of proparacaine after the povidone iodine as proparacaine has been demonstrated to have antimicrobial properties and assist with patient comfort.

GENERAL INVESTIGATIONAL PLAN

Study rationale- Intravitreal injections are one of the most common procedures performed by ophthalmologists. The study endpoints are to improve the patient experience while minimizing negative outcomes, one of the most worrisome of these outcomes is endophthalmitis. The study will address first patient experience and ensure that the treatment is not detrimental to antisepsis.

Indication- To compare the effects of proparacaine before and after povidone iodine application on patient experience, and to compare bacterial colonies in conjunctival cultures obtained from patients undergoing intravitreal injection to ensure adequate antisepsis.

General approach/Treatment plan (See figure 1)- The study will take place during intravitreal injections. The anticipated study is as follows: After a procedural time out to verify patient, agent, and laterality, proparacaine will be applied to the ocular surface. A conjunctival culture will then be obtained followed by the application of povidone-iodine to the eyelashes and eyelid margins. The eyelids will then be retracted away from the intended injection site for the duration of the procedure. At this point, half of the patients will be randomized to receive 5% povidone-iodine drop to the conjunctival surface followed by conjunctival culture then re-application of 5% povidone-iodine drop to the conjunctival surface. A needle will then be inserted perpendicular to the sclera, 3.5-4.0 mm posterior to the limbus between the vertical and horizontal rectus muscles. The other half of patients will undergo application of another drop of topical anesthetic followed by conjunctival culture. After the culture, this group of patients will have 5% povidone iodine applied to the conjunctival surface. A needle will then be inserted perpendicular to the sclera, 3.5-4.0 mm posterior to the limbus between the vertical and horizontal rectus muscles.

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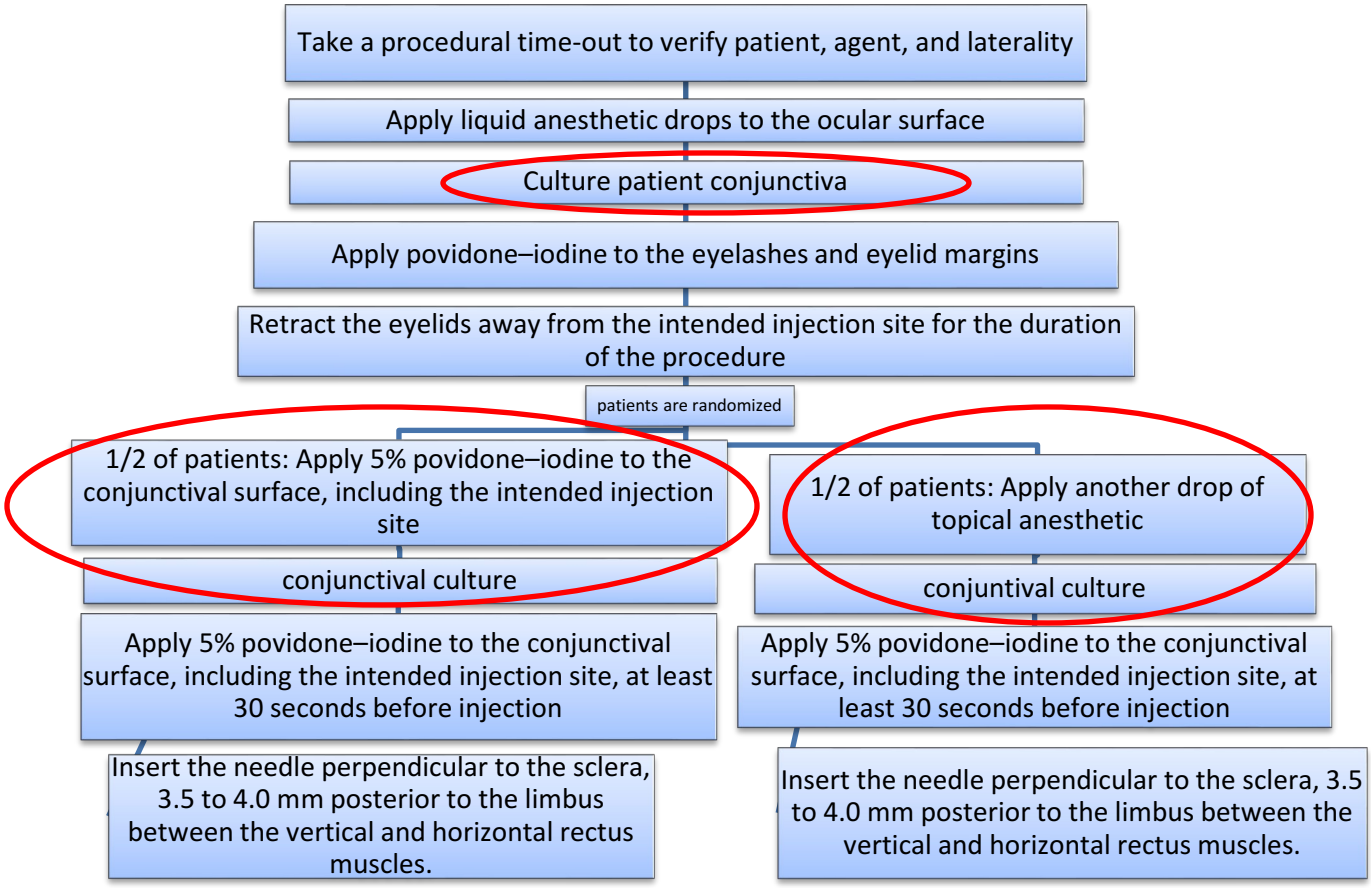
Figure 1



** the circles highlight deviations from the typical protocol

Human subjects

Sixty patients (male and female) undergoing intravitreal injection who do not have active eye infections will be enrolled after undergoing informed consent.

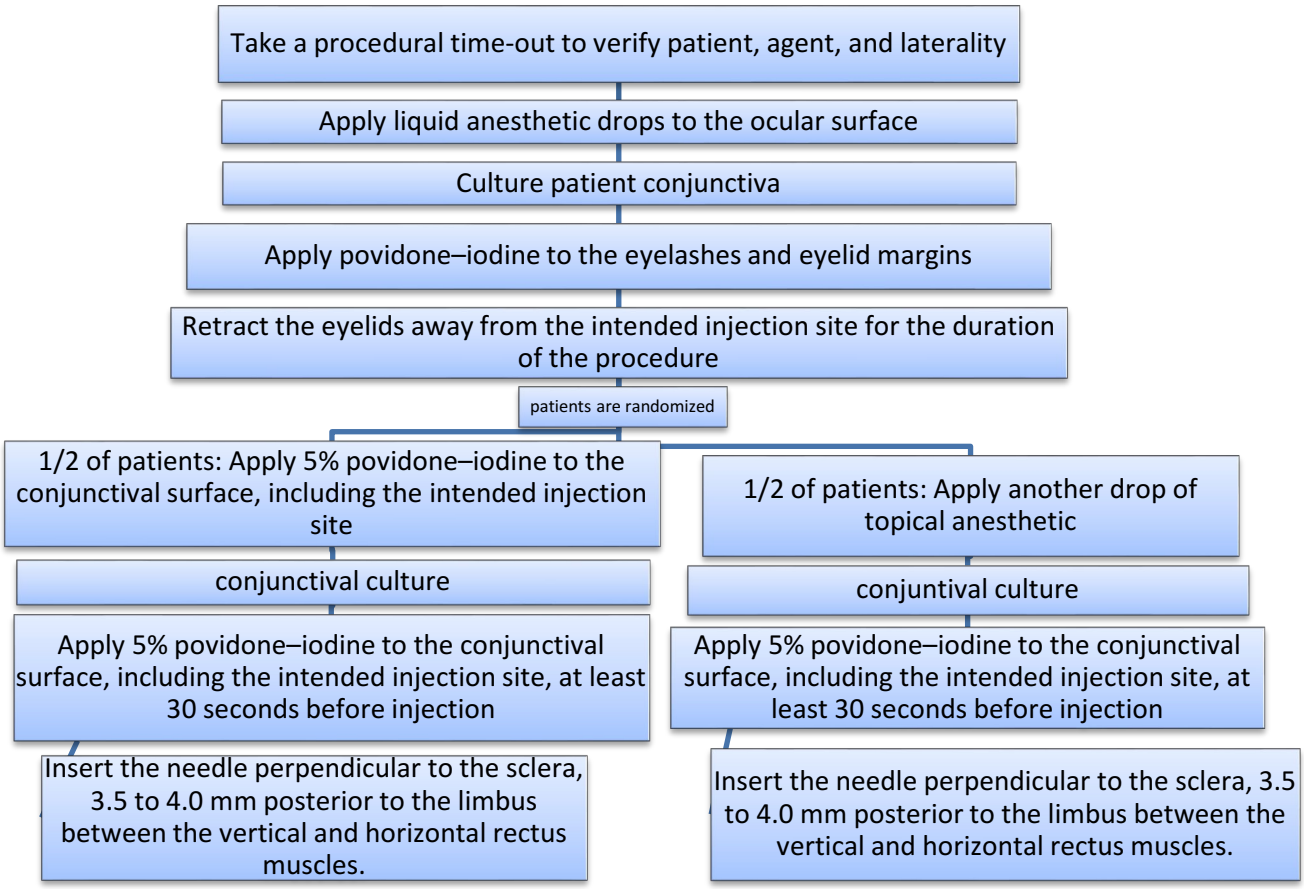
Exclusion criteria: 1. Age less than 18. 2. Patients with active eye infections

The main risk encountered by human subjects would be infection given extra manipulation prior to intravitreal injection. These risks will be minimized by using sterile culture techniques. All cultures will be followed by application of povidone iodine to comply with current recommendations to sterilize conjunctiva prior to intravitreal injection. It is also possible that patients will experience increased discomfort due to the conjunctival cultures. Per the protocol, cultures will follow topical anesthetic application.

Data collection:

Conjunctival cultures will be incorporated into the current intravitreal injection procedure

followed by Mayo Clinic.:



a. Conjunctival cultures

Bacterial cultures will be performed from conjunctival samples. Bacterial speciation will be performed on any bacteria that grows using the usual procedure to determine the bacterial species collected by the study.

b. Proparacaine Eye drops

Proparacaine 0.5% with preservative benzalkonium chloride 0.01% (Akorn) will be analyzed for its effect on bacterial growth *in vivo* with and without povidone iodine.

c. Data analysis and interpretation

Whether cultures are positive or negative will be compared between groups. Outcomes will also be measured by comparing the semiquantitative number of bacterial cultures (the microbiology lab will report cultures as 1+ through 4+) according to the Mayo Clinic Microbiology laboratory protocol. Patients who have positive cultures will have specific bacterial species determined which will also be analyzed. Demographic characteristics will be recorded including date of

birth and sex. Information surrounding the indication for injection will also be obtained as well as type of medication injected and number of previous injections. Finally, medication data will be included with specific focus on antibiotics—topical or systemic and eye drops.

In addition, patients will complete the previously detailed survey regarding their experience. Patient experience will be compared between groups and to existing data from this previously utilized survey described in PMID: 25901838.

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Treatment plan:

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Safety

The current protocol for intravitreal injections requires that patients be treated with povidone iodine immediately prior to intravitreal injection for antisepsis. The protocol for this study will not deviate from the standard protocol in that way. The safety of the study will be monitored by the PI. If more than 4 patients are noted post-procedurally to require additional return visits for conjunctival irritation or infection, the study will be discontinued.

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