A Pilot Study: Control of pain in intravitreal injections using topical NSAIDs (COPIVIN)

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A Pilot Study: Control of pain in intravitreal injections using topical NSAIDs (COPIVIN)

PI Name and Institutional Affiliation
Mihai Mititelu, MD, MPH, Assistant Professor (CHS), Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health

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Co-Investigator(s)
Maxwell Wingelaar, MD
Jonathan Chang, MD

Study Coordinator(s)
Clinical Eye Research Unit study coordinator staff

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Project Summary
Intravitreal injections are a very common form of treatment for a variety of ocular pathologies. The use of these injections has only increased given the large utility they provide. They both improved visual outcomes and provided patients an overall better quality of life. However, a problem experienced by patients who undergo these injections is the need for multiple reoccurring injections to maintain control of their disease.[1,2,3] It has long been an issue to provide patients optimal pain relief both during and after their intravitreal injections. Topical anesthesia is often utilized through frequent rounds of proparacaine eye drops. Other providers often use Lidocaine gel or Lidocaine-soaked cotton swaps with variable results in terms of pain control.[2,4] Subconjunctival lidocaine has also been utilized with variable control of pain, however patients did report anxiety with the thought of being given an additional injection.[5,6] Patient pain is subjective and difficult to objectively quantify when comparing different methods of post-injection control. One commonly employed pain rating system is the Wong-Baker FACES pain scale which has been quite successful in objectively quantifying patient discomfort.[5,6] It should be noted that this scale is only reliable in a patient whom is able to understand how the scale works. Other research studies have shown adequate to improved pain control through the use of topical non-steroidal anti-inflammatory drug (NSAID) eye drops. One study looked at the use of topical Nepafenac 0.10% on post injection pain.[8] This study used the McGill pain assessment questionnaire, which not only quantified pain but the additional benefit of describing the nature of the pain the patient experienced. In a clinical research study, Makri et al looked at pain immediately and 6 hours after injection. The researchers found that when

compared to the control group (artificial tears) the group who received NSAID eye drops had better pain control.[8,1] In a similar study, Bromfenac, another topical NSAID eye drop, provided good pain relief post injection, setting a precedent for the use of topical NSAIDs in controlling IVI pain.[10]

However, studies have only reported pain relief immediately and 6 hours after injection.[10] There have not been any studies showing pain control 24 hours post injection. Furthermore, no studies to date have compared the timing of application of a topical NSAID, in the alleviation of long-term pain patients experience. Bromfenac 0.09% is our agent of choice given its previously demonstrated effectiveness in pain control and also strength when compared to other ophthalmic NSAIDs.[10] This was demonstrated in a paper by Sheppard that compared Bromfenac with other topical NSAID eye drops and proved that it offered approximately 3-4 times higher levels of COX-2 inhibition.[13] It has been approved by the FDA as a one time daily eye drop to reduce inflammation.[14] It is commonly utilized following cataract surgery to help reduce intraocular inflammation. Our study looks at this medication's utility to control pain following IVI, another invasive procedure. We would assess pain control immediately following injection, 6 hours post injection and 24 hours post injection. This will allow us to evaluate Bromfenac 0.09%'s effectiveness on overall immediate pain control as well as on ocular discomfort/soreness that can often follow IVI. Additionally, we plan to have two intervention groups that look compared Bromfenac 0.09% instillation 30 minutes prior to IVI and instillation immediately following IVI.

The primary goal of this study is to determine if topically administered Bromfenac 0.09% eye drops can reduce the discomfort that patient experience both during and after intravitreal injections. Additionally, we will investigate the effect of both pre and post injection application of topical Bromfenac 0.09% on subjective pain scores.

Our study will be a pilot study consisting of 45 patients. These patients will be selected from those that have a diagnosis requiring intravitreal injection of an anti-VEGF agent. From these patients we will select those that have already undergone intravitreal injection at least once before. This will serve to minimize bias from initial injection anxiety and will give patients a comparative data point (prior injection discomfort). Patients will be randomized into one of three groups, which will be known as group A, B or C. The groups will have drop regimens as follows:

Group A: Will receive 1 drop of topical Bromfenac 0.09% 30 minutes prior to the injection and then 1 drop of an artificial tear eye drop immediately after the injection and wash.

Group B: Will received 1 drop of an artificial tear eye drop 30 minutes prior to the injection and then 1 drop of topical Bromfenac 0.09% immediately after the injection and wash.

Group C: Will received 1 drop of an artificial tear eye drop 30 minutes prior to the injection and then 1 drop of an artificial tear eye drop immediately after the injection and wash.

All labels will be removed from the bottles and the patients will be blinded to which group they belong to. The treating physicians (Dr. Mititelu and Dr. Chang) will also be blinded to which group the patients belong to.

Immediately following the injection, each patient will be asked to rate their pain using the Wong-Baker FACES pain scale as well as the McGill Pain Questionarire (SF-MPQ). Patients will then be given instructions and will be told to expect a call at 6 and 24 hours regarding further follow up phone questionnaires. Patients will also be provided with a phone number to contact should they have any complications (ie. discomfort, increased pain, vision changes, or any other questions). Patients will be provided with a copy of the Wong-Baker FACES pain scale and the McGill Pain Questionnaire to take home with them. Patients will be called 6 hours post-injection for further assessment of their pain using both the Wong-Baker FACES pain scale and the McGill Pain Questionnaire (SF-MPQ). At 24 hours, patients will again be contacted and their pain will be assessed one final time using both the Wong-Baker FACES pain scale and the McGill Pain Questionnaire (SF-MPQ). This will serve as the last point of data gathered for our study for our patients. They will continue regular follow up with their ophthalmologist as scheduled.

Background and Significance

Intravitreal injections (IVI) are a common form of treatment for multiple retinal pathologies. They are rapidly becoming one of the most common forms of treatment performed in the field of ophthalmology and have often improved visual outcomes for patients. Despite the massive benefit. the downside is that patients often require multiple repeat injections to maintain control of their disease state. Many patients fear injections due to the anxiety and pain during the injection and the experience discomfort after the procedure.[1,2]

Multiple strategies have been attempted to reduce the discomfort that patients experience. One of the most common being topical proparcaine and lidocaine gel. This can provide some immediately relief, but often does little to control pain that some patients experience hours after the injection.[2,3] Increased lidocaine concentration has been applied to the eye with cotton-swaps and has provided adequate analgesia during the injection, but patients often still experienced pain hours afterwards.[2] Despite the use of different concentrations of lidocaine and various types of topical eye drops (tetracaine, epinephrine with cocaine, proparacaine) little relief was provided many hours post injection.[4,5,6]

To rate the pain immediately following injections, studies have utilized the Wong-Baker FACES pain scale. This scale proved to be an effective measure of subjective pain in patients and allowed studies to adequately compare pain scores across treatments

(topical anesthesia drops, gel, lidocaine-soaked cotton swabs) versus control groups. It must be mentioned that this scale is only accurate and useful if patients are able to understand the pain scale and to properly rate what they are experiencing. This scale is particularly useful in elderly patients as it is very visual in nature.[5,6]

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have been looked at as a method of controlling immediate and post injection pain. Diclofenac, Nepafenac 0.1% and Bromfenac 0.9% has been shown to be an effective method of controlling post injection pain up to 6 hours after intravitreal injection.[8,9,10] Diclofenac has also been utilized in patients with diabetic retinopathy prior to undergoing pan-retinal photocoagulation (PRP) and was found to be effective at reducing the discomfort experienced.[9] All theNSAIDs mentioned above showed improvement in pain, mainly at 6 hours post injection.

To evaluate the pain experienced hours after injection, the short form McGill pain assessment questionnaire (SF-MPQ) was utilized.[12] Given it measures not only the level of pain, but also the type of pain that the patient is experiencing, the SF-MPQ proved to be an effective and comprehensive way to quantify and qualify the discomfort of the patient after IVI. Studies showed that by using this scale a statistically significant reduction in post injection pain was reported with topical NSAIDs.

The McGill pain assessment questionnaire has also been utilized in patient with severe dry eye. It proved effective as an easy to use questionnaire for patients to report pain and allowed the study to obtain statistically significant results.[11]

All studies we have reviewed assess pain immediately after and then again at 6 hours after injection. However, the studies did not report any findings or data points at 24 hours post injection. We will look at the use of the topical drop Bromfenac 0.09%, which has shown reduction in post injection pain.[10] We will evaluate Bromfenac 0.09% effect on pain if given 30 minutes pre-injection or immediately post injection. Surveys will be completed immediately after injection, 6 hours post-injection, and 24 hours post-injection.

Risks associated Bromfenac are minimal, and in clinical trials done by the manufacturer, mainly consisted of surface irritation. Some patients did report headaches and increased eye redness; however these symptoms were described only in 2-7% of patients. More severe complications such as corneal thinning and erosions were reported in the post-marketing surveillance group and were more associated with chronic use.[13] A study performed by Georgakopoulos et al looked at Bromfenac 0.09% in preventing and decreasing post-injection pain. Of the 65 patients enrolled in that study, none had any adverse reactions to the topical Bromfenac 0.09%.[10]

Specific Aims/Study Objectives

Hypothesis and Purpose

Our hypothesis is that intervention with a topical NSAID will alleviate pain experienced at intravitreal injection (IVI) and post-IVI. We will assess the effectiveness of topical Bromfenac 0.09% on pain after IVI. In addition, we will investigate whether pre or post injection instillation of topical Bromfenac 0.09% has a greater effect on post-injection pain.

Duration
The study will last 1 day (24 hours) total for each subject. We plan to enroll patients that require an intravitreal injection of an anti-VEGF medication for their eye disease. We plan to enroll 45 patients for this pilot study. The data analysis will be performed at the end of the study. It is expected that the study will be completed, and the results will be available within 1 year from time of commencement.

Outcome measures
1. Assessment of topical 0.09% Bromfenac's analgesic effect pre- and post-injection in patients undergoing intravitreal injections of anti-VEGFs as measured by the McGill Pain Questionnaire (SF-MPQ). (Time Frame: 6 hours and 24 hours after IVI)
2. Assessment of topical 0.09% Bromfenac's analgesic effect pre- and post-injection in patients undergoing intravitreal injections of anti-VEGFs as measured by the Wong-Baker FACES pain scale. (Time Frame: immediately following IVI)

Research Design and Methods

Recruitment and Location
Subjects are patients with a retinal disease requiring anti-VEGF therapy who are under the care of Dr. Mihai Mititelu and other retinal specialists at the University of Wisconsin Hospital and Clinics (UWHC). Ophthalmologists involved in the patients' clinical care will be the first to approach patients about the study. For patients who are interested and meet the criteria, the study team will explain the study, guide the patient through the study specific consent form, and answer subject questions.

Subjects

Subject population
The study population will consist of 45 eyes of patients recruited by ophthalmologists at UWHC.

- Inclusion criteria
    - Age $\geq$ 18 years
    - Eyes with retinal pathology requiring anti-VEGF therapy that have previously had an IVI
- Exclusion criteria
    - History of previous eye surgery other than cataract extraction
    - Herpetic eye disease
    - Uncontrolled glaucoma
    - Uveitis
    - Acute conjunctivitis

- Patients less than 18 years of age
- Pregnancy
- Known previous adverse response or contraindication to intravitreal injection, Bromfenac, or other NSAIDs.
- Keratitis including povidone-induced keratitis
- Bullous keratopathy
- Diagnosis of dry eye syndrome
- Uncontrolled diabetes
- NSAID use 3 days prior to IVI

Consent procedures

Only patients who require anti-VEGF therapy will be assessed by the treating physician for eligibility for the study. For the patients who qualify for the study, the study team will explain the study to them, including the risks. The subjects will have the opportunity to ask questions. Patients who agree will then be asked to sign the consent form. They will receive a copy of the consent form. Women of childbearing age who are unsure of their pregnancy status will be excluded from the study unless they first undergo a pregnancy test.

Research Design

1. This is a prospective pilot study of approximately 45 eyes with retinal pathology requiring anti-VEGF therapy.

2. Patients identified as candidates who express interest in participating will sign a consent form and will clinically undergo standard care IVI and randomly placed in one of three groups: Group A, B or C. Each group will consist of 15 patients.

a. Standard of care IVI entails first anesthetizing the eye with topical numbing eye drops and then cleansing the ocular surface and eyelids with a betadine cleaning solution. A lid speculum will then be placed in order to keep the ocular surface free form lashes and to minimize interference from the eyelids during the injection. Once these steps have been completed the appropriate injection of an anti-VEGF agent will be administered. The lid speculum will then be removed. The patient's eye will then be cleansed of any remaining betadine eye wash solution.

3. Group Explanations (Patients will not be aware of what group they belong to via removal of any labels on the bottles):

- Group A: Will received 1 drop of topical Bromfenac 0.09% 22 minutes prior to the injection and then 1 drop of an artificial tear eye drop immediately after the injection and wash.
- Group B: Will received 1 drop of an artificial tear eye drop 22 minutes prior to the injection and then 1 drop of topical Bromfenac 0.09% immediately after the injection and wash.

- Group C: Will received 1 drop of an artificial tear eye drop 22 minutes prior to the injection and then 1 drop of an artificial tear eye drop immediately after the injection and wash.

4. All patients involved in the study will be assessed for subjective pain score immediately (1 minute) following IVI using the Wong-Baker FACES pain scale and the McGill Pain Questionaire (SF-MPQ). This result will be recorded.

5. Subjects will be contacted at home at their preferred contact number at 6 hours post injection for further assessment of their level of pain. This will be assessed by using both the Wong-Baker FACES pain scale and the McGill Pain Questionnaire (SF-MPQ). Results will then be recorded.

6. Subjects will be contact the following day (24 hours post-injection) at home at their preferred contact number at 24 hours post injection for assessment of the pain level again both the Wong-Baker FACES pain scale and the the McGill Pain Questionnaire (SF-MPQ).

7. No further follow up appointment will have recorded data and patients will follow up with their normal provider as scheduled.

Intravitreal injection Procedure

Group A: Topical Bromfenace prior to intravitreal injection and artificial tears immediately following intravitreal injection

Group B: Artificial tears prior to injection and topical Bromfenac immediately following intravitreal injection

Group C: Artificial tears prior to and following intravitreal injection

Injections procedure will then proceed as follows:

Preparations for the injection will then be made first by tilting the patient back in the exam chair. The eye that is to be injected will be marked by placing a sticker on the patient's forehead above the indicated eye. Depending on the group 1 drop of artificial tears (Groups B and C) or Bromfenac (Group A) will be instilled in the eye intended for injection. After instillation of the first drop a timer will be set for 10 minutes. After 10 minutes has elapsed, a drop of topical tetracaine 0.5% will be instilled. A timer will then be set for 5 minutes. After 5 minutes have elapsed, the eye will cleansed with betadine 5% solution by instilling 2 drops of betadine in the eye. A timer will be set for 2 minutes.

After 2 minutes have elapsed topical lidocaine (Akten) gel 3.5% will be instilled in the eye marked for injection. A timer will then be set for 5 minutes. After 5 minutes, the physician will come into the room for the intravitreal injection and will proceed with injection of Avastin in the superotemporal quadrant of the eye after placing a eyelid speculum to hold the lids open. The treating physician will be masked as to what group the patient has been placed in. After the injection has taken place, 1-2 fingers will be held up and the patient will be asked how many they see. This step is done to assess no visual changes following intravitreal injection. The eyelid speculum will then be removed. After this is done the patient's eye will then be rinsed with an eyewash cleansing solution to remove any excess betadine. After thorough cleansing with the eye wash. The treating physician will then leave the room. The Wong-Baker and SF-MPQ pain questionnaires will then be administered by a trained study member. The patient, depending on what group they belong to will then be given one final eye drop. It will be either artificial tears (Groups A and C) or Bromfenac (Group B). The patient will then be told to expect a call 6 hours and 24 hours later. They will be given a paper copy of both the Wong-Baker and McGill Pain Questionnaires. They will be told to keep these easily accessible as these will be utilized during their 2 phone follow up calls. The patient will then leave the clinic.

Of note all physicians involved in providing intravitreal injections are Retina fellowship trained and use the same injection protocol, including choice of anesthesia, type of medication/needle/syringe, location of actual injection, etc. Injections will be given in the same location (for ex. Superotemporal quadrant as above) to ensure consistency, while not deviating from standard of care in which this location is commonly used by retina practitioners for intravitreal injection. This ensures that there will be minimal variation in the overall injection experience.

The patient's care will not differ from standard of care if they decide to participate in this study.

Being involved in the study group may prolong the patient's overall visit length by approximately 20-30 minutes. This time would include enrollment in the study, consent, group placement, as well as choice and use of numbing agent. These additional activities would not interfere in any manner with standard of care activities, specifically topical anesthesia followed by intravitreal injection using sterile technique.

Data and Safety Monitoring Plan

Risk Identification and Minimization

The risk that patients involved in this study will be exposed to will be instillation of topical Bromfenac 0.09%, a non-steroidal anti-inflammatory drug (NSAID) drop. The drop will be administered via a single use bottle of the medication and the same bottle will not be used on multiple subjects to minimize risk of cross-contamination.

Patient's will also be given an intravitreal injection of an anti-VEGF agent, but this will not be a change from what their appointment would normally entail. All of our study patients will be those whom would normally undergo an injection for their diagnosis regardless of their inclusion/exclusion from the study.

Bromfenac 0.09% is an NSAID drop and has been shown to be relatively safe in patients. This is especially true for our method of using this medication as it will only be applied topically. With that being side it does have a side effect profile which includes, foreign body sensation in the eye, conjunctival hyperemia, eye irritation, eye discomfort, eye pruritus, eye redness, headache, and rarely iritis. The manufacturer of this drop reports these events to have occurred in 2-7% of their patients during clinical trials. Post-marketing surveillance has led to less common, but still possible side effects which included corneal erosions, corneal perforation, corneal thinning, and epithelial breakdown in some patients. These are typically associated with chronic, frequent use.

It should be noted that any of patient who has previously has a poor interaction with any type of NSAID drop will not be included in our study.

Patient will be assessed immediately following their intravitreal injection for their subjective pain scores using the Wong-Baker FACES pain scale. They will also be provided a number to call should they have any questions of eye irrigation post injection. All of the patient's in our study will have previously had intravitreal injections so they will be already familiar with the process.

To minimize risks, only experienced professionals will administer the medication. All subjects will be monitored closely for any adverse reaction and treated appropriately if any of these would develop. If any adverse reactions do occur, the principle investigator will be notified and appropriate action will be taken to assist and treat the patient appropriately.

Patients will be contact at 6 hours and 24 hours post injection for subjective pain scores using the McGill Pain Questionaire (SF-MPQ). During this telephone encounter patients will also have the opportunity to ask any questions or report any symptoms that they may be experiencing.

Data and Safety Monitoring Procedures

Data collected will be monitored by the Clinic Eye Research Unit (CERU) team listed on this protocol.

Data will be assessed first after the first 7 subjects in each group have been enrolled and then again after the final 8 subjects in each group have been enrolled.

Unanticipated problems, adverse events, protocol deviations, and protocol violations will be reported as soon as they are discovered and will be recorded.

The study will be stopped if more than 30% of our subjects have an unanticipated adverse reaction to the medical indicating an issue with the medication. The study will also be stopped if any breach in confidentiality is detected.

Potential risks

The potential risks related to study participation include:

1. Drug reaction to topical Bromfenac 0.09% which includes, increase in IOP, foreign body sensation in the eye, eye pruritus, eye redness, headache, conjunctival hyperemia, eye irritation, eye discomfort, and rarely iritis. Also have a small risk of corneal erosions, corneal thinning, corneal perforation, and epithelial breakdown.
2. Increased inflammation and endophthalmitis from the intravitreal injections. Although extremely rare, it is possible to have an increase in inflammation and even endophthalmitis from an intravitreal injection.
3. Large, controlled trials and meta-analyses have been done looking at adverse events from intravitreal Anti-VEGF agents. These have shown that “anti-VEGF monoclonal antibodies did not significantly increase overall mortality, cardiovascular mortality, stroke, myocardial infarction, VTEs, or hypertension.
4. Confidentiality breach.

Protection of subjects

Subjects will be examined at a standard of care appointment. For those that enroll into the pilot study, their pain (post IVI) will be assessed at the conclusion of the appointment. Subjects will be phoned 6 and 24 hours after the IVI to assess pain level. All complications will be recorded. Patients will be instructed to call immediately for an appointment if they notice any standard care risks such as a change in the vision, appearance of the eye, or development of pain in the eye. They will be provided with a 24/7 contact number should they have any difficulties. Data collection forms will include the study identification number; no names will be used in the forms. Presentations and publications will not identify individual patients.

Statistical Considerations

Our study is a pilot study and will include a total of 45 patients. We will evaluate 3 different groups and each group will consist of 15 patients.

For Outcome 1, correlative studies of pain relief do not exist after IVI. Therefore, a power calculation cannot be extrapolated. Outcome 1 is written as a pilot experiment to

gather data for interim analysis. If statistical significance is not achieved at the interim analysis, the data will provide us with the deviation required to calculate the number of subjects needed for further recruitment in an expanded study.

For Outcome 2, based on initial calculations to achieve a power of 80% and a standard deviation of 1.8 gathered from the literature, 14 subjects in each group will be needed.[3] We plan to use 15 subjects per group to ensure statistical significance is achieved. We will not re-use these subjects in future studies.

Data and Record Keeping

Research intervention will be conducted in a private room; collection of sensitive information about subjects will be limited to the amount necessary to achieve the aims of the research. Data collection forms will include the study identification number; no names will be used in the forms. Presentations and publications will not identify individual patients.

All paper data will be stored in locked cabinets. All the electronic data will be stored in UW IT approved password-protected computers and/or UW IT approved devices. This will be kept at UWHC sites in a room with number lock available only to individuals listed in study protocol. The confidentiality of records will be maintained in accordance with applicable state and federal laws. All the identifiers and information in paper format will be shredded. The electronic data that includes any patient identifiers will be deleted at the conclusion of the study. Raw data including information regarding injection comfort level will be kept to aide in future studies.

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