**Title**

Comparison of the anesthetic effect of different dosages of tetracaine 0.5% ophthalmic solution on corneal sensation

**Trial registration**

Not yet registered.

Comparison of the anesthetic effect of different dosages of tetracaine 0.5% ophthalmic solution on corneal sensation

**Protocol version**

August 10th 2019. Version 1.2.

**Funding**

Costs were covered by the authors. No funding was received from any organization.

**Roles and responsibilities**

Names, affiliations, and roles of protocol contributors

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*Name and contact information for the trial sponsor*

There are no sponsors for this trial.

**Introduction**

**Background and rationale**

*Research question*

What is the effect of different dosages of tetracaine 0.5% ophthalmic solution on corneal sensation?

*Background*

Tetracaine is a long action aminoesther local anesthetic. The mechanism of action is the reversible blockage of voltage-dependent sodium channels, which are in the cytoplasmic membrane of the corneal nerve fibers (1). It is most commonly available in a 0.5% solution for ophthalmic use. There are trials proving tetracaine efficacy for applanation tonometry (2), for postoperative pain relief after strabismus surgery (3), for Laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) (compared with other local anesthetics) (4), for phacoemulsification (compared to lidocaine gel) (5) and for pain relief caused by corneal abrasion (6). Nomura et al. compared the time of corneal anesthesia using different local anesthetics, including tetracaine. They measured sensitivity with a Cochet-Bonnet anesthesiometer and noticed that the lowest sensitivity presented at 2.5 minutes from drops application and recovered at 12.5 minutes (7). In our search, we could only find one trial comparing duration of the effect of tetracaine 0.5% used at different dosages but is was performed in equine models (8). Different volumes of a single drop of tetracaine, did not affect the time of action in a trial performed in rabbits (9). The recommended dosage varies among pharmaceutical companies. Some recommend applying a single drop, and add another if a greater effect is needed (10), while others recommend one or two drops every 5 to 10 minutes, up to five times depending on the planned procedure (11) (12).

*Justification for undertaking the trial*

We could not find any trial comparing the time of action of tetracaine at different dosages performed in human models. There is evidence that a single drop of tetracaine 0.5% solution for phacoemulsiphication is insufficient in 88.9% of cases (5). This trial may provide evidence for the correct prescription of tetracaine depending on the intended procedure and minimize patient discomfort caused by a shallow effect of anesthesia.

*Harms from intervention*

Cochet-Bonnet anesthesiometer is an instrument that measures corneal sensitivity using a nylon fiber with an adjustable length. It is a method with a proven repeatability (13). Temporal quadrant of the cornea is the most sensitive (14). No adverse effects associated with the use of this instrument were reported on these papers (13) (14) (7).

Adverse effects from the use of topical tetracaine are infrequent, and usually do not leave sequels (15). Severe complications associated with tetracaine are rare and are more likely related to the abuse of this medication (e.g. sterile corneal lysis on a Mooren ulcer manner) (16).

*Explanation of comparators*

We chose to compare the effect of two and three drops at three minutes intervals to a single drop of tetracaine to find out if there is any benefit on applying a greater dosage, and also to find out if there is any increased risk for adverse events.

**Objectives**

*Specific objectives or hypotheses*

*General hypotheses.* The duration and the degree of the maximal anesthetic effect are greater at a greater tetracaine dosage.

*Nule Hypotheses.* There are no differences among groups on esthesiometry.

*General objective*. To measure and to compare the duration and the degree of the maximal anesthetic effect of 1, 2 or 3 drops of tetracaine 0.5%, at 3 minutes intervals, using Cochet-Bonnet anesthesiometer.

*Specific objectives.*

* To measure the duration of the maximal anesthetic effect (the period in which corneal sensation is lowest) after the application of 1, 2 or 3 drops of tetracaine 0.5% at 3 minutes intervals.
* To measure the duration of corneal anesthesia defined as the total time it takes to patient to recover his baseline corneal sensation after the application of 1, 2 or 3 drops of tetracaine 0.5% at 3 minutes intervals.
* To measure the degree of the maximal anesthetic effect, defined as the first measured corneal sensation after the application of 1, 2 or 3 drops of tetracaine % at 3 minutes intervals.
* To describe the population’s demographic data.
* To measure baseline corneal sensation.
* To describe the presence of epithelial defects after the measurement of corneal sensation with the Cochet-Bonnet anesthesiometer under topical anesthesia.
* To describe the presence of any adverse event.

**Trial Design**

*Description of trial design*

Randomized, double-blinded clinical trial.

**Methods: Participants, interventions, and outcomes**

**Study settings**

*Description of study settings*

Study to be performed at Regional General Hospital Number 12 “Lic. Benito Juárez”, from the Social Security Mexican Institute, Mérida city, state of Yucatán. Country: México.

**Eligibility criteria**

*Inclusion and exclusion criteria for participants*

Inclusion criteria:

* Subjects 18 years old or older that live in Mérida.
* Any gender

Exclusion criteria:

* Any known systemic disease.
* Any known ophthalmic disease.
* Contact lens wear.
* Previous ophthalmic surgery.
* The presence of symptoms or signs of any ophthalmic disease.

**Interventions**

*Interventions for each group:*

With previous authorization from the local research ethics committee 3202, volunteers will be assessed for eligibility.

Initially subjects who accept to participate, will answer a quick eligibility survey (appendix 2.1, Filter 1). Those who turn to be adequate to continue, will take a second filter (appendix 2.1, Filter 2) consisting in an ophthalmic assessment:

* Ophthalmic clinic history. Questions will be asked about systemic or ophthalmic diseases, ophthalmic surgeries, use of ophthalmic medication, systemic medication that could alter corneal sensitivity, such as oral anti-inflammatory drugs; contact lens wear.
* Directed questions towards ophthalmic symptoms such as red eye, tearing, photophobia, itching, burning, blurred vision, or any other symptom expressed by the patient.
* Physical exploration. By slit-lamp biomicroscopy we will evaluate eyelids, anterior segment, and fundus without pharmacologic mydriasis.

Eligible patients will be asked to sign the informed consent.

At the end of the test patients can continue their normal activities.

Patients with a disability can be eligible only if such is not a consequence of a systemic disease.

Patients will be assigned to an ID number, and then they will be randomly assigned to one of three groups:

* Group 1. These subjects will receive two drops of placebo (balanced salt solution, BSSMR, AlconMR) and one tetracaine drop (Ponti®, Laboratorios Sophia®) at 3 minutes intervals each.
* Group 2. Subjects will receive 1 drop of placebo and two of tetracaine at 3 minutes intervals each.
* Group 3. This group will receive 3 drops of tetracaine at 3 minutes intervals each.

A third person different from the person performing the esthesiometries, will apply the drops to the patients according to the assigned intervention. The patients and the examiner will be blinded to the intervention assignment.

The test will only be performed on the right eye of every subject.

The esthesiometry will be performed with a Cochet-Bonnet anesthesiometer, with a 0.12mm diameter nylon fiber on the temporal quadrant of the cornea. On other studies measurements were performed on every quadrant of the cornea, but only once. In the present study we will measure sensitivity up to twenty-two times. Thus, to reduce mechanical trauma to the cornea, we will only measure sensitivity of the temporal quadrant. This decision is based on the division on the cornea employed on the papers by Lawrenson & Ruskel, who divided the cornea into four quadrants: temporal, nasal, superior and inferior (14).

The nylon fiber will be sterilized at the beginning of every test, plunging 1mm of the tip of the nylon fiber in 10% iodine povidone during 10 minutes, and then rinsed in sterile injectable water (17).

The procedure to perform the esthesiometry is explained next:

1. The subject will be asked to sit still, looking forward. They will be asked to verbally express whether they feel a touch on the cornea of any magnitude at any time.
2. The person performing the test will stand at the right of the subject and looking towards him.
3. Initially the Cochet-Bonnet anesthesiometer will be adjusted at 60mm, because it is the minimum stimulus applicable with this instrument.
4. The stimulus will be performed always by the same person in a manual manner, by touching the temporal cornea perpendicularly, in an area between 1 and 3mm from the limbus in the clear cornea. Pressure will be applied until the fiber starts to bend.
5. The stimulus will be applied 3 times. If the patient feels it twice, the measurement will be considered positive, and it will be registered as the baseline corneal sensation. If no stimulus is felt, the measurement will be negative.
6. If the measure turns to be negative, the nylon fiber will be shortened in order to increase the magnitude of the stimulus, and the measurement will be repeated.

Once the baseline corneal sensation is recorded, the examiner will abandon the room, and another researcher will apply the assigned intervention.

Tetracaine and placebo will be put in an identical dropper known only by the researcher applying the drops.

The drops will be applied at 3 minutes intervals based on the tear exchange rate (18), and on the results by Nomura et al. They observed that after the application of tetracaine, at the time of the second esthesiometry at minute 5, the anesthetic effect was already dropping (7). The objective of applying the tetracaine more than once, is to increase the time the cornea is exposed to the local anesthetic.

The corneal sensation measurements will be performed every 3 minutes after the application of the last drop until the subject recovers his or her baseline corneal sensation, or until 63 minutes pass, even though baseline corneal sensation has not been reached. We aim to stop the test at this time to decrease the number of measurements, and to avoid the patient discomfort due to a long test time.

Time will be measured with a chronometer. The drops application will be described next:

On the 3 groups the first drop will be applied at minute -6; the second one at minute -3; and the third one at minute 0 in order to start with the esthesiometries at minute 3.

Thus, according to each group, placebo and tetracaine will be applied as follows:

* Group 1:
  + Application 1: 1 drop of balanced salt solution.
  + Application 2: 1 drop of balanced salt solution.
  + Application 3: 1 drop of 0.5% tetracaine.
* Group 2:
  + Application 1: 1 drop of balanced salt solution.
  + Application 2: 1 drop of 0.5% tetracaine.
  + Application 3: 1 drop of 0.5% tetracaine.
* Group 3:
  + Application 1: 1 drop of 0.5% tetracaine.
  + Application 2: 1 drop of 0.5% tetracaine.
  + Application 3: 1 drop of 0.5% tetracaine.

After the last application, the person in charge of the measurments will enter the room to start the procedure as follows:

1. The subjecta will sit still and look forward. They will be asked to verbally express whether they feel a touch on the cornea of any magnitude at any time.
2. The person performing the esthesiometry will stand at the patient’s right looking towards him.
3. The esthesiometry will begin with the Cochet-Bonnet adjusted at 10mm.
4. The stimulus will be applied manually always by the same person. The nylon fiber is approached to the temporal cornea (1 to 3mm proximal to the temporal limbus) in a perpendicular manner, until contact and the fiber starts to bend.
5. The stimulus will be applied three times. If the subject feels it twice or more, it will be considered as a positive measure. If he feels it only once or non, it will be a negative measure.
6. If the measure turns to be negative, the nylon fiber will be readjusted at a shorter length (5mm shorter) for the stimulus to be greater and the measurement will be repeated.
7. If the measure turns to be positive, the nylon fiber will be adjusted 0.5mm larger to decrease the magnitude of the stimulus and the measurement will be repeated. The goal is to find out what is the minimum stimulus perceptible by the subject at that moment and record the results.
8. For the next measure 3 minutes later, the nylon fiber will be enlarged 10mm and the previously described procedure will be repeated.
9. The magnitude of the minimum stimulus felt by the patient will be recorded every 3 minutes in millimeters.
10. Fake stimulus can be applied at any time in search of false positive results. 3 or more false positive measures will warrant elimination of the subject from the trial, and the test will be stopped at that moment. The recorded results will not be taken into consideration for data analysis.

At the end of the test, the subjects will be examined at the slit lamp in search of adverse events.

For antibiotic prophylaxis we will apply to all subjects a single dose of chloramphenicol 0.5% ophthalmic solution.

For discomfort prophylaxis we will apply to all subjects a single dose of diclofenac 0.5% ophthalmic solution.

For red eye and dryness sensation, we will apply to all subjects a single dose of sodium hyaluronate 2%/ oxymetazoline 0.025% ophthalmic solution.

If an epithelial defect greater than 1mm is identified after the test, prophylactic treatment with ciprofloxacin ophthalmic solution will be given at one drop every 6 hours, as well as sodium hyaluronate 0.15% ophthalmic solution every 4 hours. Follow up will be warranted next day. Punctate epithelial defects will not be considered as such.

If any other not considered adverse event is identified after the test, treatment and follow up will be assigned depending on the corresponding features and severity.

The subjects will be instructed to get in touch with the study coordinator if alarm signs are identified, such as: pain, discharge, blurred vision, tearing, photophobia, and red eye. A phone number will be provided.

*Criteria for discontinuing or modifying allocated interventions for a given trial participant*

* Non-cooperative patients will be dismissed from the test. Previously mentioned prophylactic drops will be applied.
* Patients who cannot withstand the test and decide to stop it before it ends, can leave the study at any time. Prophylactic drops will be applied.
* Patients who present adverse effects to tetracaine and decide to stop the test, can discontinue the study at any time they wish.

**Outcomes**

*Primary outcomes*

* *Duration of the maximal anesthetic effect.* Defined as the time (minutes) corneal sensation keeps being lowest. The last time interval at which corneal sensation was lowest will be recorded as the duration of the maximal anesthetic effect.
* *Duration of corneal anesthesia.* Defined as the total time it takes to a patient to recover his baseline corneal sensation after the application of tetracaine. The time interval at which the corneal sensation equals the baseline corneal sensation will be recorded as the duration of corneal anesthesia. Although tests will stop at 63 minutes whether the subject has reached his basal sensitivity or not, the duration for those who didn’t will be recorded as 66 minutes in order to obtain the approximate mean or median duration, depending on the normality test.

*Secondary outcomes*

* *Degree of the maximal anesthetic effect.* Defined as the first measured corneal sensation after the application of tetracaine.
* *Basal corneal sensation.* Defined as the result of the measurement before application of tetracaine.
* *Demographic data.* Sex and age will be recorded.
* *Presence of any adverse event.* If any adverse event is identified after the test at the slit-lamp, it will be recorded. Features and severity will be described.
* *Presence of epithelial defects after the test.* Defined as the presence of any epithelial defect greater than 1mm. This outcome will be assessed with fluorescein dye at the slit-lamp.

*Independent variables:*

* Sex
* Age

*Dependent variables:*

* Tetracaine dosage.
* Placebo.

**Participant timeline**

* Invitation and enrollment will take place beginning on December 26th 2019 until achievement of the calculated sample size. This task will be in charge of researchers different from those in charge of randomization.
* Eligible volunteers will sign informed consent and will have an ID number assigned by a researcher different from the one in charge of randomization. Each ID number will have been already randomized to one of the three study groups, blinded to the subjects and to the person in charge of corneal sensation measurements.
* Statistical analysis is programmed to start at January 7th 2020, and last for 5 days.
* Final manuscript is scheduled to be ready by January 18th 2020.

**Sample size**

Calculated sample size is 75.

Calculation is based on the next assumptions:

Where:

Zα = z value related to α = 0.05 (extracted from the reference table of Z value)

Zβ = z value related to β = 0.20 (80 % power).

SD = standard deviation

μ1 = group A mean

μ2 = group B mean

Zα =1.96

Zβ =-0.84

DE = 1.5

μ1 = 2.2

μ2 = 1.0

Sample size calculation

n = 24.5 subjects per group

n = 73 for the total sample

Sample size calculation was based on the classic formula to calculate sample size for means comparison. In order to achieve this result, it is required to know the value of the expected difference (μ1- μ2) and the measure of data dispersion from which it came from, standard deviation (SD) obtained from previous studies.7 Other components are considered: Zα (1.96) and Zβ ˄(-0.84); μ1 = group A mean and μ2 = group B mean.

**Recruitment**

There are approximately 150 employees in the hospital per shift, and 140 patients per shift scheduled for a visit and most are accompanied by a relative. The strategy for recruitment is to approach relatives waiting for their patient’s appointment and invite them to volunteer. Employees will be approached at their work space.

**Methods: Assignment of interventions**

**Allocation: sequence generation**

Every subject will be assigned to an ID number from 1 to 75. Before recruitment begins, randomization of ID numbers from 1 to 75 will be performed with the software QuickCalcs; Random number Generator (GraphPad software ® Inc.). This list will be hidden from the subjects and the person in charge of corneal sensation measurements.

**Implementation**

One of the authors, in this case Hernández-Chavarría C, will be in charge of generating the allocation sequence and will assign ID numbers to interventions. He will also be in charge of applying the drops depending on the study group.

Enrolment will be carried out by authors Navarro-Saucedo R, Hernández-Chavarría C and Cámara-Castillo HG.

During the test, esthesiometries will all be performed by the author Navarro-Saucedo R.

*Blinding*

The person in charge of corneal sensation measurement will be blinded to assignment of interventions by not having access to the correspondent list. Plus, he will be outside the test room at the moment of drops application.

Trial participants will be blinded to the assigned intervention group by not having access to this list. Also, placebo and tetracaine will be put in droppers looking the same. The content will only be known by the care provider in charge of drops application and intervention assignment. The researcher in charge of randomization will not intervene in the ID number assignment to each subject.

Unblinding will be permissible whenever adverse events show up, and the subject request to know. The procedure for unblinding is described next:

* If the adverse event is unbearable by the subject, the test will be immediately stopped.
* The examiner who is also blinded to the intervention group, will ask the care provider in charge of the list of intervention groups to unblind the group assigned to the patient with a given ID number.
* The care provider in charge of the list with the intervention groups will check the list, and provide only the requested information, with care not to expose the list.
* The examiner can then explain the subject to which intervention group he or she is assigned to.
* Prophylactic drops will be applied. Treatment and follow up will be provided.

**Methods: Data collection, management, and analysis**

**Data collection methods**

*Plan for assessment*

Subjects who accept enrolment will first take the eligibility survey (appendix 2.1). This survey has two sections or filters. The first filter is a series of four yes or no questions. If all questions are negative, the second filter will begin.

Subjects eligible for the trial will be enlisted on the volunteers registry list (Appendix 2.2).

This list will be handed to the care provider in charge of the intervention assignment. This person will also be responsible for the data collection instrument (appendix 2.3), which is an individual sheet, and the data concentration sheet (appendix 2.4), where data from all the subjects will be gathered from the collection instruments.

While one care giver is measuring sensitivity, another will be writing down results every 3 minutes on the data collection instrument.

*Plans to promote participant retention and complete follow-up*

The participant retention will not be a problem during this study, because time between every measure is only 3 minutes long.

**Data Management**

*Plans for data entry*

The eligibility survey will be applied and filled by the authors who are not in charge of intervention assignment (Navarro-Saucedo and Cámara-Castillo). They will also write the names of the subjects on the volunteers’ registry list sequentially, once subjects are declared eligible. The ID number will be assigned at this point.

The person in charge of intervention assignment (Hernández-Chavarria) will gather all the eligibility surveys and the volunteer’s registry list and enter data in the electronic data concentration sheet (spread sheet).

During the test, while one care giver is measuring corneal sensation (Navarro-Saucedo), another (Hernández-Chavarría) will be writing down results every 3 minutes on the data collection instrument. The former person will also enter data on the data concentration sheet.

*Data coding, security and storage*

Electronic data will be kept safe in a personal laptop, with security password. At the beginning of the trial, only the person in charge of intervention assignment and data entry will have access. After data collection is finished, only the authors will have access to the files.

Storage of the physical documents will be in charge of Hernández-Chavarría (intervention assigner) and will be kept safe and locked up.

The data concentration sheet is an electronic spread sheet where all data will be entered for initial processing. Details are next enlisted:

Rough data will be entered first.

* The ID numbers will be listed on the first column in sequential order.
* Second and third column age and gender respectively.
* Next, the intervention group according to the result of the randomization.
* Next, baseline corneal sensation in terms of the nylon fiber length (millimeters).
* The next 21 columns will contain the results (in millimeters of nylon fiber) from esthesiometries in 3 minutes intervals beginning at minute 3, until minute 63.

After data verification, the information will be arranged by group on different sheets of the same file for data analysis.

*Process to verify data quality*

After the data concentration sheet is totally filled, authors will double-check data by comparing every eligibility surveys and data collection instruments with the data concentration sheet.

**Statistical methods**

Main outcomes analysis

The duration of maximal anesthetic effect, and the duration of corneal anesthesia, will be described as means with standard deviation in case of a normal distribution of data. Conversely, they will be described as medians with 95% confidence interval; an ANOVA/ Kruskal-Wallis test will be employed to compare more than three measures of the esthesiometry depending on data distribution. Additionally, Tukey post-hoc test will be employed.

The degree of the maximal anesthetic effect will be described as mean with standard deviation or median with 95% confidence interval and compared with the same statistical methods than the main outcomes.

Categorical analysis based on proportions will be evaluated by Chi-square test or exact Fisher’s test.

Shapiro-Wilk normality test will be used to determine distribution of all variables of the study.

**Methods: Monitoring**

**Data monitoring**

Data monitoring committee will be composed by the author Cámara-Castillo and an additional person apart from the authors.

The role of the monitoring committee is to double check rough data in the data concentration sheet by comparing the information with the written sources subject by subject. A comment on the electronic file will be added when errors are found, and the error will be corrected. Since there are no external sponsors, no conflicts of interest are declared by any of them.

*Stopping guidelines*

No interim analysis will be performed. If any severe adverse effect such as infectious keratitis secondary to the test is found in any subject, the trial will be immediately stopped even before culture results. Follow up will be warranted.

If any other unexpected adverse event is found, the decision to stop the trial will be discussed among authors. After analyzing the situation, the final decision to stop the trial will be taken by majority of votes.

**Harms**

*Plans of action in case of adverse events and other unintended effects*

* Collection. At the end of the test, every eye will be examined at slit lamp with fluorescein dye in search for epithelial defects that could have been caused by mechanical damage. Also, all the patients will be provided with the authors telephone number. Details about alarm signs (such as red eye, pain and blurred vision) will be provided.
* Assessment. In case of an epithelial defect larger than 1mm, we will prescribe ciprofloxacin 0.3% ophthalmic solution every 6 hours for five days, and visits will be scheduled every day until disappearance of the defect.
* Reporting. Adverse events will be reported in the corresponding column of the collection instrument.

**Auditing**

The author Cámara-Castillo will be in charge of auditing, once every week.

**Ethics and dissemination**

**Research ethics approval**

The local research ethics committee 3202 has reviewed and approved this protocol.

The institutional register number is: R-2019-3202-005.

**Protocol amendments**

Relevant modifications of the protocol will be communicated to the relevant parties. The part of the original content and the corresponding modifications will be specified in a memo and sent via e-mail to other investigators, research ethics committee, trial participants, trial registries, journals and regulators.

**Consent or assent**

*Obtention*

The authors Navarro-Saucedo R, Hernández-Chavarría C and Cámara-Castillo HG will obtain informed consent or assent after subjects have passed the eligibility survey. Risks, alarm signs and symptoms will be explained, and a contact number will be provided.

**Confidentiality**

After enrollment, surveys containing personal information will be kept under lock by the author Hernández-Chavarría. Once data collection is complete and electronic files are filled, they will be stored in the cloud provided by the author’s institutional account. This account is personal, and only the author has the password to access the files. A carpet with the corresponding files will be shared with the other authors. Data will be stored in this electronic carpet during and after the trial.

**Declaration of interests**

Dr. Gonzalez-Salinas reports personal fees from Tarsus Pharmaceuticals Inc., Kedalion Therapeutics Inc., LayerBio Inc., Allegro Ophthalmics LLC., and Laboratorios Sanfer, outside the submitted work. None of the previous disclosures conflict with the present work. Also, no conflicting relationship exists for any other author.

The authors Navarro-Saucedo R, Cámara-Castillo HG, Hernández-Chavarria César and Solórzano-Ugalde Diego A, declare not to have any conflict of interests.

**Access to data**

All authors will have access to the final trial dataset.

**Ancillary and post-trial care**

No provisions are considered for participants in this trial.

Participants suffering harm form trial participation will receive the number of visits required until full recovery, as well as medication.

**Dissemination policy**

*Results communication*

The results will be published in a peer-reviewed journal for ophthalmology practitioners.

The final work will be presented in support for candidature for academic degree as ophthalmologist surgeon by the author Navarro-Saucedo R.

Publication restrictions will be those stated by the selected journal.

*Authorship eligibility guidelines*

Authorship in this protocol is based on the International Committee of Medical Journal Editors criteria.

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**Appendices section**

Appendix 1.1

Informed consent for adults

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| IMSSN | | | | | **MEXICAN INSTITUTE OF SOCIAL SECURITY**  **EDUCATION, RESEARCH AND HEALTH POLICIES UNIT**  **HEALTH RESEARCH COORDINATION**  **INFORMED CONSENT**  **(ADULTS)** | | |
| INFORMED CONSENT FOR PATICIPATION IN TRIALS | | | | | | | | |
| Name of the trial: | | Comparison of the anesthetic effect of different dosages of tetracaine 0.5% ophthalmic solution on corneal sensation | | | | | | |
| External sponsors (if any) | | No external sponsors involved. | | | | | | |
| Date and place: | | Mérida, Yucatán, (day/ month/ year) | | | | | | |
| Registry number: | | R-2019-3202-05 | | | | | | |
| Justification and objective of the trial: | | To find out how long does the maximum effect of tetracaine 0.5% last (anesthetic medication routinely used in ophthalmology) at different doses on the cornea (the superficial clear front part of the eye) in order to be able to anticipate the desired effect depending on the planned procedure, and to avoid uncomfortable sensations at any moment. | | | | | | |
| Procedure: | | Corneal esthesiometry with Cochet-Bonnet esthesiometer under local anesthesia with tetracaine 0.5% ophthalmic solution. It consists on appling a stimulus with a nylon fiber at different lengths, before and after medication instillation, every 3 minutes until normal corneal sensitivity is recovered, or after 63 minutes top. We will ask you to verbally express the moment you feel the stimulus in your cornea. | | | | | | |
| Possible risks and harms: | | Risks are mainly those derived from tetracaine. Corneal epithelium (most superficial layer of the cornea) can suffer abrasion if the subject rub his eyes while being under the effect of the anesthetic resulting later in pain, tearing and discomfort with light. To avoid this, please do not rub or touch your eyes at least one hour after the procedure. Corneal anesthesia can decrease blinking frequency and tearing, thus causing blurred vision that improves with blinking. This adverse effect is self-limited when the effect of the tetracaine ends. Tetracaine drop application can produce burning sensation during approximately 30 seconds. Adverse effects are rare and include eyelid swelling, redness, and posteriorly itch and irritation that can last for a few days. Severe adverse effects such as corneal ulcers and perforation have been noted to occur only in cases of tetracaine abuse, and have never been reported at the doses handled in this trial. Esthesiometry itself, is the measurement of corneal sensitivity to a known pressure, applied with a nylon fiber. The contact of this fiber with the cornea can produce a slight discomfort sensation. Although we have not found any adverse event due to the esthesiometry, we could expect corneal abrasion (described earlier) that heals in a 24 to 48 hours period. An infection called keratitis can overcome a corneal abrasion. It is characterized by pain, redness, blurred visión, tearing, spasm of the eyelids, discomfort with light, secretion, and severe cases can lead to sequelae such as decreased vision, scars in the cornea, or in the worst-case eye loss. To avoid this, the esthesiometer will be desinfected among patients, and a single drop of topical antibiotic will be applied to every patient. For the detection of corneal abrasion, after the procedure we will use a fluoresceine dye strip. In case it was found, topical antibiotic will be applied every 4 hours to prevent infection, and a new visit will be provided 24 hours later to repeat fluorescein dye, and so on every 24 hours until the abrasion heals. If needed, the antibiotics will be provided by the research group. | | | | | | |
| Possible benefits from pariticipating in this trial | | As part of the protocol, we will perform an ophthalmic assessment which includes visual acuity measurement, physical exploration on the slit lamp of ocular adnexa, anterior segment and fundus. This serves as a screening for possible ocular pathologies that the subject could be unaware of, and it represents a direct benefit for the patient. No chardsges will be applied. As an indirect benefit, we will generate information on the optimal tetracaine dose, as it is a frequently used drug for many diagnostic and therapeutic procedures. | | | | | | |
| Information about results and treatment alternatives | | A printed copy of the initial assessment will be handed to the patient. In case of any ophthalmic pathology detection, the subject will not be eligible to participate in the trial. Treatment prescription and complementary diagnostic tests are not offered by this research group for pathologies detected on the initial assessment. | | | | | | |
| Participation or retreat: | | The subject is free to decide whether to participate or not on the trial and can ask to abandon the test at any moment. Any question can be solved by the enlisted authors. | | | | | | |
| Privacy and confidentiality | | The results from the trial are intended to be published on scientific journals. The authors are committed to maintain the subject’s identity private, and do not unveil it in any publications. In case the subject agrees, the compiled data can be used for future studies. | | | | | | |
| In case of biologic material collection (if applies): | | | | | | | | |
|  | I do not authorize sampling. | | | | | | | |
|  | I do authorize sampling for this study. | | | | | | | |
|  | I do authorize sampling for this and future studies. | | | | | | | |
| Medical treatment availability for insured patients (if applies) | | | | | | It does not apply. | | |
| Benefits at the end of the trial: | | | | A copy of the initial assessment will be handed to the subject. If the subject requests it, a copy of the results from the esthesiometry can be supplied. | | | | |
| In case of doubts or questions related to the study, please address to: | | | | | | | | |
| Responsible researcher: | | | Ricardo Navarro Saucedo (first author) / Matrícula 98333647/ Third year ophthalmology resdient/ Hospital General Regional No. 12 Benito Juárez/ IMSS/ Phone number 4731417049 | | | | | |
| Collaborators: | | | Diego Antonio Solórzano Ugalde (coauthor)/ Anterior segment subspecialist, Ophthalmologist surgeon, working in the ophthalmology department at HGR No. 12 Benito Juárez, IMSS; and main professor of the specialty at the Autonomous University of Yucatán, campus HGR No 12 Benito Juárez, IMSS. | | | | | |
| In case of doubts or questions about your rights please address to: Ethics on Research Committee of the CNIC from the IMSS: Avenida Cuauhtémoc 330 4° piso Bloque “B” de la Unidad de Congresos, Colonia Doctores. México, D.F., CP 06720. Phone number (55) 56 27 69 00 extension 21230, e-mail address: [comision.etica@imss.gob.mx](mailto:comision.etica@imss.gob.mx) | | | | | | | | |
| Subject’s name and signature | | | | | | | **Ricardo Navarro Saucedo/ Matrícula 98333647**  Name of the person obtaining the consent | |
| Witness 1  Name, address, relationship to the subject and signature | | | | | | | Witness 2  Name, address, relationship to the person and signature | |
|  | | | | | | | | |
| **Clave: 2810-009-013** | | | | | | | | |

Appendix 1.2

Informed consent (legal representatives of subjects with any disability)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| IMSSN | | | | **MEXICAN INSTITUTE OF SOCIAL SECURITY**  **EDUCATION, RESEARCH AND HEALTH POLICIES UNIT**  **HEALTH RESEARCH COORDINATION**  **INFORMED CONSENT TO PARTICIPATE OON RESEARCH STUDIES**  **(LEGAL REPRESENTATIVE FOR SUBJECTS WITH A DISABILITY)** | |  |
| Name of the trial: | | Comparison of the anesthetic effect of different dosages of tetracaine 0.5% ophthalmic solution on corneal sensation | | | | |
| External sponsors (if any) | | No external sponsors involved. | | | | |
| Date and place: | | Mérida, Yucatán, (day/ month/ year) | | | | |
| Registry number: | | R-2019-3202-05 | | | | |
| Justification and objective of the trial: | | To find out how long does the maximum effect of tetracaine 0.5% last (anesthetic medication routinely used in ophthalmology) at different doses on the cornea (the superficial clear front part of the eye) in order to be able to anticipate the desired effect depending on the planned procedure, and to avoid uncomfortable sensations at any moment. | | | | |
| Procedure: | | If the subject’s disability affects the patient’s capability to respond to the stimulus on the cornea, or if the person cannot understand or follow instructions, then he or she is not eligible to participate in this study. Corneal esthesiometry with Cochet-Bonnet esthesiometer under local anesthesia with tetracaine 0.5% ophthalmic solution. It consists on appling a stimulus with a nylon fiber at different lengths, before and after medication instillation, every 3 minutes until normal corneal sensitivity is recovered, or after 63 minutes top. We will ask you to verbally express the moment you feel the stimulus in your cornea. | | | | |
| Possible risks and harms: | | Risks are mainly those derived from tetracaine. Corneal epithelium (most superficial layer of the cornea) can suffer abrasion if the subject rub his eyes while being under the effect of the anesthetic resulting later in pain, tearing and discomfort with light. To avoid this, please do not rub or touch your eyes at least one hour after the procedure. Corneal anesthesia can decrease blinking frequency and tearing, thus causing blurred vision that improves with blinking. This adverse effect is self-limited when the effect of the tetracaine ends. Tetracaine drop application can produce burning sensation during approximately 30 seconds. Adverse effects are rare and include eyelid swelling, redness, and posteriorly itch and irritation that can last for a few days. Severe adverse effects such as corneal ulcers and perforation have been noted to occur only in cases of tetracaine abuse, and have never been reported at the doses handled in this trial. Esthesiometry itself, is the measurement of corneal sensitivity to a known pressure, applied with a nylon fiber. The contact of this fiber with the cornea can produce a slight discomfort sensation. Although we have not found any adverse event due to the esthesiometry, we could expect corneal abrasion (described earlier) that heals in a 24 to 48 hours period. An infection called keratitis can overcome a corneal abrasion. It is characterized by pain, redness, blurred visión, tearing, spasm of the eyelids, discomfort with light, secretion, and severe cases can lead to sequelae such as decreased vision, scars in the cornea, or in the worst-case eye loss. To avoid this, the esthesiometer will be desinfected among patients, and a single drop of topical antibiotic will be applied to every patient. For the detection of corneal abrasion, after the procedure we will use a fluoresceine dye strip. In case it was found, topical antibiotic will be applied every 4 hours to prevent infection, and a new visit will be provided 24 hours later to repeat fluorescein dye, and so on every 24 hours until the abrasion heals. If needed, the antibiotics will be provided by the research group. | | | | |
| Possible benefits from pariticipating in this trial | | As part of the protocol, we will perform an ophthalmic assessment which includes visual acuity measurement, physical exploration on the slit lamp of ocular adnexa, anterior segment and fundus. This serves as a screening for possible ocular pathologies that the subject could be unaware of, and it represents a direct benefit for the patient. No chardsges will be applied. As an indirect benefit, we will generate information on the optimal tetracaine dose, as it is a frequently used drug for many diagnostic and therapeutic procedures. | | | | |
| Information about results and treatment alternatives | | A printed copy of the initial assessment will be handed to the patient. In case of any ophthalmic pathology detection, the subject will not be eligible to participate in the trial. Treatment prescription and complementary diagnostic tests are not offered by this research group for pathologies detected on the initial assessment. | | | | |
| Participation or retreat: | | The subject is free to decide whether to participate or not on the trial and can ask to abandon the test at any moment. Any question can be solved by the enlisted authors. | | | | |
| Privacy and confidentiality | | The results from the trial are intended to be published on scientific journals. The authors are committed to maintain the subject’s identity private, and do not unveil it in any publications. In case the subject agrees, the compiled data can be used for future studies. | | | | |
| **Consent declaration** | | | | | | |
| After reading and solving every doubt about this study: | | | | | | |
|  | I do not agree that my relative or represented participate in this study. | | | | | |
|  | I agree that my relative or represented participates in this study, and I also authorize sampling only for this study. | | | | | |
|  | I agree that my relative or represented participates in this study, and I also authorize sampling for this study and future studies, storing his or heer blood sample up to \_\_ years after which it will be destroyed. | | | | | |
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| **In case of doubts or questions related to the study, please address to:** | | | | | | |
| Responsible researcher: | | | Ricardo Navarro Saucedo (first author) / Matrícula 98333647/ Third year ophthalmology resdient/ Hospital General Regional No. 12 Benito Juárez/ IMSS/ Phone number 4731417049 | | | |
| Collaborators: | | | Diego Antonio Solórzano Ugalde (coauthor)/ Anterior segment subspecialist, Ophthalmologist surgeon, working in the ophthalmology department at HGR No. 12 Benito Juárez, IMSS; and main professor of the specialty at the Autonomous University of Yucatán, campus HGR No 12 Benito Juárez, IMSS. | | | |
| In case of doubts or questions about your rights please address to: Ethics on Research Committee of the CNIC from the IMSS: Avenida Cuauhtémoc 330 4° piso Bloque “B” de la Unidad de Congresos, Colonia Doctores. México, D.F., CP 06720. Phone number (55) 56 27 69 00 extension 21230, e-mail address: [comité.eticainv@imss.gob.mx](mailto:comité.eticainv@imss.gob.mx)  If during the study you identify or percieve any discomfort, pain, irritation or changes in the skin caused by the sampling or drug application, you can address to: Drug Vigilance Area, phone number: (55) 56276900, ext. 21222, e-mail adress: [iris.contreras@imss.gob.mx](mailto:iris.contreras@imss.gob.mx) | | | | | | |
| Name and signature of both parents or tutors or legal representatives | | | | | Name of the person obtaining the consent | |
| Witness 1  Name, address, relationship to the subject and signature | | | | | Witness 2  Name, address, relationship to the person and signature | |
| **Clave: 2810-009-014**  **1 de 2** | | | | | | |

Appendix 2.1

Eligibility Survey

Eligibility survey

Date:

1. First filter
   1. Dou you have any diagnosed systemic or ophthalmic disease?

☐yes ☐No

* 1. Have you ever hade ye surgery?

☐yes ☐No

* 1. Are you a contact lens wearer?

☐yes ☐No

* 1. Do you use any ophthalmic medication?

☐yes ☐No

(In case of any positive response, the subject is not eligible for the test. Otherwise, continue with physical exploration.)

1. Second filter. Ophthalmic clinic history and physical exploration.

|  |  |  |
| --- | --- | --- |
| Name |  | |
| ID number |  | |
| Date of birth |  | |
| Age |  | |
| Gender |  | |
| Pathologic personal background | ☐Non  ☐**Diabetes mellitus**  ☐ **Arterial hypertension**  ☐**Other systemic diseases**  ☐ **Rheumatologic disease**  ☐ **Systemic medication**  ☐ Allergies  Others: | |
| Ophthalmic background | ☐Non  ☐ **Surgeries**  ☐ **Inflammatory diseases such as uveitis, conjunctivitis**  ☐ **Chronic infectious diseases**  ☐ **Glaucoma**  ☐ **Ophthalmic medication use**  Others: | |
| Actual symptoms | ☐ Asymptomatic  ☐ **Pain**  ☐ **Itching**  ☐ **Burning**  ☐ **Blurred vision**  ☐ **Foreign body sensation**  Others | |
| Physical exploration | | |
|  | Right eye | Left eye |
| Visual acuity |  |  |
| Ocular adnexa | ☐No alterations found  ☐**Apparent pathologic discharge**  ☐**Anomalous eyelashes implantation**  ☐**Abnormal eyelid position**  Other abnormalities: | ☐No alterations found  ☐**Apparent pathologic discharge**  ☐**Anomalous eyelashes implantation**  ☐**Abnormal eyelid position**  Other abnormalities: |
| Anterior segment | ☐ Conjunctiva white and quite  ☐ Normal fornix  ☐**Hyperemia, folicules, suspicious discharge, or any inflammation suggestive signs.**  ☐ Clear cornea  ☐**Corneal opacity**  ☐ Formed anterior chamber, no inflammation signs.  ☐ Normal iris, normal pupil reflexes.  ☐Clear lens. | ☐ Conjunctiva white and quite  ☐ Normal fornix  ☐**Hyperemia, folicules, suspicious discharge, or any inflammation suggestive signs.**  ☐ Clear cornea  ☐**Corneal opacity**  ☐ Formed anterior chamber, no inflammation signs.  ☐ Normal iris, normal pupil reflexes.  ☐Clear lens. |
| Fundus | ☐ Clear media  ☐Optic nerve with normal color, and physiologic cup to disc rate.  ☐Macula with foveolar reflex  ☐Vascular pattern within normal limits  ☐No retinal dettachment.  ☐**Any inflammatory sings**  Other alterations: | ☐ Clear media  ☐Optic nerve with normal color, and physiologic cup to disc rate.  ☐Macula with foveolar reflex  ☐Vascular pattern within normal limits  ☐No retinal dettachment.  ☐**Any inflammatory sings**  Other alterations: |
| Diagnosis | ☐Ophthalmologically healthy  ☐**Other** | |
| Plan | ☐ The subject is eligible to participate on the trial.  ☐ **The diagnosis is associated with changes on corneal sensitivity, thus the subject cannot participate.**  ☐A visit to the ophthalmologist is required.  ☐No further attention is required. | |

Appendix 2.2

Volunteers registry list

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| ID number | Name | Age | Gender (Male: 1, Female: 2) |
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Appendix 2.3

Data collection instrument

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| ID number |  |
| Esthesioimetry measurement (nylon fiber adjusted length in mm) | |
| Basal |  |
| Minute 3 |  |
| Minute 6 |  |
| Minute 9 |  |
| Minute 12 |  |
| Minute 15 |  |
| Minute 18 |  |
| Minute 21 |  |
| Minute 24 |  |
| Minute 27 |  |
| Minute 30 |  |
| Minute 33 |  |
| Minute 36 |  |
| Minute 39 |  |
| Minute 42 |  |
| Minute 45 |  |
| Minute 48 |  |
| Minute 51 |  |
| Minute 54 |  |
| Minute 57 |  |
| Minute 60 |  |
| Minute 63 |  |
| Epithelial defect (Yes: 1, No: 2) |  |

## Appendix 2.4

Data concentration sheet

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| Subject ID number | Age | Gender (Male 1, female 2) | Group (1, 2 o 3) | Basal sensitivity | 3 min | 6 min | 9 min | 12 min | 15 min | 18 min | 21 min | 24 min | 27 min | 30 min | 33 min | 36 min | 39 min | 42 min | 45 min | 48 min | 51 min | 54 min | 57 min | 60 min | 63 min | Eputhelial defect: (yes 1, No: 2) |
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Appendix 4

Cochet-Bonnet aesthesiometer equivalence chart for a nylon monofilament size S: 0.0113mm2 (0.12mm in diameter)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Nylon length in mm | 60 | 55 | 50 | 45 | 40 | 35 | 30 | 25 | 20 | 15 | 10 | 5 |
| Mean pressure values in mm/gr/S | 11 | 12 | 13 | 16 | 21 | 27 | 35 | 52 | 75 | 100 | 145 | 200 |
| Mean pressure values in gr/mm2 | 0.96 | 1.08 | 1.16 | 1.40 | 1.84 | 2.40 | 3.20 | 4.60 | 6.64 | 8.84 | 12.84 | 17.68 |

(20)

**Biological specimens**

No sampling or biological specimens will be performed in this trial.