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TUFTS MEDICAL CENTER
TUFTS UNIVERSITY
Tufts University School of Dental Medicine Oral Surgery

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Efficacy of Arnica montana in reducing postoperative edema and pain following third molar extraction

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Study team telephone number: (617) 636-6515

INTRODUCTION

You are being invited to take part in this research study because you are scheduled to have at least two of your wisdom teeth (third molars) extracted at Tufts University School of Dental Medicine (TUSDM). In this study, we want to see if people who receive homeopathic Arnica montana (SinEcch™) have less facial swelling and pain following wisdom tooth extraction in comparison to people who did not receive Arnica montana and instead receive a placebo.

Taking part in this research study is entirely your choice. You can decide to refuse to participate in this study. If you decide to participate in this study, you can then choose to stop taking part in the study at any time for any reason. If you refuse to participate in the study or stop being in this study, it will not affect your care or treatment outside this study, payment for your health care, or your health care benefits.

Please read all of the following information carefully. Ask Dr. Joey Chang or his representative, to explain any words, terms, or sections that are unclear to you. Ask any questions that you have about this study. Do not sign this consent form unless you understand the information in it and have had your questions answered to your satisfaction.

If you decide to take part in this research study, you will be asked to sign this form. You will be given a copy of the signed form. You should keep your copy for your records. It has information, including important names and telephone numbers, to which you may wish to refer in the future.

New things might be learned during this study that you should know about. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you are eligible to participate and decide to be in the study, the Principal Investigator may still choose to stop your participation in this study if he thinks it is in your best medical interest. Other reasons why you may be withdrawn from the study include the following: if you present with a wound infection during the postoperative period; if you take any non steroidal anti-inflammatory medications such as Motrin, Ibuprofen etc. or other analgesic medications during the course of the study other than the prescribed study medications; noncompliance;

unwillingness to participate any further; failure to present for follow-up visits; the study doctor will determine if you need additional treatment and/or follow-up observation as a result of participation in this trial. If you withdraw or are withdrawn from the study, any data collected from you before your withdrawal will still be used for the study.

As a participant in this study, your identity, medical records, and data relating to this study will be kept confidential, except as required by law. The U.S. Food and Drug Administration, which regulates investigational drug and device studies, and the study sponsor may also look at records that identify you if applicable to the study.

If you have question about your rights as a research study subject, call the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board (IRB) at (617) 636-7512. The IRB is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of people who take part in the studies. Federal law requires the IRB to review and approve any research study involving humans. This must be done before the study can begin. The study is also reviewed on a regular basis while it is in progress.

This research study has been reviewed and approved by the IRB of Tufts Medical Center and Tufts University Health Sciences.

PURPOSE OF STUDY

Doctors and patients are concerned about controlling post-operative pain and swelling associated with third molar surgery. Arnica montana is an herbal medicine used since the 16th century for various aspects of wound healing including swelling, pain and bruising. The herbal medicine is derived from a plant. Today, there is widespread use of homeopathic Arnica Montana in the United States and worldwide.

This study is being conducted in order to evaluate the effectiveness of a commercially available oral form of homeopathic Arnica montana, SinEcch™, for treatment of postoperative swelling and pain following wisdom tooth (third molar) extraction. We want to see if people who receive Arnica montana have less facial swelling and pain following wisdom tooth extraction in comparison to people who did not receive Arnica montana and instead receive a placebo. A placebo is a pill composed of sugar. Currently SinEcch™ is marketed to reduce swelling and bruising; this study will also see if it can help reduce pain associated with wisdom tooth extraction.

You are being invited to participate in this study because you have been scheduled to have your wisdom teeth extracted following standard of care procedures. This study will involve taking the medications supplied during the study and by taking 3D photographs of your face before and after the surgery, using 3dMD facial screening software. The system will take two pictures of your face and record measurements to create a 3 dimensional model. The 3dMD face system uses a combination of patterns on your face, such as pores and freckles on the skin to calculate from. The device will map out what your face looks like before the surgery. Then, it will map out after surgery during the 2 post-operative visits. By comparing the before and after images, we will find out if you have any swelling in your mouth or cheeks from the procedure. You will also

be asked to rate how painful your wisdom teeth are on a pain rating scale before the surgery. This baseline measure will be compared with the pain ratings given later on after surgery.

Up to 70 people will be enrolled at Tufts University School of Dental Medicine. Our goal is to have 50 people complete this study. SinEcch™ is commercially available and can be purchased online.

The sponsor of this study is Alpine Pharmaceuticals.

PROCEDURES TO BE FOLLOWED
Your participation in the study will last for 5-7 days after your scheduled surgery.

Eligibility screening (approximately 30 minutes)
This visit may occur during your consultation visit for your wisdom tooth extraction, typically 10-15 days before the scheduled surgery. If there is not time to complete this screening visit during the consultation, these activities may occur the day of surgery.

You will be asked to read this informed consent form (ICF). You will be given ample time to have any questions answered. If you decide to participate, you will be asked to sign this ICF, and you will be given a copy.

You will be asked to provide demographic information about yourself and complete a medical history form. An oral exam, including evaluation of oral cavity and soft tissues, will be completed following standard of care procedures. We will review your information and confirm whether you are eligible to participate in the study.

We will then take a 3D photograph of your face for research purposes (alternatively, this can be taken at Visit 1 instead). You will be asked to remove any jewelry on your head or neck, metal facial decorations, or metal hair clips prior to the photograph.

Visit 1—Day of Surgery (this visit lasts for about 2.5 hours out of which 30 minutes would be for research purposes)
On the day of your surgery, you will be asked to arrive one and half hours prior to your procedure as standard of care at TUSDM.

Your medical history will be reviewed during this hour and any changes will be noted. Eligibility and subject withdrawal criteria will be reviewed to ensure you still qualify for the study. An oral exam will be conducted.

If you are a female, we will ask you to complete a urine pregnancy test to make sure you are not pregnant.

You will be assigned to one of two groups: the Arnica montana group or the placebo group. The placebo group will be given a sugar pill. You will be randomized to one group, which means you will have an equal chance in being in either group. It is like flipping a coin or drawing names

out of a hat. Only Dr. Chang and a designated study coordinator will know what group you are in; you will not know which group you are in.

One hour before surgery, we will give you a capsule (either Arnica montana or a sugar pill) to swallow with a small sip of water. This is for research purposes only.

We will then take a 3D photograph of your face for research purposes. It will be taken prior to the surgery during this one and half hour time block. (Note: if this 3D photograph was previously taken during the Eligibility Screening, it will not be repeated here).

We will ask you to rate your level of pain prior to having the surgery.

The tooth (teeth) extraction will then be performed as the standard of care by your provider. We will record information about the teeth that were extracted from your provider for study purposes.

Immediately after tooth (teeth) extraction, you will be kept in a recovery room for approximately 1-2 hours at the Department of Oral and Maxillofacial Surgery, TUSDM, as per standard of care.

We will discharge you following all post-operative instructions as per standard of care. You will be sent home with the blister pack of either Arnica montana (SinEcch™) or the sugar pills (placebo). You will receive specific instructions about how and when to take the pills. You will have to take the medication 12 times in total, spread throughout the day of your surgery and the three days following your surgery, as per the instructions provided. You will also be prescribed Vicodin as per standard of care. You can also take Tylenol (acetaminophen) for the control of pain.

We will ask you to rate your level of pain post-surgery.

We will also send you home with a pain diary which you will be asked to fill out once a day until your last study visit.

The night of your surgery, a member of the study team will call you to see how you are doing and ask if you took your medications. This is for study purposes only.

<u>Visit 2— First Postoperative Visit (3 days ±1 day after Visit 2)</u>
This visit is only for research purposes. Your medical history will be reviewed and any changes will be noted. Eligibility and subject withdrawal criteria will be reviewed to ensure you still qualify for the study.

An oral exam will be completed, including evaluation of extraction socket following standard of care procedures.

A second 3D photograph of your face will be taken.

We will ask you to rate your level of pain.

We will record any information from your medical record about the wisdom tooth extraction up through one week after the date of your surgery.

Visit 3—Second Postoperative Visit (5 days ±1 day after surgery)

You will return for a follow-up visit as standard of care. All procedures and interventions other than the third 3dMD scans and returning the study medications will be done as standard of care at TUSDM. The 3dMD scans will be experimental for this visit. We will ask you to rate your level of pain. You will need to return the pain diary and any remaining study medications at this time.

RISKS

Participation in this study does not increase or decrease the standard of care risks associated with wisdom tooth extraction.

The risks associated with the 3dMD photographs are minimal. There is a minor physical risk as cables to the instruments and computer can poses a tripping hazard. This will be reduced by taping cables to the floor.

Risk of loss of confidentiality will be minimized by following the procedures in the Confidentiality section.

Arnica montana is a relatively safe drug in the very diluted concentration that is used for this study. Homeopathic Arnica montana, as used in this study, has minimal risks since homeopathic Arnica montana is nontoxic due to its degree of dilution. Because it is nontoxic, homeopathic Arnica montana is regulated by FDA as an over-the-counter (OTC) drug. Alpine Pharmaceuticals states that, with nearly a million dosing packs of SinEcch™ distributed since 1997, only 18 cases have resulted in adverse reactions, mostly consisting of mild gastrointestinal symptoms and skin rashes.

Arnica taken in quantities larger than the prescribed dose is unsafe. It is considered poisonous in very large doses. When taken by mouth in large doses it can also cause irritation of the mouth and throat, stomach pain, vomiting, diarrhea, skin rashes, shortness of breath, a fast heartbeat, an increase in blood pressure, heart damage, organ failure, increased bleeding, coma, and death.

Allergy to ragweed and related plants: Arnica may cause an allergic reaction in people who are sensitive to the Asteraceae/Compositae family. Members of this family include ragweed, chrysanthemums, marigolds, daisies, and many others.

By participating in this study, nothing will be subtracted from your standard of care treatment; your wisdom tooth extraction will be completed following standard of care procedures at

TUSDM. You will also receive postoperative pain killers (Vicodin) to manage your pain as per standard of care.

BENEFITS

There are no medical benefits to you from participating in this study. However, subjects who are randomized to receive homeopathic Arnica montana (SinEcch™) may experience a potential benefit of a decrease in postoperative swelling. Subjects who are randomized to the placebo control group are not expected to experience a medical benefit for postoperative swelling as a result of participation in this research study.

ALTERNATIVES

You may choose not to participate in the study. You may choose to have the previously scheduled procedure completed at the TUSDM Oral Surgery Clinic or Tufts Dental Associates clinic at normal clinic fees.

RESEARCH RELATED INJURY

Emergency medical treatment will be given to you if you are hurt or get sick as a direct result of being in this research study. You or your insurance carrier will be required to pay for any such medical care. Any needed medical care is available at the usual cost. All needed facilities, emergency treatment, and professional services are available to you, just as they are to the general public. The institution will not pay for your treatment if you become ill or injured as part of this study.

COSTS

There are no costs associated with your participation in this study. Standard of care costs (such as extraction) remain your responsibility.

PAYMENT

You will receive a total of $175 in Amazon gift cards for participating in the study. A $25 gift card will be given after you sign the consent form and are enrolled to participate in the study. A $100 gift card will be given upon the completion of Visit 2. A $50 gift card will be given upon the completion of Visit 3.

If you drive to your appointments and choose to park at the Tufts Medical Center parking garage on 274 Tremont Street, you will receive a parking voucher to cover the cost.

PRIVACY AND CONFIDENTIALITY

All of your information we collect from you for this study will be stored in a secure location in the PI's office (DHS-5th Floor) and kept strictly confidential except as may be required by law.

If any publication results from this study, you will not be identified by name without prior consent.

To ensure confidentiality of your information, you will be assigned a unique alphanumeric code. Your file will be kept in a secure, locked cabinet in a secure room when the documentation is not being reviewed. The information will only be shared between the researchers. Source documents and case report forms will be coded and free of your name. All HIPAA requirements will be followed. All electronic files will be kept on a password protected computer in a secure, locked office. This will be accessible by study personnel only.

We will not label your 3dMD images with your name, only your unique alphanumeric code. The photographs will be deleted at the end of the study.

If you agree to take part in this research study, your personal information will not be given to anyone unless we receive your permission in writing. It will only be given if the law requires it. It will also only be given for regular hospital treatment, payment, and hospital management activities.

We will make every effort to keep your information private, but it cannot be completely guaranteed. Certain government agencies, the Institutional Review Board of Tufts Medical Center and Tufts University Health Sciences, and the study sponsor (Alpine Pharmaceuticals) may check records that identify you. This might include your medical or research records and the informed consent form you signed. The records of this study might also be reviewed to make sure all rules and guidelines were followed.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US law. This website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this website at any time.

PHOTO RELEASE

In consideration of my engagement as a subject, I hereby grant the following rights and permissions to Dr. Joey Chang. Dr. Chang has the right to take full face photographs of me using the above named 3-D camera for the purposes of this research study. He has the unrestricted right and permission to use and re-use these photographic pictures of me for further use in this study. I understand that my photographs will not be used for any other purpose and that they will be destroyed at the end of this investigation. I hereby release, discharge, and agree to hold harmless Dr. Chang, his heirs, legal representatives, and assigns, and all persons acting under his permission or authority or those for whom he is acting, from any liability by virtue of any blurring, distortion, alteration, optical illusion, or use in composite form, whether intentional or otherwise, that may occur or be produced in the taking of such photographs or in any subsequent processing of them.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

If you sign this document, you give permission to the Principal Investigator named above and research staff at Tufts University School of Dental Medicine as well as other individuals at Tufts University School of Dental Medicine who may need to access your information to do their jobs (such as for treatment, payment (billing) or health care operations) to use or disclose (release) your health information that identifies you for the research study described above.

The parties listed in the preceding paragraph may disclose the health information described below to the following persons and organizations for their use in connection with the research study:

- Individuals or organizations working under the direction of the Principal Investigator(s) for the study,
- Outside individuals or entities that have a need to access this information to perform activities relating to the conduct of this research, such as analysis by outside laboratories on behalf of Tufts University School of Dental Medicine.
- Other researchers and institutions that are conducting or participating in this study,
- The study sponsor (Alpine Pharmaceuticals) and any companies that they use to oversee, manage, or conduct the research,
- The Office for Human Research Protections in the U.S. Department of Health and Human Services, the United States Food and Drug Administration (FDA) and other federal and state agencies that have the right to use the information as required by law, and
- The members and staff of any Institutional Review Board (IRB).

The health information that we may use or disclose (release) for this research study includes all information in your medical record related to the diagnosis and management of your third molar extraction, including the record of your care, as well as any information collected or created during the course of this study.

Tufts University School of Dental Medicine is required by law to protect your health information. By signing this document, you authorize Tufts University School of Dental Medicine to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You may not be allowed to see or copy the information described on this form as long as the research is in progress, but you have a right to see and copy the information upon completion of the research in accordance with hospital policies.

You can decide to sign or not to sign this form. However, if you choose not to sign this form, you will not be able to take part in the research study and you may not receive any research-related clinical care.

This authorization does not have an expiration date. You may change your mind and revoke (take back) this authorization at any time. Even if you revoke this authorization, this site's clinical, administrative and research staff may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this authorization, you must write to: HIPAA Privacy Officer for Research at One Kneeland Street, Room 334, Boston, MA 02111. If you revoke this authorization, you may no longer be allowed to participate in the research described in this form.

WHOM TO CONTACT

Principal Investigator: Dr. Joey Chang – (617) 636-6515

Documentation of Consent

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered to my satisfaction. I agree to take part in this study.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to stay in this research study.

_____ _____

Date Participant's Signature

I have fully explained to _____ the nature and purpose of the above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Date Principal Investigator or Representative's Signature