Use of Topical Non-Steroidal Anti-Inflammatory DRUGS to Reduce Pain in Oral Lichen Planus and Oral Lichenoid Lesions

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Protocol Proposal

A four-week randomized, double blind, cross-over, placebo-controlled trial was planned. Ethical approval was obtained from the Institutional Review Board (IRB) at the University of Washington before the start of the study, participants agreed to participate in this study had to sign a written informed consent. The present trial was also registered (#NCT03509675). The research was conducted in accordance with the ethical principles stated in the World Medical Association's Helsinki Declaration.

A coin was flipped to decide which medication would be used first to start the randomization. Based on the coin toss, drug A was chosen for the first block of two participants. Then, block randomization was further assigned by blocks of two, alternating the drugs. The medicines were distributed in identical plastic containers, packed by an external pharmacist who was unaware of the protocol, and successfully labeled as A and B containers.

During the intervention, neither investigators nor the participants knew which of the treatments they were using.

Population and Study Sample

Potential participants were screened through the Oral Medicine patient registry at the University of Washington. Prospective patients aged 18–80 were examined by the attending at

the Oral Medicine Clinical Services (OMCS) faculty. All potential study participants with a clinical diagnosis of symptomatic oral lichenoid mucositis with or without a biopsy were identified. Individuals were eligible for inclusion if they met the following criteria:

- Speak English
- Have a symptomatic form of the disease
- At least 18 years of age

The exclusion criteria were as follows:

- Occurrence of dysplasia in the histopathological specimen
- Known or suspected sensitivity to NSAID medication
- History of asthma
- History of gastrointestinal ulceration
- History of bleeding disorders
- Pregnancy

The patients were asked to participate in the research at their first or follow-up visits at the OMCS.

Sample Size and Sample Selection

The most similar study to the present one was done by Saxen et al., in which a 45% change in VAS scores between the treatment groups was found. With the assumption of a 45% difference in VAS scores, a standard deviation of 0.69, a two-sided significance level of 0.05,

and a statistical power of 80%, a sample size of 36 was calculated. When accounting for the effect of a cross-over trial and analyses, a sample size of 36 should be able to show significance with a change in VAS scores between 25% and 30%, significantly less than that found in the work of Saxen et al.

Collection of Data

The data collected included the following:

- VAS at baseline, end of day 4 and following the end-of-the week application of the active intervention and the placebo
- Gender
- Race and ethnicity
- Duration of the primary chief complaint
- Medication trials for the condition
- Current medical conditions
- Current prescription drugs
- Current OTC drugs
- Known allergies to drugs or food substances
- Clinical diagnosis of the disease
- Classification of the OLP (if noted): reticular, erythematous, erosive, bullous

Topical Formulation

The topical suspension of the topical NSAID was 100 mg per 5 ml concentration of ibuprofen, with similar ingredients as OTC children's ibuprofen and was compounded by an external drug services. Another placebo suspension was also compounded with the same taste but without the active ingredient.

Placebo (bottle A)	Active study drug (bottle B)

• Ora plus (purified water, microcrystalline cellulose, carboxymethylcellulose sodium, carrageenan, calcium sulfate, trisodium phosphate, citric acid, and sodiumphosphate as buffers, and dimethicone antifoam emulsion. Preserved with methylparaben and potassium sorbate) • Stevia • Avicel Ph 105 • Xanthan gum • Grape flavor	• **Ibuprofen** • Citric acid, potassium sorbate, glycerin, polysorbate 80 NF, sorbitol 70% Sol, water (distilled water), methocel 2% suspension • Xanthan gum • Grape flavor

Table 1 the ingredients of the medication used in the study.

Assessment

We used tracking forms for the participants to record both their daily usage and VAS scores at baseline, day 4, and day 7. (see Appendix A). Participants were asked to mark their pain level before starting the first bottle in the morning of day one. 100mm VAS scales were used with the anchors of (non-intense) on the right side and (extremely intense) on the left. The

patients were seen for a free assessment to evaluate their condition during the intervention and report any adverse reactions.

Intervention

After we obtained written consent from the patients regarding their participation in the research, they received a research packet with the relevant data forms, the consent form, and two bottles; each bottle had an individual label marked with “A” or “B”. The coding which identified the contents of A and B was sealed by the pharmacy and was kept with one of the committee members as well as with the pharmacy

The participants were asked to record their baseline score of spontaneous pain on a horizontal 10 cm VAS before commencing the use of the provided rinses. If the participants were already on an active treatment at the time of enrollment, they were asked to discontinue for 7 days’ prior for a wash-out period before starting the research protocol.

All participants were instructed to use the first suspension four times a day for 7 days. They were instructed to rinse before the meals; breakfast, lunch, dinner and also before bedtime. After every application of the rinse, they were asked to check a box in order to record their use of the rinse. The instructions included rinsing with 5 ml of the suspension for 1 minute without swallowing it, and then expectorating. The patients were instructed not to eat or drink for the following 20 min after the application of the drug. At the end of days 4 and 7, the participants were asked to record their spontaneous pain level on the VAS. After the first week, they discontinued any treatment for 7 days (wash-out) before starting the second suspension.

All participants were instructed to use the second suspension on the same schedule as the first, and with the same instructions. The participants were contacted initially after the first day of the intervention to discuss any concerns or questions they may have. Every week, reminder phone calls were made for them to fill out the forms from the investigator and to check for any side effects from the intervention.

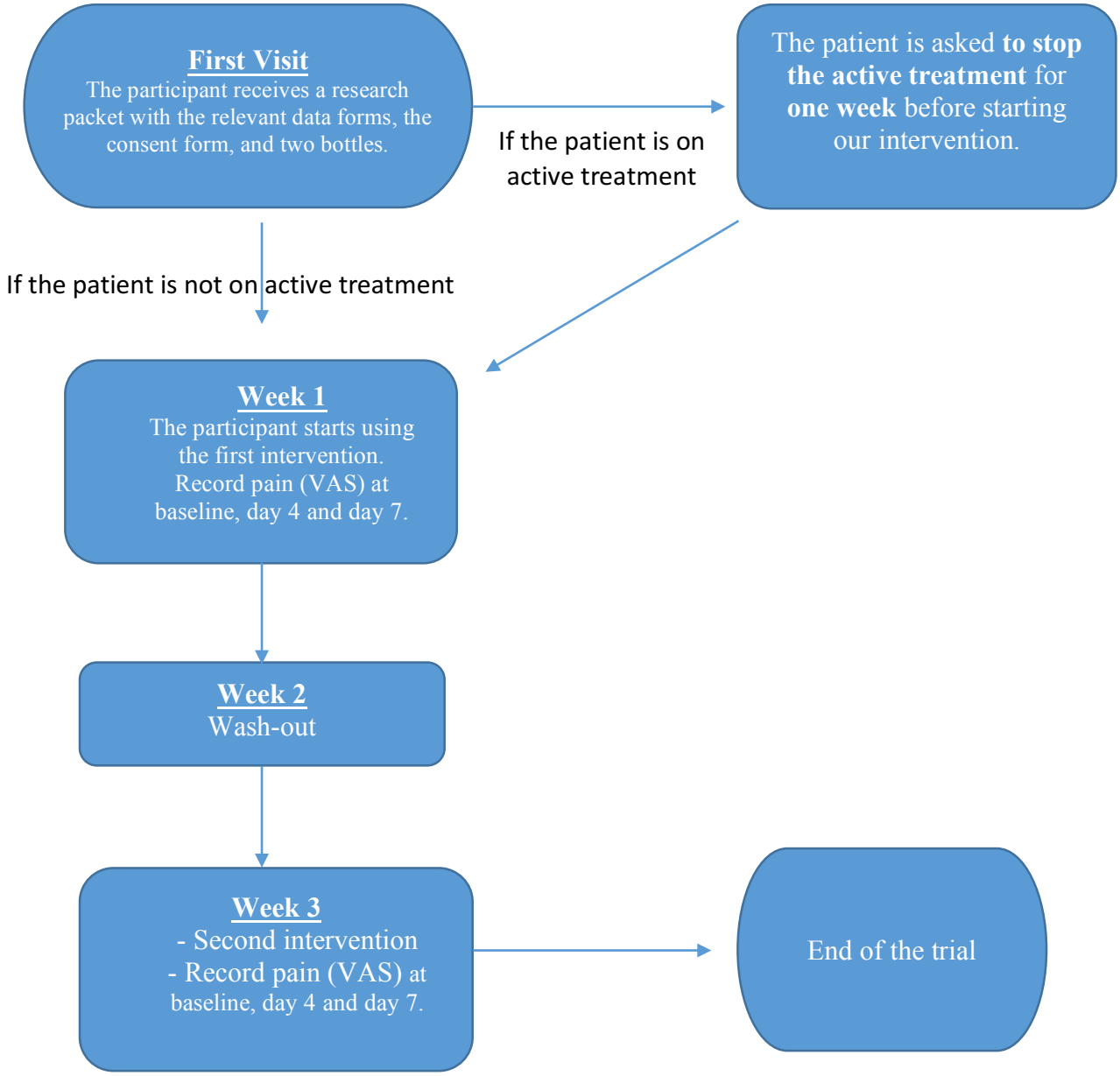

Figure 1 Flow diagram showing the process of the intervention.

Data

We protected the patients' information by assigning each individual with a study number that was correlated with the medical record number on a master list. The master list was secured in a password-protected file on a password-protected computer stored in a locked office. The collected data were stored separately. The list was not placed on a portable device. Only the research committee members and the personnel required for the statistical analysis had access to the files.

The study data will be kept indefinitely but will only be linked until December 31, 2019. Only the investigators will have access to the identifiable data, unless otherwise required by law.

Data Analysis Strategies

The VAS results were measured in millimeters and entered as whole numbers. T-tests for means were used to compare VAS scores at the following time points: baseline, days 4 and 7 of treatment condition # 1, at baseline #2 (following the wash-out period), and at days 4 and 7 of treatment condition #2.

Multiple linear regression was used to determine the difference in effect between the active medication and placebo groups by including the difference between reports at baseline, day 4 and at day 7. Both univariate models and models including age and duration of chief complaint were used to assess the effect of these variables. There was insufficient variance in both gender and race to assess for these effects. Although randomization of the treatment order should eliminate order effect, tests for order effect were performed using regression analyses.

For drug effect assessment, in addition to using VAS scores themselves, percent change in VAS scores was used to normalize distributions.

Ethics and Human Participant Issues

All experimental protocols were reviewed and approved by the institutional review board IRB and Committee on human participant research at the University of Washington.

University of Washington consent form
Consent Form
Use of Topical Nonsteroidal Anti- inflammatory to Reduce Pain for oral Lichen Planus patients

Researchers:

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Researchers' statement

We are asking you to be in research study. The purpose of this consent is to give you the information you will need to help decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your right as a volunteer, and anything else about the research or this form that is not clear. This process is called "informed consent" We will give you a copy of this form for your records.

PURPOSE OF THIS STUDY

The University of Washington, Department of Oral Medicine is conducting a study to find out if the use of topical application of non-steroidal anti-inflammatory can reduce pain and discomfort in patients with diagnosis Oral Lichen Planus or Oral Lichenoid Lesions.

STUDY PROCEDURES

If you decide to participate in this research study, there will be one visit lasting up to 15 min. **Today you will receive two bottle of suspensions (A &B)** and a data collection form. One of the bottles will contain the topical anti-inflammatory we are using in the trial and in the other one there will be an inactive substance.

If you are already using topical medication prescribed by your care provider, you will be asked to stop your current topical treatment for a week .

Before using the first suspension, you will mark your level of pain on the sheet (we will show you how) at the end of the day before starting the study. For each application you will place a check mark in the corresponding box on the form. At the end of days 4 and 7 of use of the first suspension, you will be asked to mark your level of pain with a vertical line on the line drawing on the sheet. After that you will stop using medication for your oral condition for another week in which you will use nothing.

At the beginning of week #3, before using the **second suspension**, please mark your level of pain on the sheet and for each usage you will place a check in the corresponding box on the form. By this week, you will start the second bottle and use it four times a day and again check the box on the form for each application. At the end of days 4 and 7 you will mark your pain level on the form again and your participation in the treatment part of the study will conclude at the end of day 7.

Following this, **we would like to see you again for a 15 minutes**, no charge visits in which we will evaluate you again and receive the forms from you.

RISKS, STRESS, OR DISCOMFORT

Discontinue the standard care of treatment:

Discontinuing the standard care of treatment may cause discomfort, increase your pain, or inflammation. You can talk to the research team about any discomfort and if the discomfort reaches a point you cannot tolerate, you have the freedom to discontinue the study and use your standard treatment.

Adverse Reaction from the suspensions:

Hypersensitivity might emerge as a risk factor for using the topical NSAID. Please stop the medication if you experience any of the following: hives, facial swelling, asthma (wheezing), shock, skin, reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away. If you experience any signs of other adverse reactions, please contact the research team as soon as possible.

Privacy

Although we will make every effort to keep your information confidential, no system for protecting your confidentiality can be completely secure. It is possible that persons might discover you are in the study, or might obtain information about your participation in the study.

Unknown risks:

As this medication has never been used specifically for your condition, we are not sure of all the possible adverse events that you might encounter. You can talk to the research team about any discomfort and if the discomfort reaches a point you can't tolerate you have the freedom to discontinue the study and use your standard treatment.

ALTERNATIVE FOR TAKING PART IN THIS STUDY

Being in this study is voluntary. You may refuse to participate and you are free to withdraw from the study at any time without penalty or loss of benefit to which you are otherwise entitled. Participating or not participating will not affect your clinical care in any way.

BENEFITS OF THIS STUDY

Being in the study may be of no direct benefit to you. However, Knowledge may be gained that may benefit others in the future.
It is not the purpose of this research project to identify or provide you with any medical information or diagnosis.

CONFIDENTIALITY OF REASERCH INFORMATION

Your participation in this study, and the information we gather will be kept confidential. The information we collect as part of this research study will not be included in your medical record. We will code your study information. We will keep the link between your name your study information in a locked file at University of Washington. Your study data will be kept indefinitely but the link between your identifier and the research data will be destroyed after the records retention period required by state and/or federal law. Only the investigators listed above will have access to your identifiable data unless otherwise required by law. Although we will make every effort to keep your information confidential, no system can be completely secured. It is possible that unauthorized persons might discover that you are in this study, or might obtain information about you.
We will share what we learn with other health professional through medical publication. None of this publication will include information that could identify you.
A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

OTHER INFORMATION

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits that you are otherwise entitled.

Subject statement

This study has explained to me. I volunteer to take part in this research. I have had chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researcher listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subject Division at (206) 543-0098. I will receive a copy of this consent form. I give permission to the researchers to use my medical records as described in this consent form.

Printed name of subject signature of subject Date

Copies to: Researcher
Subject