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Exploring Melatonin as a Treatment for Oral Ulcers

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Honors Thesis

EXPLORING MELATONIN AS A TREATMENT FOR ORAL ULCERS

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ABSTRACT

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The hormone melatonin is best known for its role in the sleep-wake cycle, but its anti-inflammatory and antioxidant effects have significant implications that have not been fully explored in oral health. Some studies use melatonin to treat gastrointestinal ulcers, including duodenal ulcers and oral mucositis, but we found no study reporting its effects on more common oral ulcers, like aphthous stomatitis. We hypothesize that the anti-inflammatory and antioxidant characteristics of melatonin could effectively prevent and heal oral ulcers. In this paper, we review the literature on melatonin to propose its use as a treatment for oral ulcers. We also include the methods for two clinical trials to determine the efficacy and ideal concentration of melatonin as a topical treatment for oral ulcers. This paper provides insight on understanding aphthous stomatitis's etiopathogenesis, melatonin's safety profile, and offer an overdue indication for melatonin's use in the oral cavity.

Keywords: Melatonin, aphthous stomatitis, anti-inflammatory, antioxidant, canker sores, oral health diseases, dentistry

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Introduction: Exploring Melatonin as a Treatment for Oral Ulcers

Melatonin is a highly conserved molecule with a diverse physiological function. It is a well-known circadian rhythm regulator, but its function as a cytoprotective agent is less documented. Melatonin is reported to prevent and heal tissue damage in the gastrointestinal tract (GIT) and has a promising safety profile. We suggest that it may effectively treat common oral ulcers, such as aphthous stomatitis. We justify this proposal by reviewing literature on melatonin and making connections to aphthous stomatitis.

Canker sores, or aphthous stomatitis, are painful and common, non-contagious oral ulcers. Aphthous stomatitis is one of the most common diseases of the oral cavity, affecting around 20% of the population (1). Aphthous ulcers are associated with a number of health conditions (2). While many cases of stomatitis are considered idiopathic, recurrent aphthous stomatitis (RAS) may be influenced by diet, stress level, genetic predisposition, viral and bacterial infection, hormone level fluctuation, mechanical injury, systemic disease, and other factors (2), as presented in Figure 1. Despite the pervasiveness of RAS, its etiopathogenesis is still unclear (3). This is likely due to the variety of causes of the ulcers, which are still being characterized.

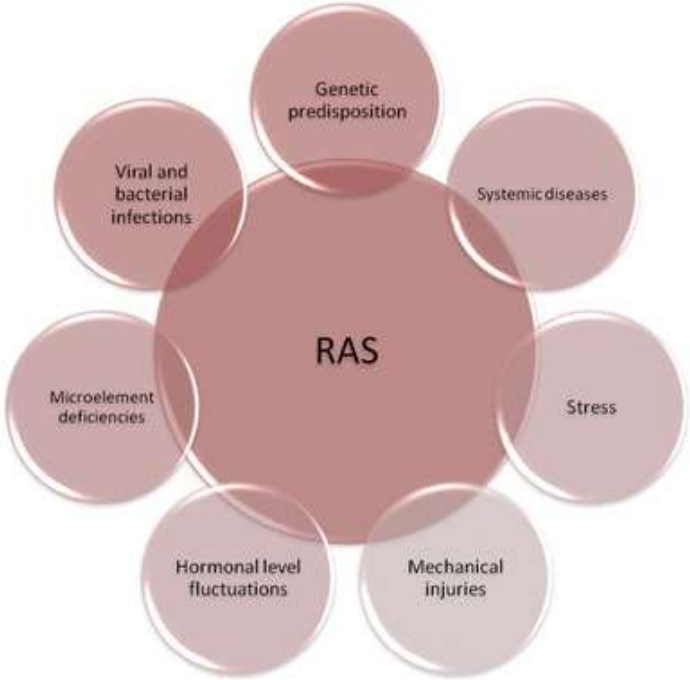

Figure 1: Representation of the causes of recurrent aphthous stomatitis (RAS) Image from Slebioda, et al. 2014

The many causes of aphthous stomatitis and limited understanding of its etiopathogenesis have made treatment difficult. A variety of home remedies exist and are recommended for pain relief. Current methods include:

- Topical anaesthetic gel (e.g. Orajel: Benzocaine, menthol, and zinc chloride)
- Analgesic patch (e.g. Pain-Relieving Patch: Camphor, Menthol & Methyl Salicylate)
- Homeopathic method (e.g. Hyland: Borax, Calendula, Causticum, Mezereum, Natrum Muriaticum)
- Home remedies (e.g. Milk of magnesia, antiseptic mouth rinse, baking soda/water mouth rinse, and many more)

Despite these options, there is little evidence for a substantial, effective treatment for aphthous stomatitis (3).

Melatonin demonstrates anti-inflammatory and antioxidant effects that have not been fully explored in oral health. It is possible that these characteristics of melatonin could have a healing effect on oral ulcers, such as aphthous stomatitis. This paper includes an overview on melatonin's physiology in the human body and provides research support toward melatonin's anti-inflammatory and antioxidant properties. A brief overview of aphthous stomatitis is included, as well as results of research with melatonin as a treatment for other ulcers in the GIT. This paper includes a review of available information on the safety of melatonin and concludes with a research design proposal to determine melatonin's plausibility as a treatment option for oral ulcers. A clinical trial, as outlined in this paper, would serve to test the efficacy of melatonin as a treatment for oral ulcers.

Melatonin Overview

Melatonin has two primary categories of function: sleep regulation and cytoprotection. Before discussing its protective role, a brief overview is useful to understand its primary function as a regulatory molecule. Melatonin is best known for regulating circadian rhythm of the sleep-wake cycle. The site of melatonin synthesis associated with the sleep-wake cycle occurs in the pineal gland, where it is released throughout the body via the blood and cerebrospinal fluid (4). Photoreceptors in the pineal gland inhibit melatonin synthesis in the presence of light and synthesize melatonin for systemic release in the absence of light (5). In one of the first comprehensive reviews of the pineal gland, Arendt (5) states that pineal cells may be manipulated *in vitro* to produce melatonin using a fabricated light/dark schedule. Mayo Clinic (6) further supports that melatonin's production and release from the pineal gland is dependent on light. Figure 2 demonstrates that exposure to light downregulates the amount of melatonin synthesized, while darkness increases melatonin levels.

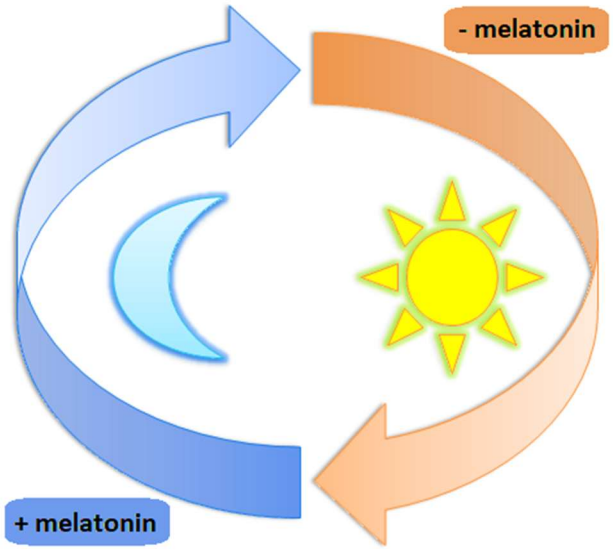

Figure 2: This simple diagram portrays melatonin activity in the sleep-wake cycle. The + indicates an increase during the night while the - represents a decrease during daylight hours.

Melatonin's role in circadian rhythm is well-founded, but researchers debate the efficacy of exogenous (externally administered) melatonin in treating sleep disorders. A review by Matheson et al. (7) analyzes methods for managing insomnia disorder. They incorporate clinical trials using melatonin but conclude that the limitations in these

studies do not provide sufficient evidence for its effectiveness. Conversely, meta-analyses performed by Auld et al. (8) conclude that melatonin is effective in treating insomnia and other sleep disorders. Auld et al. use a stricter inclusion criterion for their research than Matheson et al.; they only incorporate double and single-blind clinical trials with randomizations and appropriate controls. While Matheson et al. do exclude studies without randomization, they include secondary articles and observational studies. They also do not include melatonin's efficacy as a primary outcome as do Auld et al. Sletten et al. (9) provide further evidence for exogenous melatonin's successful treatment of insomnia in a double-blind, randomized clinical trial. A meta-analysis by Buscemi et al. (10) reports mixed results, depending on the type of sleep disorder being studied. The issue is not whether melatonin's imbalance factors into sleep-related disorders, but whether exogenous melatonin is a viable solution. While most literature supports exogenous melatonin's efficacy, it depends on the type of disorder. Consistent parameters are needed to improve future research and allow for better meta-analysis.

As previously mentioned, the pineal gland is recognized as the primary site of melatonin synthesis for the sleep-wake cycle. However, high concentrations of melatonin are found in extrapineal tissues, along with the enzymes necessary for its synthesis. These other locations include the cerebellum, liver, immune cells, respiratory epithelium, reproductive organs, and the GIT (11). It is also found in most bodily fluids, including saliva, cerebrospinal fluid, bile, and breast milk. It is interesting to note that in the case of a pinealectomy (removal of the pineal gland), the typical day and nighttime cycle of melatonin is lost (12). However, its blood concentration is maintained during the day because the GIT synthesizes about 500 times the quantity of melatonin produced in the

pineal gland (12). Melatonin's prevalence in all tissues and fluids, particularly the GIT, suggests physiological functions beyond sleep regulation.

Melatonin plays a unique role in the GIT. Current literature shows that in addition to circadian regulation, melatonin heals wounds and lesions, scavenges free-radicals (shows antioxidant activity), and protects of mucosal tissue in the GIT (13). Clinical trials of melatonin demonstrate its effectiveness in treating such a wide variety of conditions that Reiter et al. (14) perhaps accurately conclude that its true function has not yet been characterized. Despite its promising secondary functions, it is still classified as a dietary supplement by the Food and Drug Administration (FDA) and has no indication for the treatment of any disease (15). While melatonin's mainstream classification is a circadian rhythm regulator, its peripheral mechanisms should be further investigated. These secondary roles could yield significant clinical and personal applications.

Melatonin Cytoprotection

The second primary function of melatonin appears to be protection of mucosal tissue. One review from Konturek et al. (16) investigates melatonin's role in preventing and healing wounds in the GIT. They explain that melatonin is responsible for increasing nitric oxide synthase and cyclooxygenase-prostaglandin activity, which help increase blood flow to damaged tissue. The increase in blood flow allows for an improved immune response and thus maintains the health of the mucosal tissue. Melatonin also reduces pain by inhibiting proinflammatory cytokines around the wound. These conditions prompted a clinical trial testing the efficacy of melatonin in preventing esophageal wounds (17). Using rats as an animal model, they gave the test group a melatonin pretreatment and did not treat the control group. Both groups were then

induced with esophageal lesions and analyzed for nitric oxide and prostaglandin levels, among other factors. The lesions measured in the test group were much smaller than the control group, prostaglandin levels were higher in the test group, and blood flow was increased in the test group. The results from these studies show melatonin's potential for preventing skin damage in humans. Their blood analyses contribute to a better understanding of melatonin's mechanism of action in protecting mucosal tissue damage. Konturek et al. continue to advocate for melatonin as a therapeutic agent, shown in another study later that same year (12). Although not the first to do so, Konturek et al. are widely recognized and cited for their work on melatonin's protective action.

Reactive oxygen species (e.g. free radicals and peroxides) occur naturally but may become harmful to our cells when produced in excess. Oxidative stress can occur when environmental factors lead to an increase in reactive oxygen species, and antioxidants are chemical compounds that stop the harmful effects of reactive oxygen species. While Konturek et al. do mention melatonin's antioxidative roles in their work, other authors provide more specific research. Reiter et al. (14) explain several mechanisms for melatonin's antioxidative behavior. It may directly detoxify a reactive oxygen, indirectly recruit other antioxidative enzymes, inhibit pro-oxidative enzymes, and chelate metals responsible for hydroxyl radicals. Antioxidants are essential for regulating cellular oxygen levels and for protecting cells during oxidative stress. The mechanisms proposed by Reiter et al. are supported by others who assert that melatonin's role as a skin protectant is underappreciated in medicine (18, 19).

To our knowledge, melatonin is not adequately utilized in oral health as it is in other regions of the GIT and conditions affecting the oral mucosa may benefit from

melatonin's cytoprotective effects. Despite minimal reports, melatonin has been used to treat some conditions affecting the oral cavity. A series of studies by a research team in Iran investigate melatonin's influence on two interdependent diseases: periodontal disease (PD) and type II diabetes mellitus (DM) (20). Periodontal disease typically results from poor oral hygiene and causes the gums to become swollen and painful. Since both diseases cause oxidative stress and inflammation, they propose using melatonin as a potential treatment. In a double-blind clinical trial, one test group received 6 mg of melatonin per day while the control group received a placebo. The researchers report that a melatonin supplement with nonsurgical therapy improves patient PD, which they determined by assessing the gingival recession, bleeding on probing, and measuring the pocket depth between the gums and the teeth. They also report that adjunct melatonin increases serum levels of melatonin and decreases markers of inflammation.

In 2020, this same team published further research on the cytoprotective effects of melatonin in patients with DM and PD (21). 50 participants with DM and PD received either a placebo or melatonin treatment in a randomized and double-blind clinical trial. Both groups received 2 tablets to take before bed each night; the test group received two 250 mg tablets with 3 mg of melatonin per tablet and the control group received two 250 mg placebo tablets. Since this group already found that melatonin improves PD, they narrowed their focus to analyzing the antioxidant and inflammatory markers in serum samples. Serum levels were measured before and after the study. They report a significant increase in mean serum levels and mean changes in serum levels for the selected markers between the test group and control group. Other studies support their findings (22, 23), including a study by Amulghrabi et al. (24) that compares salivary

melatonin levels in healthy subjects to patients with periodontal disease, aggressive periodontal disease, and gingivitis. They report much lower salivary melatonin levels in all test groups compared to the healthy group, with the lowest levels measured in subjects with aggressive periodontal disease. These studies on periodontal disease offer insight into melatonin's potential for treating oxidative stress and inflammation in the oral mucosa. Melatonin's therapeutic effects should be investigated further, as they may provide relief to those suffering from wounded and inflamed tissue.

Melatonin and Aphthous Stomatitis

Aphthous stomatitis is one of the most common diseases of the oral mucosa, affecting around 20% of the population (25). The many causes of aphthous stomatitis and limited understanding of its etiopathogenesis have made treatment difficult. It is often linked to other health conditions and the ulcers vary in their severity, frequency, and time to heal. Home remedies are recommended for pain relief, but there is little evidence for a substantial and effective treatment. The previously mentioned clinical trials explore the anti-inflammatory and antioxidant properties of melatonin on wound healing, but none report melatonin's effects on common oral ulcers, like aphthous stomatitis.

Figure 3: Portrayal of radio and chemotherapy induced mucositis. Image from Dr. Ajay Malik, 2012 (35).

Melatonin has been used to treat ulcers in the GIT, including gastric ulcers (26), peptic ulcers (27), duodenal ulcers (28) and perhaps most notably, oral mucositis (29-31). Mucositis is one of the most common side effects of radio- and chemotherapy in cancer patients, as portrayed in Figure 3.

Mucositis ulcers are larger and more painful than aphthous stomatitis and pose serious health risks to patients. Abdel et al. (29) review the popular treatments for mucositis. They highlight clinical trials and the outcomes that each agent had on patient mucositis. While some current treatments are effective, there are concerns with inconsistent results and research methods, insufficient data, and undesirable side effects. Antioxidants are a candidate for treatment of mucositis but are not yet recommended due to few clinical trials with inconsistent results. Abdel et al. (29) propose melatonin as a novel treatment over other antioxidants, since it is much more effective in preventing tissue damage caused by oxidative stress, it stimulates the activity of free radical-scavenging enzymes, and it can cross cell membranes to regulate the mitochondria of target cells (32). Although radio- and chemotherapy are not common causes of aphthous stomatitis, oxidative stress and inflammation are common factors between both conditions. As observed by Abdel et al. and others, melatonin's action could prove effective in protecting against and healing ulcers in the GIT, including in the oral cavity.

Melatonin Safety

Melatonin shows a promising safety profile and is generally recognized as safe (GRAS) for short term use. The National Drug Monograph of melatonin reports no death or serious adverse reactions to melatonin use but advises special populations to avoid its use (15). These include pregnant and lactating women, children and adolescents with seizures, and patients with depression. More research is needed to determine evidence of dependency and tolerance. Melatonin may interfere with medications and other drugs (e.g. sleep-aids, hypertension medications, anti-depressants, diabetes medications, and

immunosuppressants), so patients should consult a physician prior to taking melatonin (15).

The most common short-term side effects of melatonin include mild and include dizziness, nausea, headaches, drowsiness, and vivid dreams. Andersen et al. (33) report no short or long-term detrimental side effects in their review, even in extreme doses. A double-blind clinical trial performed by Seabra et al. (34) reports no toxicological effect in patients administered 10 mg of melatonin over a 28-day period, compared to a placebo group. Researchers recommend further investigation of the long-term effects of melatonin and improved recommendations for special populations.

Melatonin is currently sold in the United States as a dietary supplement but is prescription-only in Europe. Dietary supplements are regulated by the FDA, but to a much lesser extent than compounds classified as drugs. Melatonin does not have an FDA indication for treatment of any disease, and it does not include boxed warning. The safety of melatonin is rarely the outcome of primary articles; it is more often evaluated in literature reviews and meta-analyses. Melatonin's safety profile could lead to its more widespread use in the medical community.

Proposed Clinical Study for Melatonin Treatment of Oral Ulcers

We propose that the investigation of melatonin's effects on oral ulcers, such as aphthous stomatitis, begin with two clinical trials. The first, to determine whether melatonin demonstrates healing effects on oral ulcers, and the second, to determine the lowest effective dosage of melatonin. These two clinical trials evaluate melatonin's efficacy as a treatment for oral ulcers and contribute to the literature on melatonin safety

by reporting any adverse side effects. The results from this study may lead to an overdue indication for melatonin as a safe and effective treatment for oral ulcers.

To obtain significant data, we propose that these two studies be randomized and double-blind, with a sample size of at least 70 participants. Participants must have one or more oral ulcers. It is recommended that pregnant women and children do not take melatonin, so exclusions must be made. Due to insufficient data on melatonin's drug-drug interactions, people taking other medications must also be excluded from the study. People working night shifts must also be excluded due to melatonin's possible drowsy effects. Our exclusion criteria are more fully explained in our first intake sheet (see Appendix A) and consent form (see Appendix B). Qualifying participants for our initial study will receive a random ID number to protect their privacy. We will randomly assign participants to a treatment of either a 5 mg melatonin dissolve tablet or a placebo dissolve tablet, to be applied to the affected area(s) before retiring to bed. Participants will take photos of their ulcer(s) each night and in the morning for the duration of their participation in the study. We will collect and analyze data on ulcer size over time, pain over time, color of ulcer, and any side effects experienced via a daily research journal (see Appendix C). Our methods for measuring ulcer size and daily data collection are explained in greater detail in our Institutional Review Board Application, which we were not able to include in the appendix.

If melatonin demonstrates protective and healing action for oral ulcers, we will conduct a second clinical trial to deduce its lowest effective dosage. We will randomly assign another 70 participants each a random ID number to protect their privacy. This study will test four concentrations (5 mg, 2.5 mg, 1 mg, and 0.5 mg) of melatonin in an

oral dissolve tablet compared to a placebo group receiving no melatonin treatment. We will randomly assign participants to one of the test groups or the placebo group. The same participant exclusion criteria, data collected, and data collection methods described in the first study will be used in the second study. We expect to determine the lowest effective dosage of melatonin by comparing the data across each test group to the placebo group and to each other.

The data collected from these two double-blind studies will be converted into numerical figures for statistical analysis. The test group and placebo group data will be sorted with an identifying legend. A numerical score will be assigned to each participant's ulcer(s) based on the measurement criteria and data collection methods. Data will be analyzed for each parameter (i.e. reported pain, coloration, size) over time and a statistician will be consulted for final statistical analysis using a p-value of 0.05 for significance.

Conclusion

Melatonin's unique behavior in the human body has many applications to be investigated. Its anti-inflammatory and antioxidant actions have been the focus of recent publications, and its promising safety profile may open the door for widespread use. These protective effects have led melatonin to be considered as a treatment for many conditions, including COVID-19 (Zhang, 2020). Studies reveal that melatonin has no harmful side effects, but more research is needed to understand its long-term effects. Melatonin has been used to treat other gastrointestinal ulcers and has known wound healing effects, but this has not been taken advantage of in oral healthcare. Aphthous stomatitis is one ulcerative condition affecting the gastrointestinal tract that could benefit

from melatonin's therapeutic properties. Melatonin is a viable option to be considered for treating aphthous stomatitis and should be further studied using well-designed clinical trials.

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APPENDIX

Appendix A: This is the first intake sheet for interested participants in the proposed clinical trials. Special populations must be excluded from this study, which this questionnaire addresses.

Appendix B: This is the consent form for interested subjects to participate in the proposed clinical trials. It contains an overview of research procedures, risks and discomforts, benefits, confidentiality, compensation, and a statement of consent.

Appendix C: This is a sample of the daily journal participants agree to complete during their participation in the study. Here the participants record the pain, sensitivity, color, and appearance of their ulcer each night and morning. Participants record the time of day they take each photo and whether they apply their treatment. The daily journal allows for data to be collected for either one or two ulcers.

APPENDIX A

Canker Sore Treatment

Today's date and time: _____ Participant ID #: _____

Name: _____ Male: ☐ Female: ☐

Birth date: _____ Age: _____

Phone number: _____ Email: _____

1. Do you have canker sore like symptoms currently? Y N
2. Do you regularly have canker sores? Y N
3. Do you have any allergies? (Please specify below) Y N
4. Do you have the means to take pictures of your ulcer? Y N
5. Are you currently taking any of the following medications: tranquilizers, sedatives, antidepressants, or sleep-aids? Y N
6. Are you pregnant or attempting to get pregnant? Y N
7. Do you have an autoimmune disorder? Y N
8. Do you work a night shift? Y N
9. Are you required to drive a vehicle at night? Y N
10. Which method do you prefer for daily reminders? (Circle one): Text Email None
11. If you have allergies, please specify:

_____

12. Please list any medication you are currently taking (including prescription and non prescription):

_____

13. Have you received your treatment plan and measuring tool? Y N

APPENDIX B

Consent to be a Research Subject

Introduction

This research study is being conducted by Sandra Hope, Ph.D. at Brigham Young University to determine the effects of an experimental treatment for canker sores. You were invited to participate because you have at least one canker sore. Your participation in this study should last about 14 days from the onset of your sore(s), depending on how long the symptoms last. Be aware that we will study only one treatment for one *or* two sores, for each round of participation. Following your first round of participation, you may sign up again for another round of the study, at which time you will be required to sign new consent forms and be randomly assigned a new treatment.

You will apply the treatment to a canker sore in the evening prior to going to sleep at night. The ingredient being tested for activity against canker sores is a common ingredient in over-the-counter (non-prescription) sleep aids. For this reason, you cannot participate in the study if you are taking any prescription or non-prescription tranquilizers, sedatives, or sleep aids. If you are pregnant, trying to get pregnant, or are under age 18, participation in this study is not permitted. You cannot participate in the study if you work a night shift or have an expectation to drive during night hours, due to the sleep affects of the active ingredient.

Procedures

If you agree to participate in this research study, the following will occur:

- You will be given a non-identifying research participation ID, to protect your privacy and the integrity of the study.
- You will be randomly assigned a treatment method to be applied to the ulcerated area(s) each evening prior to sleeping at night, as long as symptoms last.
- You will be given a periodontal probe to measure the growth of your canker sore. We will provide you with removable labels to attach to the probe that will serve as a timestamp. They will indicate the day of treatment, and whether it is morning or night. One of the labels will include your treatment ID to protect your identity.
- You will take a picture of the canker sore(s) and an additional picture with the periodontal probe held next to the ulcer so that we may measure its growth.
- You may choose to receive an email or text every morning as a reminder to fill out the handwritten morning report, which includes uploading pictures and a pain assessment.
- Total time commitment will depend on the duration of your canker sore, and your desire to participate in additional treatments.

Risks/Discomforts

- Participants acknowledge that canker sores may be uncomfortable and painful whether they participate in this study or not.

- Participants may experience pain due to sensitivity when using the periodontal probe to measure the size of the ulcer.
- Due to high sensitivity of canker sores, participants may experience pain/discomfort when applying treatment to the ulcer.
- Participation in this research study is voluntary. You have the right to withdraw at any time or refuse to participate entirely without jeopardy to anything.
- If an infection or allergic reaction does occur, contact the BYU Health Center at 801-422-5156. Prevention of pain or embarrassment is available by the subject deciding to forego participation in this study.

Benefits

There are no benefits for participating in this study, other than potentially having your canker sore treated.

Confidentiality

Results will be anonymous in order to protect your medical privacy. You will receive an identifying number in order to preserve privacy. All photos you submit must be labeled with your identifying number, the date, and time of day. All photos must not reveal your face above the cheekbone.

We intend to publish the results of these studies, and the key that indicates the identity of each participant will not be stored with the digital records of data. The paper data with participant information will be kept in a locked cabinet and stored for 5 years and then destroyed. The goal is for the investigator to monitor the effects of the canker sore treatment over time.

Compensation

No compensation will be offered for participating in this study.

Participation

Participation in this research study is voluntary. You have the right to withdraw at any time or refuse to participate entirely without jeopardy to anything.

Questions about the Research

If you have questions regarding this study, you may contact Sandra Hope, Ph.D. at 801-422-1310, sandrahope2016@gmail.com or Will Sutherland at 530-722-8430, wsuth3rland@gmail.com for further information.

Questions about Your Rights as Research Participants

If you have questions regarding your rights as a research participant contact IRB Administrator at (801) 422-1461; A-285 ASB, Brigham Young University, Provo, UT 84602; irb@byu.edu.

Statement of Consent

I have read, understood, and received a copy of the above consent and desire of my own free will to participate in this study.

Name (Printed): _____ Date: _____

Signature: _____

Photographic Release Form

As part of this project, I will be taking photographs of you (or your child) during your participation in the research. Please indicate what uses of these photographs you are willing to permit, by initialing next to the uses you agree to and signing at the end. This choice is completely up to you. I will only use the photographs in the ways that you agree to. In any use of the photographs, you (or your child) will not be identified by name.

___ Photographs can be reviewed by the research team.

___ Photographs can be used for project illustrations.

___ Photographs can be used for classroom presentations.

___ Photographs can be used for academic conference presentations.

___ Photographs can be used for fundraising presentations/proposals.

___ Photographs can be used for newspaper, magazine, or journal publication.

___ Photographs can be posted to a website.

I have read the above descriptions and give my express written consent for the use of the photographs as indicated by my initials above.

Name (Printed): _____ Signature: _____ Date: _____

APPENDIX C

Study Journal **Participation ID #**_____

Evening Data Date:_____

Sore 1: Rate the pain/sensitivity of the canker sore you will treat (circle one):

1	2	3	4	5
No pain		Moderate		Severe

What color is it (you may check up to two)? ☐ Pink ☐ White ☐ Red ☐ Other_____

How does the surface appear (choose only one)? ☐ Flat ☐ Erupted

Optional Sore 2: Rate the pain/sensitivity of the canker sore you will treat (circle one):

1	2	3	4	5
No pain		Moderate		Severe

What color is it (you may check up to two)? ☐ Pink ☐ White ☐ Red ☐ Other_____

How does the surface appear (choose only one)? ☐ Flat ☐ Erupted

What time were pictures taken? _____ pm

Sore 1: Treatment applied? ☐ Yes ☐ No **Optional Sore 2:** Treatment applied? ☐ Yes ☐ No

---

Morning Data Date:_____

Sore 1: Rate the pain/sensitivity of the canker sore you treated (circle one):

1	2	3	4	5
No pain		Moderate		Severe

What color is it (you may check up to two)? ☐ Pink ☐ White ☐ Red ☐ Other_____

How does the surface appear (choose only one)? ☐ Flat ☐ Erupted

Optional Sore 2: Rate the pain/sensitivity of the canker sore you treated (circle one):

1	2	3	4	5
No pain		Moderate		Severe

What color is it (you may check up to two)? ☐ Pink ☐ White ☐ Red ☐ Other_____

How does the surface appear (choose only one)? ☐ Flat ☐ Erupted

What time were pictures were taken? _____ am

Sore 1: Treatment applied? ☐ Yes ☐ No **Optional Sore 2:** Treatment applied? ☐ Yes ☐ No