Photocopy and Use Authorization

In presenting this thesis in partial fulfillment of the requirements for an advanced degree at Idaho State University, I agree that the library shall make it freely available for inspection. I further state that permission for extensive copying of my thesis for scholarly purposes may be granted by the Dean of the Graduate School, Dean of my academic division, or by the University Librarian. It is understood that any copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Signature _____

Date _____

Herpes Simplex Virus-1: A Pilot Study Using Hand Sanitizer

by

Amanda Gibbs

A thesis

submitted in partial fulfillment

of the requirements for the degree of

Master of Science in Department of Dental

Hygiene Idaho State University

Fall 2023

Committee Approval

To the Graduate Faculty:

The members of the committee appointed to examine the thesis of AMANDA GIBBS find it satisfactory and recommend that it be accepted.

Leciel Bono, RDH-ER, MS, FADHA
Major Advisor

JoAnn Gurenlian, RDH, MS, PhD, AAFAAOM, FADHA
Committee Member

Chris Sanford, PhD, CCC-A
Graduate Faculty Representative

Idaho State University

April 8, 2022

Mandy Gibbs
Dental Hygiene
MS 8048

RE: Study Number IRB-FY2022-172 : Herpes Simplex Virus-1: Shortening Duration Using Purell Sanitizer. A Pilot Study

Dear Ms. Gibbs:

Thank you for your responses to a previous review of the study listed above. These responses are eligible for expedited review under OHRP (DHHS) and FDA guidelines. This is to confirm that I have approved your application.

Notify the HSC of any adverse events. Serious, unexpected adverse events must be reported in writing within 10 business days.

You may conduct your study as described in your application effective immediately. This study is not subject to renewal under current OHRP (DHHS) guidelines.

Please note that any changes to the study as approved must be promptly reported and approved. Some changes may be approved by expedited review; others require full board review. Contact Tom Bailey (208-282-2179; email humsubj@isu.edu) if you have any questions or require further information.

Sincerely,

Ralph Baergen, PhD, MPH, CIP
Human Subjects Chair

Office for Reseach - Research Outreach & Compliance
921 South 8th Ave., Stop 8386 | Pocatello, ID 83209-8286 | (208) 282-1336 | isu.edu/research

Acknowledgement

There are many people who have helped me in this thesis journey. Firstly, I am truly grateful for Leciel Bono who was always willing to help, and never made me feel bad about the number of after-hour calls and texts. JoAnn Gurenlian has an amazing way with words and is very good at saying what I mean and sounding professional when I fail to find a way. What laughter and tears I have shed on this journey, but I knew I was in good hands when they didn't give up on me. Thank you for the encouragement and guidance you both gave me.

Secondly, my research assistants played huge role in making this study happen, I could not have done it without Kaitlyn Leibert, Camille Biorn, and Peggy Lelesi. They volunteered many hours by first sitting through the training session, continually reaching out to people looking for volunteers, and then making sure each volunteer completed the study. I consider you three my very dear friends and will be forever grateful for your help in this journey.

Thirdly, I am forever grateful for my rock who is my husband, Jimmy Gibbs. So many people ask me how I am working, with kids and a farm, and getting my master's degree. I always tell them-it is because of him. When I told him I was going to do this journey, his response was, "If anyone can do it, it is you." Thank you for keeping the house running and always believing in me, I love you. We did it!

Table of Contents

Herpes Simplex Virus-1: A Pilot Study Using Hand Sanitizer

Thesis Abstract – Idaho State University 2023

The purpose of this pilot study was to determine if the use of a 70% ethanol alcohol hand sanitizer alters the duration, size of the lesion, level of pain upon administering treatment, and overall daily discomfort during outbreak. This study was a double-blind randomized controlled trial (RCT) using 70% ethanol alcohol hand sanitizer for the experiment and medical grade mineral oil for the control group. The experiment and the control were dispensed in lip gloss containers for application. Descriptive statistics and the independent sample *t*-test were used to analyze data (p=0.05). A total of 20 individuals completed the research study: 10 in the experimental group and 10 in the control group. There was no statistically significant difference between the experimental and control groups in terms of duration, size of lesions, pain, and discomfort; therefore, the null hypothesis was not rejected.

Keywords: Herpes simplex virus, HSV-1, duration, size, level of pain, and discomfort

Chapter 1

Introduction and Background

Herpes Simplex Virus-1 (HSV-1), more commonly known as a cold sore or a fever blister, is a highly contagious virus. An estimated 40-80% of adults and children in the United States have had at least one HSV-1 infection (Mahoney, 2014). Many different components can contribute to HSV-1 such as injury or trauma to the lip, sunlight, and stress (Mahoney, 2014). HSV-1 can be spread by touching the infected area and self-inoculating or by spreading the virus to others through direct contact (Mahoney, 2014). This highly contagious virus manifests as an orofacial lesion that begins as an erythematous base of papules, progresses to vesicles within hours of initial appearance (this is considered the most contagious stage), and then ends in ulcerated crusts (Richardson et al., 2013).

HSV-1 has been difficult to treat. Currently there is no cure available, and the virus is building resistance to antiviral medications (Bergmann et al., 2017). Treatments for HSV-1 lesions may be administered through oral medication, topical cream or gel, a patch that adheres to the lesion, photodynamic therapy, amino acid, local anesthetic, or laser therapy (Boes et al., 2020; Singh et al., 2005; Sivla-Alvarez et al., 2021; Ramalho et al., 2021). Some treatments are over-the-counter while others need a prescription or are an in-office therapy. Early treatment is crucial regardless of the medicine of choice (Whitley, 2006b; Hull, 2009; Spruance, 1990).

There are several variables to consider when determining the best treatment route for HSV-1 lesions such as whether the lesion is primary or recurrent, what the patient's preference is, or whether the patient is immunodeficient (Cernik et al., 2008). The most common treatment for a primary HSV-1 lesion is oral antiviral medications (Cernik et al., 2008). Recurrent HSV-1

lesions are most commonly treated with topical antivirals in conjunction with oral antivirals (Hull et al., 2009; Spruance & McKeough, 2000).

Taylor et al. (2002) explained that after the virus has entered the host, multiple stages then occur during the HSV-1 infection process, and the final stage establishes a latent infection in the host often lasting a lifetime. Unlike many viral infections that constantly replicate, no viral progeny (or very little) is produced during latency for HSV-1. Only limited gene transcriptions are detected during the latency phase (Taylor et al., 2002). The latency site is located in the sensory neurons in ganglion tissue and recurrence of the virus is found in one third of the population (Taylor et al., 2002; Quinn et al., 2000; Young et al., 1988). The HSV-1 recurrent infection is usually mild, but the illness can be uncomfortable and disfiguring, leaving a psychological impact that should not be underestimated especially among young patients with multiple recurrences (Hobbs et al., 2008).

Statement of the Problem

Finding an agent to disrupt or kill the HSV-1 virus has been difficult. One possible option is 70% ethanol alcohol hand sanitizer which has become a popular disinfectant known for its powerful virucidal and bactericidal effects (Rutala & Weber, 2008). Ethanol alcohol is the main ingredient in hand sanitizer and in concentrations of 60%-80%, is known to kill the HSV-1 virus (Rutala & Weber, 2008). More research is needed to determine the efficacy of the use of 70% ethanol alcohol hand sanitizer as an HSV-1 treatment option.

Purpose of the Study

The purpose of this pilot study was to determine if the use of 70% ethanol alcohol hand sanitizer alters the duration, level of pain and discomfort during treatment, and the size of the HSV-1 lesion.

Professional Significance of Study

This study provided valuable information for those individuals suffering from HSV-1 lesions. Ethanol alcohol at 70% used as an HSV-1 treatment may create an accessible, inexpensive, and effective therapy. Shortening the outbreak duration will help relieve individuals from the pain, discomfort, unsightly sores, and reduce the risk of transmission to themselves and others. This study was valuable not only to those who suffer from HSV-1 lesions but also for oral health professionals by providing an accessible, effective, and affordable treatment option for their patients. The results of this study might be utilized to encourage more research on 70% ethanol alcohol as a topical treatment for HSV-1 lesions.

This study supported the American Dental Hygienists' Association (ADHA, 2016) National Dental Hygiene Research Agenda (NDHRA) objective which states: "To give visibility to research activities that enhance the profession's ability to promote the health and well-being of the public" (p. 43). This study pertained to the NDHRA oral health care level, specifically new therapies and prevention modalities for oral health care focusing on new treatments as part of a discovery phase of research.

This study also supported The American Academy of Oral Medicine's (AAOM, 2016) risk factor assessment for oral diseases. The AAOM recommends all patients receive an oral disease assessment from their oral health care providers as part of their dental treatment. The AAOM also recommends oral health care providers be educated and trained on infectious diseases, learn ways to reduce the risk of disease transmission, and learn ways to control disease within a dental setting (AAOM, 2016).

Research Questions

The following research questions guided the conduct of this study:

1. Is there a statistically significant difference in the duration of the HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?
2. Is there a statistically significant difference in the level of pain during the treatment application process of an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?
3. Is there a statistically significant difference in the level of discomfort during an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?
4. Is there a statistically significant difference in the size of the HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?

Hypotheses

The following hypotheses guided the conduct of this study:

1. There is no statistically significant difference in the duration of the HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.
2. There is no statistically significant difference in the level of pain during the treatment application process of an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.

3. There is no statistically significant difference in discomfort during an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.
4. There is no statistically significant difference in the size of an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.

Definitions

Discomfort. Slight pain (Oxford Languages, n.d.). For the purpose of this study, discomfort was measured using the visual analog scale (VAS). The VAS scale used a 100 mm long line between "no discomfort" and "extreme discomfort". Participants placed a single mark on the line that fits their pain level. This measurement displayed the discomfort the lesion caused on a daily basis.

Duration. The time during which something exists or lasts (Merriam-Webster, n.d.).

Duration of an HSV-1 lesion. For most immunocompetent individuals, an HSV-1 lesion is an annoying ailment that heals in 10 days (Opstelten et al., 2008). Through clinical examination, duration was determined when spontaneous sloughing of the crust occurs or lesion is healed if no is crusting present.

Hand sanitizer. A liquid or gel, typically one containing alcohol, that is used to clean hands and kill infection-causing microorganisms (Oxford Languages, n.d.).

HSV-1 lesion. Herpes simplex virus-1 (HSV-1) is a common human pathogen, causing infections of orofacial mucosal surfaces (Taylor et al., 2002).

Pain. The physical feeling caused by disease, injury, or something that hurts the body (Merriam-Webster, n.d.). For the purpose of this study pain was measured using the visual

analog scale (VAS). The VAS scale used a 100 mm long line between “no pain” and “worst pain ever felt”. Participants placed a single mark on the line that fits their pain level. This measurement displayed any pain associated during the application process of the treatment.

Summary of Chapter 1

HSV-1 is a worldwide infection and is affecting 40-80% of people in the United States (Boes et al., 2020; Mahoney, 2014). HSV-1 is a very contagious virus and is most transmissible during the vesicle stage (Richardson et al., 2013). HSV-1 is difficult to treat, and with no cure available the virus is building resistance to antiviral medications (Bergmann et al., 2017). Finding a treatment that decreases the duration of the HSV-1 lesion would assist in minimizing the disease transmission stage and decrease the discomfort and embarrassment brought on by the lesion (Ramalho et al., 2021).

Chapter 2 Review of the Literature

Introduction

The purpose of this study was to gather information to determine if the use of 70% ethanol alcohol hand sanitizer alters the duration, level of pain and discomfort during treatment, and the size of the HSV-1 lesion. This literature review was divided into three main sections. The first section presented an overview of the HSV-1 including the risks of systemic infection that can affect the quality of life of individuals. The second section included an in-depth summary of multiple treatment options currently available and distinguished the different effects each treatment options have on the HSV-1 lesion. The final section of this literature review explored 70% ethanol alcohol (the active ingredient in hand sanitizer) as a virucidal agent and determined if it could be used as an HSV-1 treatment option. Databases used for this literature review included PubMed, Google Scholar, and Cochrane Library. MeSH terms used for this search included: herpes labialis, varicella zoster, herpes zoster, herpetic gingivostomatitis, herpes simplex virus, herpes simplex labialis, simplex virus, ethanol alcohol, ethyl alcohol, sanitizer, and virucidal.

Herpes Simplex Virus-1

Quality of life and overall systemic health can be influenced by conditions of the oral cavity **(**Baiju, 2017). Many viral infections manifest in the mouth making it pertinent for oral health professionals to be current with common conditions and oral manifestations of the oral cavity (Santosh & Muddana, 2020). Herpes Simplex Virus-1 (HSV-1), more commonly known as a “cold sore” or a “fever blister,” is the most common recurring viral infection in humans (Richardson et al., 2013). This highly contagious virus manifests as an orofacial lesion that first begins on an erythematous base as papules, progresses to vesicles (within hours of initial

appearance), and forms an ulcerated crust which will spontaneously slough off (Richardson et al., 2013). An estimated 40-80% of adults and children in the United States have had at least one HSV-1 infection and the HSV-1 is found to be most contagious during the vesicle stage (Mahoney, 2014). These infections can be painful, unsightly, and lesions can last over two weeks before the virus reverts to a latent stage where it remains until the next recurrence (Mahoney, 2014).

Santosh and Muddana's (2020) article explained HSV-1 often occurs at an early age of 2-3 years and exhibits painful mucosal lesions. The first initial exposure to HSV-1 can result in an array of symptoms characterized by fever, chills, nausea, malaise, loss of appetite, vomiting, dysphagia, lymphadenopathy, oral and extraoral lesions or perioral vesicles, irritability, and generalized marginal gingivitis (Bardellini, et al., 2021; Fatahzadeh & Schwartz, 2007). The initial outbreak is called Primary Herpetic Gingivostomatitis (PHGS; Bardellini, et al., 2021; Fatahzadeh & Schwartz, 2007). Unlike the vesicles and ulcers from recurrent HSV-1 lesions, PHGS ulcers affect the buccal mucosa, hard and soft palate, tongue, lips, and can cause gingival bleeding (Arduino & Porter, 2008). Finding a treatment that will minimize the highly contagious stage would help reduce the spread of the virus.

Many different components can trigger a recurrent HSV-1 outbreak such as injury or trauma to the lip, sunlight, fatigue, immunosuppressive state, fever, pregnancy, malignancy, respiratory illness, menstruation, systemic illness, age, and physical or emotional stress (Mahoney, 2014; Stoopler & Greenberg, 2003). HSV-1 can be reactivated in the trigeminal nerve ganglion when these triggers occur (Stooper & Greenberg, 2003). HSV-1 can then be spread by touching the infected area and autoinoculation, sharing kitchen utensils, or direct contact. After

the viral spread there is an incubation period of 3-9 days (Fatahzadeh & Schwartz, 2007; Mahoney, 2014; Stoopler & Greenberg, 2003).

Systemic Effects on the Body

Although the systemic effects of HSV-1 are rare, high mortality rates are found with each infection. Considering the dangerous systemic effects from HSV-1 along with the more common HSV-1 lesions (leading to pain and psychological stress) confirms the importance of finding an effective treatment. Szczubiałka and Nowakowska (2016) reported that during the latent state of an HSV-1 lesion, not only is the host vulnerable to recurrence of the disease, but the presence of the virus interferes in the host's cell life cycle and can affect the general health of the host. The viral genome plants itself in the nucleus of sensory neurons of the trigeminal ganglia (TG) and is able to avoid the host's immune system (Szczubiałka & Nowakowska, 2016). With these neurotropic and neuroinvasive properties life-threatening diseases can occur (Szczubiałka & Nowakowska, 2016). HSV-1 is associated with epithelial and stromal keratitis, encephalitis, eczema herpeticum, herpetic whitlow, and has detrimental effects on immunocompromised individuals (Farooq & Shukla, 2012; Greenberg,1996; Sarid et al. 2002; Szczubiałka & Nowakowska, 2016).

Epithelial and stromal keratitis can lead to stromal opacification and HSV keratitis (Farooq & Shukla, 2012). With approximately 1.5 million new HSV keratitis cases each year, HSV is considered to be the leading cause of infectious blindness in more developed countries (Farooq & Shukla, 2012). Both primary and recurrent HSV-1 episodes can cause ocular infection through direct contact meaning the virus can enter the mucous membranes of the host (Akhtar et al., 2008). The beginning of HSV keratitis is a superficial punctate lesion that progresses to a stellate erosion and finally a dendritic ulcer (Farooq & Shukla, 2012). Non-necrotizing stromal

keratitis and necrotizing stromal keratitis can lead to corneal neovascularization and scarring resulting in blindness (Mott et al., 2009).

Another systemic condition HSV-1 can lead to is acute necrotizing encephalitis. Often without any clinical symptoms HSV-1 can reach the brain (Duarte et al., 2019). As soon as the virus is in the central nervous system (CNS), the virus can stay latent or lead to severe acute necrotizing encephalitis (Duarte et al., 2019). Symptoms following acute necrotizing encephalitis include neuroinflammation and prolonged neuroimmune activation; both are considered a life-threatening disease (Duarte et al., 2019). One of the most common forms of viral encephalitis is HSV-1 encephalitis (Tyler, 2004a). Growing evidence has shown that both symptomatic and asymptomatic cases of HSV-1 brain infection can eventually lead to neuronal damage and neurodegenerative disorders (Duarte et al., 2019). This idea is supported by the reported presence of HSV-1 DNA in 65%-75% of seropositive individuals even without clinical signs of neurological illnesses or active infection (Mori, 2010). HSV encephalitis (HSE) is a rare disease with only 1:250,000-500,000 individuals worldwide; however, HSE is the main cause of fatal encephalitis in the Western world (Gnann & Whitley, 2017). In adults 90% of HSE cases are caused by HSV-1 (Gnann & Whitley, 2017; Whitley, 2006a). Although early diagnosis and treatment are highly effective in reducing morbidity and mortality the affected individual is often left with permanent neurologic complications (Ziyaeyan, 2011). Without treatment HSE mortality rates can reach 70% (Tyler, 2004b)

A study by George et al. (2014) identified 238,567 patients with encephalitis cases during the years 2000-2010. HSV was found to be the most frequently identified pathogen with half of the occurrences in individuals older than 50 years of age. While about 30% of cases were primary HSV infection, 70% of cases were HSV reactivation (George et al., 2014). Hemorrhages

occur in the infected area as the disease progresses and necrosis may cavitate. Symptoms in the prodromal stages of HSV-1 included behavior changes, olfactory hallucinations, and headaches (Gnann & Whitley, 2017).

HSV-1 can infect the skin causing eczema herpeticum (EH), especially if atopic dermatitis is present (Wollenberg et al., 2003a, 2003b). EH is a secondary viral infection and if left untreated can cause death (Liaw et al., 2012). EH can progress to disseminating infection with cutaneous vesicular eruptions leaving "punched-out" erosions with hemorrhagic crusts over eczematous areas (Liaw et al., 2012; Xiao & Tsuchiya, 2021). Systemic symptoms include malaise, lymphadenopathy, and fever (Seegräber et al. 2020). Atopic dermatitis affects 10-18% of the population, however EH presents in less than 3% of atopic dermatitis cases, most often presenting in infants and children (Leung, 2013).

Primary and secondary recurrent infections are common in the oral cavity and herpetic secondary infections can develop on the fingers as a result from salivary contamination called herpetic whitlow (Greenberg,1996; Sarid et al., 2002). Herpetic whitlow is a painful infection that implants under the nail beds of the fingers causing numbness, scarring, and missed workdays (Myers & Curran, 2014, p. 103). Herpetic whitlow is an iatrogenic disease and before universal infection control precautions, such as gloves, herpetic whitlow was an occupational hazard for dental professionals (Myers & Curran, 2014, p.103). Due to the common thumb sucking habit among children, most herpetic whitlow cases are found in children due to autoinoculation (Lee et al., 2020). Nail trauma plus the exposure to saliva on an individual with previous HSV infection can lead to herpetic whitlow (Shafritz & Coppage, 2014).

Immunocompromised individuals and babies can also be in life-threatening situations due to HSV-1 infections (Szczubiałka & Nowakowska, 2016). Individuals who are

immunocompromised can experience a crop of unilateral vesicles with tiny ulcers on the palatal mucosa and/or attached gingiva (Fatahzadeh & Schwartz, 2007). These ulcers are often mistaken for aphthous stomatitis and are painful (Fatahzadeh & Schwartz, 2007). Immunocompromised individuals are at risk for frequent, chronic, and severe HSV-1 infections (Fatahzadeh & Schwartz, 2007). Szczubiałka and Nowakowska (2016) stated that with the viral strands building resistance to treatments, there needs to be a novel approach to developing anti-herpes agents.

HSV-1 Infection Process

The HSV-1 is considered a large virus (150- 200nm diameter), belongs to the Herpesviridae family, and is an enveloped double-stranded DNA virus (Duarte et al., 2019; Szczubiałka et al., 2016; Taylor et al., 2002). Taylor et al. (2002) described cellular breakdown of the HSV-1 in a research investigation and explained how multiple stages occur during the HSV-1 infection process. The stages begin with viral entry, viral gene expression, viral DNA synthesis, and reproduction of infected host cells or assembly of progeny virion. Entry involves interaction between viral envelope proteins and the heparan sulfate moieties from the cell of the host leading to attachment. Attachment is then stabilized by further interaction with the glycoprotein gD and cellular receptors followed by fusion to the cellular membrane. Once fused, the HSV-1 needs to replicate by using the host cell to express viral proteins enabling the virus to spread. Herpes viruses regulate gene expression in three temporal classes: immediate early, early, and late genes. After infection immediate early genes are transcribed and activate the early genes. The early gene replicates the viral DNA which stimulates the expression of the late genes. The late genes are responsible for encoding the structural proteins. With the viral DNA entering the nucleus, viral gene transcription begins. HSV-1 establishes a latent infection in the host often lasting a lifetime. Many viral infections constantly replicate, however during HSV-1's latent

stage, no viral progeny (or very little) is produced (Taylor et al., 2002). The latency site is located in the sensory neurons in ganglion tissue (Taylor et al., 2002; Quinn et al., 2000).

Although HSV-1 is found to be most contagious in the vesicle stage, further research has found asymptomatic shedding (HSV present without the presence of a lesion) leading to increased transmission period (Ramchandani et al., 2016; Richardson et al., 2013). In a study by Ramchandani et al. (2016) held at University of Washington Virology Research Clinic in Seattle, eight immunocompetent participants with a history of symptomatic HSV-1 lesions underwent examinations five times a week for a total of five weeks. During this examination, samples were taken from 12 different orofacial sites (left nares, right nares, pharynx, tongue, left palate, right palate, left upper lip, right upper lip, left lower lip and right lower lip). Samples were placed in tubes for laboratory processing. Participants were also instructed to take samples of the buccal and gingival surfaces at home in the morning before showering or brushing teeth every day for five weeks. The swabs taken from home were then returned to the clinic on the next visit. Viral shedding is determined if HSV DNA is detected from orofacial sites. With a total of 2,626 swabs collected (about 334 swabs per person), asymptomatic shedding was found on 27.1% of the days. Symptomatic shedding (HSV-1 lesion present) was found on four of eleven days or 36.4% (Ramchandani et al., 2016). With transmission rate at its highest when the HSV-1 lesion is present, it is important to find a treatment that will decrease the duration of the outbreak.

Herpes Simplex Virus-1 Treatment Options

Options for treating HSV-1 lesions include a patch that adheres to the lesion, topical cream or gel, local anesthetic, photodynamic therapy, laser therapy, or oral medication. These treatment options are accessible by prescriptions, in-office procedures, or over the counter. With such a variety of treatment options for HSV-1, it is important to consider the duration of the

outbreak, pain or comfort level, compliance of the patients, and the convenience of the medication.

Zovirax Cream, Compeed Invisible Cold Sore Patch, and Herpatch Serum

A recent prospective, controlled, randomized assessor-blind trial study by Boes et al. (2020) compared three products in the treatment of HSV-1 lesions on 180 participants. The three products compared were Zovirax Cream (5% acyclovir as an active ingredient), Compeed Invisible Cold Sore Patch (containing no antiviral ingredient), and the Herpatch Serum (containing no antiviral ingredient). All participants were between the ages of 18-65 years and reported a history of recurrent HSV-1 lesions. Participants were excluded if they presented with painful illnesses of dentition or gingiva, were pregnant or breastfeeding, were noncompliant, currently have a severe illness, or had taken any antibiotics or anti-inflammatory drugs within two weeks prior to participating in the study. Participants were required to visit the University of Witten/Herdecke's Dental Clinic within the first 24-hours of the HSV-1 outbreak between the dates of April 2013-June 2016. The lesion had to appear as a precursor lesion, macule, papule, vesicle, or ulcer (Boes et al., 2020).

Researchers in this study collected general information of each participant, measured the lesion, classified the stage of the HSV-1 lesion, and documented the lesion with a photograph (Boes et al., 2020). The product was then dispensed to each participant in a nontransparent envelope to ensure the assessor was properly blinded. The observation period lasted a total of 10 days with participants returning for follow-up examination on days 2, 4, 6, 8, and 10. The stage of the lesion was documented by a researcher on examination days using the Clinician's Global Assessment of Therapy (CGAT), and on the final day a last photograph was taken. The CGAT assessment tool measured the reaction rate and the reaction quality of the product. Patients were

asked to complete a questionnaire on each examination day assessing the severity of symptoms, protection of the lesion, aesthetics, relief of discomfort, and intolerance. Treatment was completed when the lesion was healed or after 10 days, whichever came first. On the tenth day the participant also gauged the reaction rate and reaction quality by using the Subject's Global Assessment of Therapy (SGAT). Lastly, participants also rated the comfort, handling, functionality, and overall satisfaction of the product (Boes et al., 2020).

The primary endpoint of Boes et al. (2020) compared the difference in healing time for the three products. The secondary endpoint examined the reaction rate and reaction quality by the clinician and the subject through the use of SGAT and CGAT measurements with a grading scale from 0 to 10 (0=no response; 10=excellent response). The tertiary endpoint was the patient's questionnaire that used a grading scale of 0 to 10 (0=poor to 10=high) when measuring lesion protection, aesthetics, relief of discomfort, and intolerance. There were 180 participants who qualified for this study creating three equal groups of 60 participants. The first examination day recorded the mean diameter of the lesions as 0.65 cm which was not significantly different in size between each of the three groups (Boes et al., 2020).

Results for healing time showed no statistically significant difference. Compeed Invisible Cold Sore Patch recorded a mean of 9.67 days, Herpatch was 9.30 days, and Zovirax was 9.80 days. In regard to the secondary endpoint, reaction rate and reaction quality using CGAT (clinician) and SGAT (subject), Herpatch was found to be significantly higher in both measurements when compared to Compeed and Zovirax. With calculated alpha error of 0.05, measurements for reaction rate demonstrated the Herpatch (median of 8.00) was significantly different ($p=0.025$) from that of Compeed (median of 7.00) and Zovirax (median of 7.00). Reaction quality was significantly different ($p=0.025$) between both Herpatch (median of 8.00)

and Compeed (median of 7.00) and between Herpatch and Zovirax (median of 7.00). The tertiary endpoint was the participants' questionnaire where Herpatch reported the highest measurements for all three of these features, however, Herpatch also reported the most intolerances such as dried lips and redness (Boes et al., 2020). The findings from Boes et al. (2020) study suggested a need for improved medication, specified a baseline for HSV-1 treatment healing times, and provided beneficial information on ways to compare a new product.

Topical Treatment: Acyclovir vs. Penciclovir

A recent study by Gürbüz et al. (2021) compared two common antiviral agents for the treatment of HSV-1 lesions. Seventy participants were diagnosed with an HSV-1 lesion through the use of an IgM antibody test at Gaziantep University. Participants were informed about the study and treatment process. Exclusions for this study included participants that were pregnant, under 18 years of age, immunosuppressed, exposed to chemicals or radiation at work, recovering from radiotherapy or chemotherapy, or unable to read and understand consent form (Gürbüz et al., 2021).

This study required participants to follow-up on the first, third, fifth, and seventh day. On each follow-up appointment symptoms were graded on a scale 0-5 and recorded. Participants recorded the burning, itching, and bleeding scores, while the clinician documented the stage of the lesion (erythema, vesicle, ulceration, crusting, and crust loss). Pain values were recorded using a visual analog scale (VAS). The VAS uses a 100 mm line between “no pain” and “worst pain” and participants place a single mark on the line that fits their pain level. The Depression, Anxiety, Stress Scale (DASS-21) was used to record the emotional state related to depression, anxiety, and stress (Gürbüz et al., 2021).

The 70 participants were assigned into two random treatment groups of 35. One group received Zovirax 5% cream (50 mg acyclovir for 1 g) and the other group received Vectavir 1% cream (10 mg penciclovir for 1 g). This study was an open-label trial, allowing participants to know the assigned treatment group. The Acyclovir group was instructed to apply the cream five times a day around 4-hour intervals, during waking hours. The Penciclovir group was instructed to apply the cream at approximately 2-hour intervals, around eight times a day. Both groups were instructed to use the treatment for four days (Gürbüz et al., 2021).

Results for this study revealed the measurements for the burning and itching symptoms decreased over time. Bleeding for both groups increased on the fifth day followed by a decrease. Three of these symptoms (burning, itching, and bleeding) demonstrated no significant difference between groups ($p > 0.05$) other than the penciclovir group displayed more bleeding on the third day. No significant relationship was found for why there was bleeding on the third day other than this day might have been part of the ulceration phase. Using the VAS, the baseline recording for pain revealed no difference between the two groups. The recordings on the third day follow-up reported a significantly lower pain experience for the acyclovir group ($p<0.001$). After the third day follow-up there was no other significant difference between the groups in regard to pain levels. In all patients, erythema and vesicle stages were completed by the third day. The stages of crusting and loss of crust were compared with no significant difference ($p>0.05$) found for either treatment group (Gürbüz et al., 2021).

The DASS-21 scale was used and on day one 62.8% of the participants reported signs of depression. Anxiety was reported with 34.4% of the participants and stress was prevalent in 41.4% of participants. For participants with high depression, significantly higher itching symptoms ($p=0.006$) were found. No correlation was found between the emotional state of the

participants and the burning, bleeding, crusting, and crust loss times ($p>0.05$). Depression and pain did not demonstrate a significant relationship, however, there was a significant correlation to pain with anxiety and stress. For participants with high anxiety, increased high pain symptoms were reported. For participants with high stress intensity, decreased pain symptoms were reported (Gürbüz et al., 2021).

With this study, the majority of the measured symptoms were not found to be significantly different other than pain levels on the third day for the acyclovir group. Considering the decrease in pain and the application process (penciclovir application every two hours vs. acyclovir every four hours) acyclovir is more practical. The most common side effects associated with these two drugs are headache and drying of the application area (Chen et al., 2017) although for this study none were reported. The association with stress levels and the HSV-1 lesions is an important factor to recognize due to common recurrences when stressful life events are reported. There were some limitations to this study such as a placebo not being used in the comparison study and the open-label trial allowing for bias from the participants (Gürbüz et al., 2021).

L-lysine: An Amino Acid

L-lysine is an essential amino acid that inhibits replication of HSV and could result in a shorter duration of the HSV-1 lesion (Griffith et al., 1987). In a study regarding L-lysine's safety and effectiveness by Singh et al. (2005), participants who were selected had a history of HSV-1 occurrences and were from the Los Angeles area. To participate individuals had to show the beginning signs and symptoms of an HSV-1 infection (<24-hours of initial symptoms), have the infection confirmed on site, be within the ages of 18-65, be willing to complete a patient diary for the duration of the study (maximum 21 days), allow photos to be taken of the lesion twice, and sign a written informed consent. Individuals were not allowed to participate if they had an

immunosuppressive condition, had any allergies to Llysine-based/zinc oxide cream or product, showed signs of other skin diseases or other current disseminated HSV-1 outbreak, had used any antiviral medication or creams within the last 10 days, were pregnant, or were lactating/nursing. Among the 120 participants, 30 met the requirements (Singh et al., 2005).

On the first examination day, photos were taken of the lesions and the product was delivered to participants at that time. With a clean fingertip, participants were instructed to apply the L-lysine product over the lesion every two hours during wakefulness until the lesion was fully crusted or the lesion was gone. Participants were instructed to complete a symptom diary before reapplying the product and if the lesion was healed, the patient was to report this finding and submit all items back to the Research Division within 24 hours. A second photo was taken at that time to confirm the effectiveness of the product (Singh et al., 2005).

For this study, if the lesion healed within four days and participants did not experience any crusting, this was referred to as an "aborted" event. For those who experienced crusting, the lesion needed to be fully crusted before it was considered "cured." The ten symptoms monitored with a 10-point scale were tingling, itching, burning, tenderness, prickling, soreness, bump/swelling, small blister(s), oozing blister(s), and crusting. Four participants reported a "cured" result in less than 24 hours with each of their lesions aborted. By day three, 12 participants (40%) reported cured lesions. By the sixth day 87% of the sample reported a cure rate, and by the 11^{th} day the final participants reported the lesion as cured. The symptoms were rated from 0-10 (10 being the worst) starting on day one, then were remeasured on day three, and again for day six. For participants with no remaining lesion, a zero was entered for all symptoms. Significant improvement ($p<0.001$) was demonstrated from the first day to the third day. Data for day six ($p<0.001$) also showed symptoms of improvement (Singh et al., 2005). Based on this

data, it is suggested that a lysine-based topical cream would decrease the duration of herpes lesions, along with the symptoms associated with it.

Local Anesthetics

Another study regarding treatment of HSV-1 lesions was recently published by Bastos et al. (2020). For this study, the researchers evaluated the efficacy of a semisolid film composition made up of prilocaine and lidocaine. Participants were invited to participate in this study using radio and advertisement posters. Volunteers were screened and selected for the research project. Participants were excluded if individuals had used a systemic-specific antiviral medication in the last 15 days, were immunocompromised, were pregnant, or had heart disease. Eighty-one participants were found to be eligible for the study. The treatment process included three applications, the first being at the initial appointment. Once the first application was applied, participants were instructed to keep the semisolid composition on the lesion for a minimum of one hour before removal. The second application was applied at hour eight and the third application was applied at hour sixteen. Contained in each application was 30 mg of anesthetic with a total of 90 mg by the third application over a 16-hour period. Along with recording the remission time of the herpes symptoms, participants were also asked to record how hard/easy the application was to apply, how long before relief was felt, how long the relief lasted, and whether the anesthetic sensation was bothersome. The study concluded with two follow-up questionnaires one at six months and the other at 12 months (Bastos et al., 2020).

There was a significant difference in patient satisfaction that demonstrated an increase in the number of participants reporting a very much-satisfied score with each application from hour zero to hour sixteen. The first application reported 19.8% (16 participants) as “very much” satisfied and by the third application the satisfaction increased to 32% (26 participants). Another

measurement was discomfort and the first application 46.9% (38 participants) reported no discomfort. By the third application (hour 16), 71.6% (58 participants) reported having no discomfort resulting in a significant difference with decreased discomfort following each application. The next measurement was sensation of anesthesia and 2.5% (2 participants) reported “no” sensation of anesthetic in the first application. By hour sixteen 9.9% (8 participants) reported “no” sensation of anesthetic. On the first application, 28.4% (23 participants) reported “strong” sensation of anesthetic and a rapid decrease in sensation by hour sixteen when only 6.2 (5 participants) reported a “strong” sensation of anesthetic. Pearson's X^2 test measured the psychological effects the lesion had on individuals such as: stops leaving home for leisure, depression, embarrassment, or harms professional performance. There was improvement in each of these areas when using the three treatments. The authors concluded the use of the treatments had an effective decrease in the signs and symptoms of the herpes lesions for the patients in this study. This treatment offered a dosage convenience (only three applications in a 24-hour period) and lower cost than using other treatments. This study suggested that although there were favorable aspects in improving the symptoms and improving the psychosocial causes, more evaluation needs to be performed on duration and healing time (Bastos et al., 2020).

In Office Photodynamic Therapy

When treating HSV-1 infections acyclovir (ACV) is the standard topical treatment, however, intravenous treatment is considered more effective (Frobert, et al., 2014; Whitley & Roizman, 2001). Because ACV is the standard therapy for HSV-1 in topical and intravenous use, it is hypothesized that resistance to this drug is caused by mutations in the viral genes that are not able to phosphorylate acyclovir (Ramalho et al., 2021). If these mutations continue, it will be

even more important to have alternative treatments for people suffering from HSV-1. An innovative HSV-1 treatment being developed is photodynamic therapy (PDT). Earlier studies started to demonstrate promising results in treating HSV-1 lesions with PDT but resulted in complications when the dye used caused side effects in the surrounding area of the host (Felber et al., 1973). With PDT better understood and the use of methylene blue as a cationic charged photosensitizer, the use of PDT has demonstrated inactivation of the HSV-1 via oxidative damage to the DNA (Müller-Breitkreutz & Mohr, 1998). A study by Ramalho et al. (2021) compared PDT to topical acyclovir focusing on the healing process and reported symptoms of HSV-1.

For this study patients must be at least 18 years old, have an HSV-1 lesion in an early vesicle stage, and be immunocompetent. Patients were excluded if they were pregnant or lactating, had a skin disease, had used any antiviral medication within the last 4 weeks, or had a history of alcohol or drug addiction. With this criteria, 75 patients met the requirements and were selected to participate (Ramalho et al., 2021).

Three groups were formed using the 75 participants. Characteristics monitored were size of the lesion, tingling, pain, edema, and healing time all using the Kruskal-Wallis test and when necessary the Student-Newman-Keuls test. Comparisons were made over the course of seven days. The primary outcome for this study was wound size. For the initial appointment, the HSV-1 lesion was measured with millimeter graph paper recording the largest lesion and if there were multiple lesions present. The participant was shown how to measure the lesion with the graph paper and given written instructions to measure the lesion at the same time every day until the crust fell off. Secondary outcomes were healing time, pain, tingling, and edema. The patients recorded the number of days until the crust fell off spontaneously and not by removal of the

patient. A daily journal was kept measuring pain, tingling, and edema using a grading scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe).

Methylene blue was used with Group 1 as a photosensitizer with the laser set at a wavelength of 660 nm. The pretreatment for this group began with the lesion being cleaned, punctured, and drained of vesicular content. Following pretreatment, the photosensitizer was applied, and the number of irradiation points was dependent upon the size of the lesion. Group 2 used a topical therapy cream with the active ingredient of Acyclovir at 5% (AC). With the same pretreatment as Group 1, Group 2 received the Acyclovir 5% (Zovirax) cream and was instructed to apply it five times a day (about every four hours) during waking hours. Treatment was continued until the lesion was healed. Group 3 received both the PDT and the AC treatments, along with the same pretreatment regimen followed by PDT therapy, and then were instructed to apply AC five times a day (Ramalho et al., 2021).

Results regarding the size of the wound revealed a significant difference between the groups on the first day with group 2 (AC) reporting less reduction in size of the wound than groups 1 and 3. All three groups demonstrated a significant reduction in size on day three and there were no significant size changes made when comparing the three treatment groups on the other days. Healing time and pain also suggested that there were no statistically differences among the three treatments. The edema comparison indicated a statistical difference on day one. Group 1 (PDT) and Group 3 were similar, and both had significantly less edema when compared to Group 2 (AC). There was no difference in tingling reduction among the three groups for seven days other than on the first day. A significant reduction of tingling ($p= 0.0048$) in comparison to group 2 (AC) was observed on the first day. There was no significant difference regarding healing time when comparing the three groups (Ramalho et al., 2021).

With these findings, it was concluded that the use of PDT produced a positive effect for HSV-1 with reduction in wound size, edema, and tingling. Each group measured similarly to one another, which is impressive for PDT considering AC is considered the standard of care (Whitley & Roizman, 2001; Frobert, et al., 2014). The Ramalho et al. (2021) study strongly encouraged further investigation for treatment using PDT. A recent systematic review on clinical studies for PDT by Lotufo et al. (2020) discovered a similar conclusion, that the results seem promising but more clinical trials are needed.

Laser Therapy

Finding a treatment for HSV-1 that will not build virucidal resistance is ongoing (Bergmann et al., 2017). Low level laser therapy (LLLT) is being researched as a possible treatment option. A study by Honarmand et al. (2017) is one example of this research. This study was a single-blind randomized clinical trial that assessed the efficacy of the diode laser for treatment of an HSV-1 lesion. With a total of 60 participants, three separate groups of 20 participants each were formed. The first group received acyclovir cream 5%, the second group received the diode laser, and the third group received a "laser-off" (placebo).

For this study, the end point was when the lesion was in the crusting stage. Each participant was informed of the purpose of this study and signed a consent. Exclusions for this study were systemic diseases and taking other medications during the study. The HSV-1 lesion needed to be in the early stages between 0-36 hours. An oral medicine specialist performed the laser treatment, while an oral medicine assistant did the examinations and was blinded to the treatment. Characteristics measured were size of the lesion, pain level, and duration of lesion until crust development. The size of the lesion was determined by using millimeter graph paper. To measure pain the VAS was used. The scale was rated on 0-10 points with "0" meaning no

pain and “10” meaning most severe pain ever experienced. The pain measurements were taken before treatment and at each follow-up appointment (Honarmand et al., 2017).

Size measurements were taken before treatment and no statistically significant difference was found between the three groups. Pain measurements were taken before treatment and no statistically significant difference between the three groups were detected. Group 2 (diode laser) showed a statistically significant decrease in size of the lesion (p 0.001) area by the third day (Honarmand et al., 2017). During and after treatments, recovery time, pain intensity, and size of the lesion were measured and compared for the three groups. The mean recovery time (days) for the laser group was 2.20+/-.041, the acyclovir group mean was 3.40+/-1.042, and the laser off group was 4.30+/-1.0; this demonstrated a statistically significant difference ($p<0.0001$) between groups (Honarmand et al., 2017). Using the one-way ANOVA test, a statistically significant difference within the groups was demonstrated when measuring pain intensity. The duration of pain was measured in days for each group; the laser group showed 1.35+/-0.74, acyclovir 2.30+/-0.92, and the laser off group 2.65+/-1.27 which reported a statistically significant difference (p 0.0001) by the third day. The findings from this study demonstrated that the diode laser treatment is a good option as an HSV-1 therapy (Honarmand et al., 2017). A large barrier for this treatment option is it being an in-office treatment and not convenient to the public.

Oral Treatment Options

Valacyclovir. In a randomized, placebo-controlled, double-blind, patient-initiated study by Hull et al. (2009) an oral medication (valacyclovir) in conjunction with a topical steroid (clobetasol) was compared to an oral and topical placebo. The valacyclovir group was administered 2 g orally twice a day for the first day followed by a topical administration of clobetasol gel 0.05% twice daily for three days. The placebo group was given the same

instructions regarding administration of the oral placebo medication and placement of the topical placebo. Following applications, participants were required to return to the clinic for the next three days for examination. After the three days of examinations, visits were decreased to every other day until lesion was healed and skin was normal. After 14 days, a final follow-up phone call was made to participants (Hull et al., 2009).

Inclusion criteria for this study were participants who had a history of three recurrent HSV-1's in the last year and were at least 18 years or older. Participating women, of childbearing ages, needed reliable birth control measures during the study. Study exclusions included patients who had used oral or topical applications of an investigational drug in the last four weeks, had a history of alcohol or drug abuse, had an allergy to corticosteroids or acyclovir, had a herpes simplex virus vaccine, or had used corticosteroid cream on or near face within the last 30 days. Some systemic conditions were excluded as well such as a: history of chronic heart conditions, pregnancy, nursing, pulmonary disease, renal disease, hepatic disease, compromised immune system, severe acne, rosacea, or eczema that might interfere with the study results. Eighty-one participants qualified for this study (Hull et al., 2009).

Measurements for this study were focused on the lesion size and pain. Healing time was determined by the participants' recorded journal entries and physical examinations of lesions. Pain was measured using a scale 0 (no pain) - 10 (worst pain imaginable). Participants recorded their observations in a journal three times a day, at the same time each day (ex. breakfast, lunch, and dinner). HSV-1 lesions were labeled as classical lesions on the first day if the lesion was within one cm of the lip and not in the mucosal tissue. If a second lesion emerged within the second or third treatment day, the lesion was labeled as a non-classical lesion. The primary endpoint was the size of the lesion. The secondary endpoints were frequency of lesions aborted

(lesions that healed before surfacing and never reached the crusting stage), healing time, pain, frequency of secondary lesion, and frequency of post-treatment lesions. A number of measuring tools were used for this study to measure various characteristics. To measure frequencies, Fisher's exact test and Mann-Whitney U tests were used. Area-under-the curve (AUC) analysis measured the lesion size versus lesion duration. Aborted lesions were assigned a measurement of zero (Hull et al., 2009).

Once participants received the study medication and written instructions, participants were instructed to begin the medication within 1-hour of the next HSV-1 lesion. Out of the 81 participants, 42 developed lesions but only 39 participants completed the study. Of the two groups, 20 participants received the valacyclovir-clobetasol kits and 19 received the placebo kits. The Kaplan-Meier curve suggested the lesions in the valacyclovir-clobetasol group demonstrate a reduced healing time when compared to the placebo group ($p= 0.002$). Aborted lesions had a statistically significant increase in the valacyclovir-clobetasol group ten out of 20 when compared to the placebo group of three out of 19 ($p= 0.04$). The valacyclovir-clobetasol group (n=ten) with classical lesions had a mean healing time of 5.8 +/- 2.18 versus the placebo group (n=16) with classical lesions that had a mean healing time of 9.3 +/- 2.95 days revealing statistically significant reduction ($p= 0.002$). Pain measurements indicated no statistically significant difference between either group. There were some minor adverse side effects found in the valacyclovir-clobetasol group versus the placebo. The most common occurrence was a headache found in 18% of the participants. One complaint by a single participant in the same group reported an exacerbation of acne. Another participant from the same group indicated the feeling of a warm sensation after using the clobetasol (Hull et al., 2009).

This study demonstrated that aborted lesions significantly increased while classical lesion, size, and healing time of classical lesions significantly decreased. These results suggested that the combination of valacyclovir and clobetasol is safe and effective for HSV-1 lesions. The authors indicated that this study supports the theory that corticosteroids can be used as a new therapeutic treatment for HSV-1 lesions. The authors also recognized the need for further research for the use of corticosteroids as a treatment option for HSV-1 lesions (Hull et al., 2009).

Acyclovir. Another research article studying the efficacy of an oral antiviral medication was done by Spruance et al. (1990). This was a double-blind, randomized, and placebo-controlled study that was patient-initiated. This study reported a clinical trial of oral acyclovir (ACV) for HSV-1 lesions. Inclusions for this study were immunocompetent participants, diagnosed with early signs of HSV-1, older than 8 years of age, in good general health, and able to intake oral administrations. Women of childbearing ages participating in the study were required to be on reliable birth control methods. Exclusions for this study were pregnancy or nursing (Spruance et al., 1990).

There were 333 participants who received capsules; however, only 174 had an HSV-1 episode to treat. The capsules contained 200 mg of ACV or a placebo. The two testing groups were randomly separated with 114 ACV participants and 60 placebo participants. The medication regimen was two capsules every 4 hours while awake, five times a day for five days. Participants were instructed to start the regimen within one hour of symptoms. If participants discovered the lesion too late, they were instructed to not start the regimen but to wait until the next lesion (Spruance et al., 1990).

Once participants started the medication, they were instructed to return to the clinic within 24 hours. At this visit, a variety of characteristics were evaluated such as lesion stage,

pain, and size. After this initial examination, participants were required to return on a daily basis until the lesion was healed. Pain was measured on a scale of 0-3 with “0” being no pain and “3” being severe pain. Severe levels of pain would mean participants' daily activities were interrupted such as eating, drinking, and talking. Size was measured by length, width, and height, not including the erythematous borders. If the lesion was only erythematous a value of “0” was given. Stages of the lesion were labeled prodrome, erythema, papule, vesicle, ulcer or soft crust, hard crust, dry and flakey, residual swelling, and the final stage as normal skin. Two time frames were recorded; the first was the duration of healing time till lesion lost hard crust and the second was the duration of healing time until the presence of normal skin without erythema. If crusting never occurred, participants received a value of 0 for this measure (Spruance et al., 1990).

Pain results for ACV participants demonstrated a mean reduction of 2.5 days versus 3.8 days for the placebo group ($p= 0.01$). The mean healing time for loss of hard crust for the ACV group also had a positive effect with 6.8 days versus 7.5 days for the placebo group ($p=0.17$). The mean healing time to normal skin for the ACV group demonstrated no significant difference. The data from this comprehensive assessment revealed treatment improved the pain levels and healing time for HSV-1. The authors noted that even greater improvements were resulted when participants started the treatment in the prodromal stage versus starting treatment in the erythema stage (Spruance et al., 1990).

After reviewing the many different treatments currently being used for the treatment of HSV-1 lesions, (Compeed Invisible Cold Sore Patch, Zovirax cream 5%, Herpatch Serum, L-lysine, local anesthetics, Vectavir, PDT, AC, AC+PDT, diode laser, oral valacyclovir, and oral acyclovir) there is still much room for improvement. HSV-1 is linked to multiple systemic health conditions that have high mortality and morbidity rates, and the rising resistance to AC makes

finding new treatment for HSV-1 even more important (Bergmann et al., 2017). One possible treatment alternative could be 70% ethanol alcohol, which is known for its virucidal activity. The U.S. Food and Drug Administration (2019) and World Health Organization (2009) both approved ethanol alcohol for use as a safe and effective disinfectant hand rub.

Alternative Treatment Options

A recent study by Sauerbrei (2020), established that an inactivation effect on enveloped viruses (such as the HSV-1) occurred when ethanol alcohol was used at 60%-80%. Ethyl alcohol and ethanol alcohol are two terms used to name the same chemical compound (Madhusha, 2017). This type of compound has microbial effects against enveloped and non-enveloped viruses when used as a hand disinfectant (German Association for Applied Hygiene (VAH), 2020). German Association for Applied Hygiene (VAH), (2020) tested ethanol alcohol for toxicity levels as it is absorbed through the skin and/or inhalation of the fumes to determine the safety of its use.

Four main categories were tested for this study. The first category used suspension tests (EN 13727) and (EN 14476) to determine efficacy against bacteria and viruses that are both enveloped and non-enveloped. This is a simulation test where a sample is introduced to the bacteria or virus and then is neutralized over a period (usually 30-seconds to one-minute). The test sample is measured by the bacterial or viral reduction. Ethanol alcohol demonstrated sufficiently good results with non-enveloped viruses, enveloped viruses (including herpes simplex), and bactericidal effects over a 30-second timeframe (German Association for Applied Hygiene (VAH), 2020).

The second portion of the study investigated ethanol absorption and toxicity levels in the blood. A systematic investigation was used. Blood alcohol tests were performed on 20 subjects after disinfectants (ranging in alcohol percentages) were applied to determine the amount of

alcohol absorption. The three chosen disinfectants were: a solution with 95% ethanol, a gel with 85% ethanol, and a solution with 55% ethanol. Each subject received 20 applications of four milliliters (ml) of the assigned hand rub to use within 30 minutes. The highest ethanol blood concentration was the 95% (20.95 milligrams per liter (mg/l) after 30 minutes), followed by the 85% (11.45 mg/l after 30 minutes) ethanol, and then the 55% (6.9 mg/l after 30 minutes) ethanol (German Association for Applied Hygiene (VAH), 2020). Utah has the lowest legal driving blood alcohol content (BAC) limit in the United States at .05% or 50 mg/dL (Utah Department of Public Safety, 2017). When considering the amount of ethanol absorbed for this test to a BAC, the absorbed amounts are minuscule. The highest recorded BAC was with the 95% concentration with a reading of 20.95mg/l. This is equivalent to .002095% or 2.095mg/dL.

A third test was performed this time using surgical hand disinfectant with the same three ethanol concentrations used from test two. For this portion only 10 applications were performed within an 80-minute time frame. Using four milliliters of product for each application, each subject applied the disinfectant to the hands and forearms for three minutes. For the surgical hand disinfectant, the highest blood level concentration reported was the 85% ethanol with 30.1 mg/l after 30 minutes, followed by 95% ethanol with 17.5 mg/l after 30 minutes, and lastly the 55% ethanol with 81.5 mg/l after 20 minutes (German Association for Applied Hygiene (VAH), 2020). When comparing the amount of ethanol absorbed using the surgical hand disinfectant to BAC, the highest BAC reading was 30.1 mg/l or .00301% (3.01mg/dL). In a separate study, European Chemicals Agency (ECHA) (2020), reported that only 1-2% of ethanol alcohol is absorbed through the skin.

The fourth test performed in the German Association for Applied Hygiene (VAH) (2020) study measured the respiratory absorption of ethanol alcohol. A breathalyzer was used for this

test. Twenty subjects applied 30 hand disinfection cycles (1.2-1.5 mL each cycle) with 70% ethanol over the period of 1 hour. Ethanol concentrations occurred highest within 20-30 seconds following hand disinfection. Of the 20 subjects only six had detectable concentrations of ethanol ranging between 0.001% and 0.0025% on the breathalyzer (German Association for Applied Hygiene (VAH), 2020). The findings of this study demonstrated the effectiveness ethanol alcohol has when used as a virucidal agent and demonstrates the safety of its use. This raises the question if ethanol alcohol would have a virucidal effect on an HSV-1 lesion. This study gives further insights of some common concerns when using ethanol alcohol as a disinfectant on the skin. There are no known studies of ethanol alcohol on HSV-1 lesions.

Summary of Chapter 2

There are many antiviral medications being used to treat HSV-1 outbreaks. Antiviral medications have side effects, can be costly, are inconvenient, and are limited in effectiveness. To help individuals suffering from HSV-1, a more effective treatment that is convenient (over the counter), less costly, and has fewer side effects is needed. A possible alternative treatment for HSV-1 would be 70% ethanol alcohol. Ethanol alcohol is inexpensive, convenient, and in concentrations of 60%-80%, can kill HSV-1 (Rutala & Weber, 2008). The findings from German Association for Applied Hygiene (VAH) (2020) study demonstrates the toxicology implication for ethanol absorption and reports it as safe in the amounts of 10-30 applications of 4ml's each. When treating HSV-1 with 70% ethanol alcohol, fewer applications and less dosage amounts would be required. More research is needed to provide evidence-based information about the efficacy of the use of 70% ethanol alcohol hand sanitizer as an HSV-1 treatment option.

Chapter 3 Methodology

The purpose of this pilot study was to determine if the use of 70% ethanol alcohol hand sanitizer alters the duration, size of the lesion, level of pain upon application, and discomfort on a daily basis. To accomplish this, it was first imperative to learn about the HSV-1. Chapter one provided background information about HSV-1 outlining the problem of the disease, systemic effects related to the HSV-1, and a possible treatment option to consider. Chapter two compared many current treatment options and investigated a possible alternative treatment option. When reviewing the different HSV-1 treatment options in chapter 2, the duration of the lesion, pain levels, compliance of the patients, and the convenience of the medication were compared. Also included in chapter two was research on ethanol alcohol and its effectiveness as a virucidal agent as well as the absorption rate and toxicity levels on the human body. Chapter three described the methodology of this study including a review of the research questions, hypothesis, the research design, a description of the sampling process, method strategy, study limitations, and procedure for data collection and analysis.

Research Questions

The following research questions guided the conduct of this study:

1. Is there a statistically significant difference in the duration of the HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?
2. Is there a statistically significant difference in the level of pain during the treatment application process of an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?

3. Is there a statistically significant difference in the level of discomfort during an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?
4. Is there a statistically significant difference in the size of the HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil?

Hypotheses

The following hypotheses guided the conduct of this study:

1. There is no statistically significant difference in the duration of the HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.
2. There is no statistically significant difference in the level of pain during the treatment application process of an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.
3. There is no statistically significant difference in discomfort during an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.
4. There is no statistically significant difference in the size of an HSV-1 lesion for those in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used medical grade mineral oil.

Research Design

This study was a double-blind randomized controlled study designed to determine if the use of 70% ethanol alcohol hand sanitizer alters the duration of an HSV-1 lesion, size of the lesion, level of pain on application, and daily discomfort when compared to a control group. Ten lip balm applicators were filled with 70% ethanol alcohol hand sanitizer minutes before handing the kit to participants to ensure the hand sanitizer was fresh. Ten other lip balm applicators were filled with medical grade mineral oil any time prior to participant's arrival. These lip balm applicators provided a "touch-free" application, limiting self-inoculation and spreading. The lip balm applicators were free from any labeling except a single letter "A" or "R" located on the lid to ensure participants were blind. The "A" applicators contained the treatment (70% ethanol alcohol hand sanitizer) and the "R" applicators contained the placebo (medical grade mineral oil). Each lip balm applicator was placed in a nontransparent paper sack along with laminated paper millimeter ruler and a packet of instructions for the participants to follow (see Appendix A-D to view instruction packet). The first page of the packet (Appendix A) explained the need for this study, contained the researchers' contact information, and included instructions for the participants. Page two of the packet (Appendix B) listed the participants' personal contact information, demographics, and qualifying questions. The next eight pages of the packet (Appendix C) consisted of participants' daily instructions, contained a space for a daily journal, a place to measure the size of the lesion, two visual analogue scales (VAS) one for pain upon application and one for discomfort on a daily basis, a provided space to put the assigned letter (R or A), and instructions that explained to the participants when they need to return to the clinic. The final page was the consent form (Appendix D) which explained that participation is voluntary, how much time is required to participate, that the participants' personal information

and identity are secured, the daily journal writing agreement, and the required signature as an agreement of participation.

The calibrated research assistants passed out the kits with the packet to the participants. Instructions for application of either the 70% ethanol alcohol hand sanitizer or the medical grade mineral oil was: apply every hour (waking hour) for the first 4 days (about 12 applications a day) or until lesion is gone. To encourage participant compliance, the medication was in a convenient travel size lip balm applicator. Another way to encourage compliance was offering a drawing for all participants who completed the study. The participants had a choice to be entered into a random drawing for a $50 Amazon gift card. Those participants who chose to do this had their phone number put in a container and one phone number was randomly selected to receive the gift card. The winning participant was notified via text.

Research Participants

Sample Description

Study participants consisted of a convenience sample from Utah Tech University Dental Hygiene Clinic, Cotton Creek Dental, Idaho State University, and local community members from both Southern Utah and Long Beach California who experienced early stages of an HSV-1 lesion.

Sample Inclusion Criteria. For the purpose of this study participants needed to be:

- In the early prodromal stage of an HSV-1 outbreak (less than 24 hours from initial symptom), with the visible manifestation of a lesion.
- 18 years or older.
- Capable of following daily treatment instructions.
- Willing to complete a daily journal.

- Willing to come to the clinic twice for records and pictures during the next 14 days or until the participant is free of the lesion.

Sample Exclusion Criteria. For the purpose of this study participants could not be:

- Immunocompromised.
- Pregnant.
- Taken any antiviral medication within the last two weeks.
- Used any creams or antiviral medication in the last 10 days.

Recruitment for participants was achieved using social media (Facebook and Instagram), word of mouth, and patient recruitment at Cotton Creek Dental, Idaho State University, and Utah Tech University Dental Hygiene Clinic. Each location helped search for individuals prone to recurrent HSV-1 or anyone who experienced the prodromal stages of an HSV-1 lesion. The online Facebook and Instagram post was reposted online every week until two weeks prior to the deadline. The stated post is found on Appendix E.

Human Subject's Protection

Permission to conduct the research study was obtained from Idaho State University Human Subjects Committee (HSC) prior to the initiation of this study. Participants of the study reviewed the consent form that was in the packet received from the research assistants. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) requires participant information to be kept confidential. At the completion of this study any personal information was destroyed to secure participants identity. Data collected from this study was uploaded into Box which is a HIPPA certified electronic storage tool at Idaho State University. Box is password protected and has firewall protection. Only the principal investigator and co investigators have access to the data collected from the study. The data is stored and secured in Box for seven years,

at that point all material of the study will be destroyed by Idaho State University following university protocol. Once a file is deleted from Box, following a 30-day time period, the file is permanently purged and can no longer be recovered.

Data Collection and Analysis

The goal was to include 20 participants in the study. The researcher accepted participants from May 2022 to October 2023. On the initial examination day (day one), name, contact information, age, sex, and a photo were collected. Pain and discomfort were measured using the visual analog scale (VAS). Participants placed a single mark on the VAS in their journal that measured their level of discomfort from the lesion. Participants also placed a single mark on the VAS in their journal that fits their pain level (if any) when they applied medication for that day. The VAS has been widely used to record patient's pain progression and for diverse types of conditions including chronic pain, cancer, and ambulation (Ferraz et al., 1990; Gallagher et al., 2002). The scale is completed by patients themselves who mark on the line the point that they feel represents their perception of their current state. The VAS takes less than one minute to complete and is easy to use with minimal training. Studies of reliability have been shown to be good (r=0.94 -0.99). (Ferraz et al., 1990; Gallagher et al., 2002). For construct validity, correlations range from 0.71-0.78 and 0.62 -0.91 (Downie et al., 1978). In addition to the VAS measurements, participants learned how to take a daily measurement of the size of the lesion with a laminated millimeter ruler that was included with the packet.

Method Strategy

The primary endpoint for this study was the duration of an HSV-1 lesion. The secondary endpoints were a measurement for lesion size, pain upon administration, and daily discomfort. Duration was determined when sloughing of the crust had occurred and the lesion was no longer

present. Size was recorded by the patient's daily measurements, pain and discomfort were measured using the visual analog scale (VAS). A participant began treatment once they were approved by the research assistant, the consent form signed, and the paperwork was completed. At the first examination, a photograph of the lesion was taken, the size of the lesion was measured, and pain and duration were recorded. The packet, kit, and daily instructions were given and sent home with the participant. The participants' contact information and consent form was kept at a designated clinic in a secure location. Every day the participant wrote in a daily journal along with a daily recording of the lesion size, and a VAS measurement to record any changes with pain and discomfort. Participants were required to return on the final examination day (when lesion had healed) and a final photo was taken. At the closing of the trial, all photos and documents were charted, analyzed, and compared.

Study Limitations

Experimental studies are considered the gold standard for assessing causality (Jacobsen, 2021). Any study is not without limitation and this study was no exception. Twenty participants may be a limiting factor as study results of the use of 70% ethanol alcohol hand sanitizer may not be generalized to larger populations. Finding 20 participants with the early prodromal stage of an HSV-1 outbreak (less than 24 hours from initial symptoms) with a visible manifestation may prove to be difficult during the time frame. This study could be limited further if the 20 participants did not complete the study due to the amount of compliance that is required. Good communication and clear instructions were key factors in successfully completing this study.

Another limitation of this study was early treatment. Whitley (2006b) stressed the importance of starting treatment early. For this study participants had to meet up with the research assistants possibly causing a delay of treatment. Other studies have been able to send

kits home with willing participants who are prone to reoccurring HSV-1 lesions, this allows patient initiated-therapy giving the lesion little time to progress (Whitley, 2006b; Hull, 2009; Spruance, 1990).

Clinical trials offering placebo also are limited due to the placebo effect. Harvard Medical School (2013) reported that the placebo effect does not heal diseases, such as lowered cholesterol or decreased tumor size but it can affect symptoms modulated by the brain. This means duration will not be affected due to the placebo effect, but pain or discomfort could. Because HSV-1 can cause pain and discomfort these were important factors to measure. It could prove to be a limitation if there was a large placebo effect.

Proposed Statistical Analysis

Duration, size, pain, and discomfort were the measured units for this study. To analyze the duration, size, pain, and discomfort an unpaired t-test was used allowing the experiment to be compared to the control. T-tests are used when comparing the mean of two samples. An unpaired t-test is when there is a two-sample t-test. This study was a two-sample group, each group receiving a separate treatment. The 70% ethanol alcohol hand sanitizer for this study, was the experiment group, and the medical grade mineral oil was the control group. The level of significance was $p<0.05$.

Chapter 3 Summary

This chapter described the research design and protocol for an experimental study of the use of 70% ethanol alcohol hand sanitizer as a treatment for an HSV-1 lesion. The duration of an HSV-1 lesion was the primary endpoint for this study. Size, pain, and discomfort were the secondary endpoints. The participants were given either the 70% ethanol alcohol hand sanitizer for the experimental group or medical grade mineral oil to use for the control group.

Documentation of changes to the lesion were recorded in a daily journal until the lesion was healed. Depending on the results of this study, the findings may encourage interest for further research in this area.

Results and discussion will be reported in the form of a manuscript to be submitted for publication in the *Journal of Dental Hygiene.* The remaining sections of the thesis reflect the manuscript specifications outlined in the author guidelines located at https://jdh.adha.org/.

References

Akhtar, J., Tiwari, V., Oh, M. J., Kovacs, M., Jani, A., Kovacs, S. K., & Shukla, D. (2008). HVEM and Nectin-1 are the major mediators of herpes simplex virus 1 (HSV-1) entry into human conjunctival epithelium. *Investigative Ophthalmology & Visual Science*, *49*(9), 4026-4035. https://doi.org/10.1167/iovs.08-1807

American Academy of Oral Medicine. (2016, January 2). *Clinical practice statement: Dental care for the patient with an oral herpetic lesion*. https://www.aaom.com/index.php?option=com_content&view=article&id=161%3Aclinical-practice-statement--dental-care-for-the-patient-with-an-oral-herpetic-lesion&catid=24%3Aclinical-practice-statement

American Dental Hygienists' Association. (2016, May 9). *National dental hygiene research agenda*. https://www.adha.org/resources-docs/7111_National_Dental_Hygiene_Research_Agenda.pdf

Arduino, P. G., & Porter, S. R. (2008). Herpes simplex virus type 1 infection: Overview on relevant clinic-pathological features. *Journal of Oral Pathology & Medicine*, *37*(2), 107-121. https://doi.org/10.1111/j.1600-0714.2007.00586.x

Baiju, R. M., Peter, E. L. B. E., Varghese, N. O., & Sivaram, R. (2017). Oral health and quality of life: Current concepts. *Journal of Clinical and Diagnostic Research: JCDR*, *11*(6), ZE21. https://doi.org/10.7860/JCDR/2017/25866.10110

Bardellini, E., Amadori, F., Veneri, F., Conti, G., Paderno, A., & Majorana, A. (2021). Adolescents and primary herpetic gingivostomatitis: An Italian overview. *Irish Journal of Medical Science*. https://doi.org/10.1007/s11845-021-02621-3

Bastos, M. D. R., de Figueiredo, F. A. T., Macedo, A. P., Silva, A. C. F., Ferreira, M. P., de Freitas, O., & Pedrazzi, V. (2020). Local anesthetic improves individuals affected with herpes simplex type 1 labialis. *Journal of Medical Virology*. https://doi.org/10.1002/jmv.25982

Bergmann, M., Beer, R., Kofler, M., Helbok, R., Pfausler, B., & Schmutzhard, E. (2017). Acyclovir resistance in herpes simplex virus type I encephalitis: A case report. *Journal of Neurovirology*, *23*(2), 335-337. https://doi.org/10.1007/s13365-016-0489-5

Boes, H., Goulioumis, V., Wechsler, A., Zimmer, S., & Bizhang, M. (2020). Clinical study on the effectiveness of three products in the treatment of herpes simplex labialis. *Scientific Reports*, *10*(1), 1-9. https://doi.org/10.1038/s41598-020-63530-6

Centers for Disease Control and Prevention (1996). *Health Insurance Portability and Accountability Act of 1996.* https://www.cdc.gov/phlp/publications/topic/hipaa.html#:~:text=The%20Health%20Insurance%20Portability%20and,the%20patient's%20consent%20or%20knowledge

Cernik, C., Gallina, K., & Brodell, R. T. (2008). The treatment of herpes simplex infections: An evidence-based review. *Archives of Internal Medicine*, *168*(11), 1137-1144. https://doi.org/10.1001/archinte.168.11.1137

Chen, F., Xu, H., Liu, J., Cui, Y., Luo, X., Zhou, Y., Chen, Q. and Jiang, L. (2017). Efficacy and safety of nucleoside antiviral drugs for treatment of recurrent herpes labialis: A systematic review and meta-analysis. *Journal of Oral Pathology & Medicine*, *46*(8), 561-568. https://doi.org/10.1111/jop.12534

Downie, W. W., Leatham, P. A., Rhind, V. M., Wright, V., Branco, J. A., & Anderson, J. A. (1978). Studies with pain rating scales. *Annals of the rheumatic diseases*, *37*(4), 378-381. http://dx.doi.org/10.1136/ard.37.4.378

Duarte, L. F., Farías, M. A., Álvarez, D. M., Bueno, S. M., Riedel, C. A., & González, P. A. (2019). Herpes simplex virus type 1 infection of the central nervous system: Insights into proposed interrelationships with neurodegenerative disorders. *Frontiers in Cellular Neuroscience*, *13*, 46. https://doi.org/10.3389/fncel.2019.00046

European Chemicals Agency (ECHA). (n.d.). *Ethanol – Endpoint summary.* https://echa.europa.eu/registration-dossier/-/registered-dossier/16105/7/4/1

Farooq, A. V., & Shukla, D. (2012). Herpes simplex epithelial and stromal keratitis: An epidemiologic update. *Survey of Ophthalmology*, *57*(5), 448–462. https://doi.org/10.1016/j.survophthal.2012.01.005

Fatahzadeh, M., & Schwartz, R. A. (2007). Human herpes simplex labialis. *Clinical and Experimental Dermatology*, *32*(6), 625–630. https://doi.org/10.1111/j.1365-2230.2007.02473.x

Felber, T. D., Smith, E. B., Knox, J. M., Wallis, C., & Melnick, J. L. (1973). Photodynamic inactivation of herpes simplex: Report of a clinical trial. *JAMA*, *223*(3), 289-292. https://doi.org/10.1001/jama.1973.03220030027005

Ferraz, M. B., Quaresma, M. R., Aquino, L. R., Atra, E., Tugwell, P., & Goldsmith, C. (1990). Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. *The Journal of rheumatology*, *17*(8), 1022-1024.

Frobert, E., Burrel, S., Ducastelle-Lepretre, S., Billaud, G., Ader, F., Casalegno, J.-S., Nave, V., Boutolleau, D., Michallet, M., Lina, B., & Morfin, F. (2014). Resistance of herpes

simplex viruses to acyclovir: An update from a ten-year survey in France. *Antiviral Research, 111,* 36–41. https://doi.org/10.1016/j.antiviral.2014.08.013

Gallagher, E. J., Bijur, P. E., Latimer, C., & Silver, W. (2002). Reliability and validity of a visual analog scale for acute abdominal pain in the ED. *The American journal of emergency medicine*, *20*(4), 287-290. https://doi.org/10.1053/ajem.2002.33778

George, B. P., Schneider, E. B., & Venkatesan, A. (2014). Encephalitis hospitalization rates and inpatient mortality in the United States, 2000-2010. *PloS One*, *9*(9), e104169. https://doi.org/10.1371/journal.pone.0104169

German Association for Applied Hygiene (VAH) (2020). As a biocidal active substance, ethanol is indispensable for hygienic hand disinfection [Internet]. Bonn: Institut für Hygiene und Öffentliche Gesundheit der Universität Bonn. https://vah-online.de/files/download/vah-mitteilungen/VAH_Ethanol_biocide_29Oct2020_2.pdf

Gnann, J. W., & Whitley, R. J. (2017). Herpes simplex encephalitis: An update. *Current Infectious Disease Reports*, *19*(3), 13. https://doi.org/10.1007/s11908-017-0568-7

Greenberg, M. S. (1996). Herpesvirus infections. *Dental Clinics of North America*, *40*(2), 359-368.

Griffith, R. S., Walsh, D. E., Myrmel, K. H., Thompson, R. W., & Behforooz, A. (1987). Success of L-lysine therapy in frequently recurrent herpes simplex infection. *Dermatology*, *175*(4), 183-190. https://doi.org/10.1159/000248823

Gürbüz, M. C., Kırtak, N., & Özyurtseven, B. T. (2021). Comparison of topical acyclovir and penciclovir in recurrent herpes labialis treatment. *Cukurova Medical Journal / Çukurova Üniversitesi Tip Fakültesi Dergisi*, *46*(3), 927–933. https://doi.org/10.17826/cumj.899262

Harvard Medical School. (2021, December 13). *Treating yourself with your mind is possible, but there is more to the placebo effect than positive thinking.* https://www.health.harvard.edu/mental-health/the-power-of-the-placebo-effect

Hobbs, M. R., Jones, B. B., Otterud, B. E., Leppert, M., & Kriesel, J. D. (2008). Identification of a herpes simplex labialis susceptibility region on human chromosome 21. *The Journal of Infectious Diseases*, *197*(3), 340-346. https://doi.org/10.1086/525540

Honarmand, M., Farhadmollashahi, L., & Vosoughirahbar, E. (2017). Comparing the effect of diode laser against acyclovir cream for the treatment of herpes labialis. *Journal of Clinical and Experimental Dentistry*, *9*(6), e729–e732. https://doi.org/10.4317/jced.53679

Hull, C., McKeough, M., Sebastian, K., Kriesel, J., & Spruance, S. (2009). Valacyclovir and topical clobetasol gel for the episodic treatment of herpes labialis: a patient-initiated, double-blind, placebo-controlled pilot trial. *Journal of the European Academy of Dermatology and Venereology*, *23*(3), 263-267. https://doi.org/10.1111/j.1468-3083.2008.03047.x

Jacobsen, K. H. (2021). Introduction to health research methods: A practical guide (3rd ed.). *Jones and Bartlett Publishers, Inc.*

Lee, H., Yang, J. H., & Suh, D. H. (2020). Gangrenous herpetic whitlow initially misdiagnosed as cellulitis. *The Australasian Journal of Dermatology*, *61*(3), 274. https://doi.org/10.1111/ajd.13252

Leung, D. Y. (2013). Why is eczema herpeticum unexpectedly rare? *Antiviral Research*, *98*(2), 153-157. https://doi.org/10.1016/j.antiviral.2013.02.010

Liaw, F. Y., Huang, C. F., Hsueh, J. T., & Chiang, C. P. (2012). Eczema herpeticum: A medical emergency. *Canadian Family Physician Medecin de Famille Canadien*, *58*(12), 1358–1361. https://www.cfp.ca/content/58/12/1358.short

Lotufo, M. A., Tempestini Horliana, A. C. R., Santana, T., de Queiroz, A. C., Gomes, A. O., Motta, L. J., Ferrari, R. A. M., dos Santos Fernandes, K. P., & Bussadori, S. K. (2020). Efficacy of photodynamic therapy on the treatment of herpes labialis: A systematic review. *Photodiagnosis and Photodynamic Therapy*, *29*. https://www.sciencedirect.com/science/article/abs/pii/S1572100019303072?via%3Dihub

Mahoney, J. (2014). Cold sores. In B. C. Auday, M. A., Buratovich, G.F, Marrocco, & P. Moglia (Eds.), *Magill's medical guide* (7th ed., Vol. 2). Salem Press.

Madhusha. (2017, October 18). *Difference between ethyl alcohol and ethanol: Definition, chemical and physical properties*. Pediaa.Com. https://pediaa.com/difference-between-ethyl-alcohol-and-ethanol/

Merriam-Webster. (n.d.). Discomfort. In *Merriam-Webster.com dictionary*. Retrieved January 24, 2022, from https://www.merriam-webster.com/dictionary/discomfort

Merriam-Webster. (n.d.). Duration. In *Merriam-Webster.com dictionary*. Retrieved January 24, 2022, from https://www.merriam-webster.com/dictionary/duration

Merriam-Webster. (n.d.). Pain. In *Merriam-Webster.com dictionary*. Retrieved January 24, 2022, from https://www.merriam-webster.com/dictionary/pain

Merriam-Webster. (n.d.). Placebo. In *Merriam-Webster.com dictionary*. Retrieved January 24, 2022, from https://www.merriam-webster.com/dictionary/placebo

Mori, I. (2010). Herpes simplex virus type 1 persists in the aged brain through hypothetical expression of accessory genes. *Journal of Neurovirology, 16*(3), 203-207. https://doi.org/10.3109/13550281003739040

Mott, K. R., Bresee, C. J., Allen, S. J., BenMohamed, L., Wechsler, S. L., & Ghiasi, H. (2009). Level of herpes simplex virus type 1 latency correlates with severity of corneal scarring and exhaustion of CD8+ T cells in trigeminal ganglia of latently infected mice. *Journal of Virology, 83*(5), 2246-2254. https://doi.org/10.1128/JVI.02234-08

Müller-Breitkreutz, K., & Mohr, H. (1998). Hepatitis C and human immunodeficiency virus RNA degradation by methylene blue/light treatment of human plasma. *Journal of Medical Virology, 56*(3), 239-245. https://onlinelibrary.wiley.com/doi/10.1002/(SICI)1096-9071(199811)56:3%3C239::AID-JMV11%3E3.0.CO;2-9

Myers, S. L., & Curran, A. E. (2014). *General and Oral Pathology for Dental Hygiene Practice*. F.A. Davis.

Opstelten, W., Neven, A. K., & Eekhof, J. (2008). Treatment and prevention of herpes labialis. *Canadian Family Physician, 54*(12), 1683–1687. https://www.cfp.ca/content/54/12/1683.full

Oxford Languages. (n.d.) Hand-sanitizer. In *google-dictionary.com*. Retrieved January 24, 2022, from https://languages.oup.com/google-dictionary-en/

Oxford Languages. (n.d.) Discomfort. In *google-dictionary.com*. Retrieved January 24, 2022, from https://languages.oup.com/google-dictionary-en/

Quinn, J. P., Dalziel, R. G., & Nash, A. A. (2000). Herpes virus latency in sensory ganglia—a comparison with endogenous neuronal gene expression. *Progress in Neurobiology*, *60*(2), 167-179. https://doi.org/10.1016/s0301-0082(99)00024-6

Ramalho, K. M., Cunha, S. R., Gonçalves, F., Escudeiro, G. S., Steiner-Oliveira, C., Horliana, A. C. R. T., & Eduardo, C. de P. (2021). Photodynamic therapy and Acyclovir in the treatment of recurrent herpes labialis: A controlled randomized clinical trial. *Photodiagnosis and Photodynamic Therapy*, *33*. https://doi.org/10.1016/j.pdpdt.2020.102093

Ramchandani, M., Kong, M., Tronstein, E., Selke, S., Mikhaylova, A., Magaret, A., Huang, M. L., Johnston, C., Corey, L., & Wald, A. (2016). Herpes simplex virus type 1 shedding in tears and nasal and oral mucosa of healthy adults. *Sexually Transmitted Diseases*, *43*(12), 756–760. https://doi.org/10.1097/OLQ.0000000000000522

Richardson, V. N., Davis, S. A., Gustafson, C. J., West, C. E., & Feldman, S. R. (2013). Patterns of disease and treatment of cold sores. *Journal of Dermatological Treatment*, *24*(6), 439–443. https://doi.org/10.3109/09546634.2013.789476

Rutala, W., & Weber, D. (2008). *Chemical disinfectants*. Centers for Disease Control and Prevention. https://www.cdc.gov/infectioncontrol/guidelines/disinfection/disinfection-methods/chemical.html

Santosh, A., & Muddana, K. (2020). Viral infections of oral cavity. *Journal of Family Medicine and Primary Care*, *9*(1), 36–42. https://doi.org/10.4103/jfmpc.jfmpc_807_19

Sarid, R., Klepfish, A., & Schattner, A. (2002). Virology, pathogenetic mechanisms, and associated diseases of kaposi sarcoma-associated herpesvirus (human herpesvirus 8). *Mayo Clinic Proceedings*, *77*(9), 941-949. https://doi.org/10.4065/77.9.941

Sauerbrei, A. (2020). Bactericidal and virucidal activity of ethanol and povidone-iodine. *MicrobiologyOpen*, *9*(9), e1097. https://doi.org/10.1002/mbo3.1097

Seegräber, M., Worm, M., Werfel, T., Svensson, A., Novak, N., Simon, D., & Wollenberg, A. (2020). Recurrent eczema herpeticum–a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients. *Journal of the European Academy of Dermatology and Venereology*, *34*(5), 1074-1079. https://doi.org/10.1111/jdv.16090

Shafritz, A. B., & Coppage, J. M. (2014). Acute and chronic paronychia of the hand. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons*, *22*(3), 165-174. https://doi.org/10.5435/JAAOS-22-03-165

Silva-Alvarez, A. F., de Carvalho, A. C. W., Benassi-Zanqueta, É., Oliveira, T. Z., Fonseca, D. P., Ferreira, M. P., Vicentini, F. T. M. C., Ueda-Nakamura, T., Pedrazzi, V., & de Freitas, O. (2021). Herpes labialis: A new possibility for topical treatment with well-elucidated drugs. *Journal of Pharmaceutical Sciences*, *110*(10), 3450–3456. https://doi.org/10.1016/j.xphs.2021.06.029

Singh, B. B., Vinjamury, S. P., Der-Martirosian, C., Gandhi, S., Khorsan, R., Nanjegowda, D., Singh, V., & Udani, J. (2005). Safety and effectiveness of an l-lysine, zinc, and herbal-based product on the treatment of facial and circumoral herpes. *Alternative Medicine Review*, *10*(2), 123–127. http://www.anaturalhealingcenter.com/documents/Thorne/articles/herpes10-2.pdf

Spruance, S. L., Stewart, J. C., Rowe, N. H., McKeough, M. B., Wenerstrom, G., & Freeman, D. J. (1990). Treatment of recurrent herpes simplex labialis with oral acyclovir. *Journal of Infectious Diseases*, *161*(2), 185-190. https://doi.org/10.1093/infdis/161.2.185

Spruance, S. L., & McKeough, M. B. (2000). Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet radiation-induced herpes simplex labialis: A pilot study. *Journal of Infectious Diseases, 181*(6), 1906-1910. https://doi.org/10.1086/315528

Stoopler E., & Greenberg M. (2003). Update on herpesvirus infections. *Dental Clinics of North Am*erica, 47(3), 517-532. https://doi.org/10.1016/s0011-8532(03)00018-1

Szczubiałka, K., Pyrć, K., & Nowakowska, M. (2016). In search for effective and definitive treatment of herpes simplex virus type 1 (HSV-1) infections. *RSC advances, 6*(2), 1058-1075. https://doi.org/10.1039/C5RA22896D

Taylor, T. J., Brockman, M. A., McNamee, E. E., & Knipe, D. M. (2002). Herpes simplex virus. *Front Biosci, 7*, d752-d764. https://doi.org/10.2741/taylor

Tyler, K. L. (2004a). Herpes simplex virus infections of the central nervous system: Encephalitis and meningitis, including Mollaret's. *Herpes,* 11(Suppl.2), 57A-64A. https://www.researchgate.net/profile/Kenneth-Tyler-4/publication/8392708_Herpes_simplex_virus_infections_of_the_central_nervous_system_encephalitis_and_meningitis_including_Mollaret's/links/0f317534337fdde9ce000000/Herpes-simplex-virus-infections-of-the-central-nervous-system-encephalitis-and-meningitis-including-Mollarets.pdf

Tyler, K. L. (2004b). Update on herpes simplex encephalitis. *Reviews Neurological Diseases, 1*(4), 169-178. https://www.researchgate.net/profile/Kenneth-Tyler-4/publication/7372076_Update_on_herpes_simplex_encephalitis/links/0f317534337a8ab51a000000/Update-on-herpes-simplex-encephalitis.pdf

U.S. Food and Drug Administration (2019, April 11). *If soap and water are not available, hand sanitizers may be a good alternative*. https://www.fda.gov/consumers/if-soap-and-water-are-not-available-hand-sanitizers-may-be-good-alternative

Utah Department of Public Safety. (2017). Information about Utah's .05 BAC Law. https://highwaysafety.utah.gov/2018/12/11/information-about-utahs-05-bac-law/

Whitley, R. (2006a). Herpes simplex encephalitis: Adolescents and adults. *Antiviral Research*, *71*(2-3), 141-148. https://doi.org/10.1016/j.antiviral.2006.04.002

Whitley, R. (2006b). New approaches to the therapy of HSV infections. *Herpes: the journal of the IHMF*, *13*(2), 53-55

Whitley, R. J., & Roizman, B. (2001). Herpes simplex virus infections. *The Lancet*, *357*(9267), 1513-1518. https://doi.org/10.1016/S0140-6736(00)04638-9

Wollenberg, A., Zoch, C., Wetzel, S., Plewig, G., & Przybilla, B. (2003a). Predisposing factors and clinical features of eczema herpeticum: A retrospective analysis of 100 cases. *Journal of the American Academy of Dermatology*, *49*(2), 198-205. https://doi.org/10.1067/S0190-9622(03)00896-X

Wollenberg, A., Wetzel, S., Burgdorf, W. H., & Haas, J. (2003b). Viral infections in atopic dermatitis: Pathogenic aspects and clinical management. *Journal of Allergy and Clinical Immunology*, *112*(4), 667-674. https://doi.org/10.1016/j.jaci.2003.07.001

World Health Organization (2009). *WHO guideline on hand hygiene in health care*. https://apps.who.int/iris/bitstream/handle/10665/44102/9789241597906_eng.pdf

Xiao, A, & Tsuchiya, A. (2021, August 12). Eczema herpeticum. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK560781/

Young, T. B., Rimm, E. B., & D'alessio, D. J. (1988). Cross-sectional study of recurrent herpes labialis: Prevalence and risk factors. *American Journal of Epidemiology, 127*(3), 612-625. https://doi.org/10.1093/oxfordjournals.aje.a114837

Ziyaeyan, M., Alborzi, A., Haghighi, A. B., Jamalidoust, M., Moeini, M., & Pourabbas, B. (2011). Diagnosis and quantitative detection of HSV DNA in samples from patients with suspected herpes simplex encephalitis. *The Brazilian Journal of Infectious Diseases, 15*(3), 211-214. https://doi.org/10.1016/S1413-8670(11)70177-5

Appendix A

Participant Instructions for Cold Sore Research Study

Thank you for participating in this research study. Cold sores are a highly contagious virus. These infections can be painful, unsightly, and can last over two weeks. Many different components can contribute to a cold sore outbreak such as: injury or trauma to the lip, sunlight, and stress (Mahoney, 2014). Cold sores can be spread by touching the infected area and self-inoculating or by spreading the virus to others through direct contact. Finding an agent to disrupt or kill the virus has been difficult. More research is needed to find a fast-acting medication to help shorten the stages of the outbreak. By participating in this study, you are helping with this research.

After the research assistant has qualified you to participate, you will be randomly selected to receive either the medication being tested or a substance that has no known therapeutic value. It is very important for you to understand that by agreeing to participate in this study you will need to measure the lesion daily, apply the product for 20 seconds every hour (waking hour) for the first 4 days, and return to the clinic when the lesion is no longer visible to return the packet and a final photo.

Directions: Carry the lip balm with you each day. Apply one drop to the lesion and hold it there with the tube for 20 seconds. Repeat every hour (except at night). After each application, allow time to dry and avoid contact with the lesion. Please refrain from picking the scab of the lesion. Continue to apply hourly for 4 days. For your daily journal and documentation please:

- Measure the size of the lesion
- Record your pain level on the pain scale when applying the medicament
- Record your daily discomfort level on the discomfort scale
- Document how diligent you were at applying the medication
- Note any changes or symptoms you are feeling (increase or decrease in itching, swelling, throbbing etc.) or anything else you want to add

***If the lesion is no longer visible, please call the clinic or research assistant. You will need to return the packet and come in for the final examination photo.

***On the top of the lip balm there is a letter. Please write the letter on the last page in the journal.**

****Contact**: Your clinic or Mandy Gibbs for any questions or problems that arise.

Lead Researcher Mandy Gibbs: (801)450-3509

Reference: Mahoney, J. (2014). Cold sores. In B. C. Auday, M. A., Buratovich, G.F, Marrocco, & P. Moglia (Eds.), *Magill's medical guide* (7th ed., Vol. 2). Salem Press.

Appendix B

Participant Information

Name_____

Cell Phone_____ Home Phone_____

Email_____

Age_____ Gender_____

Are you pregnant? _____

Do you have any immune complications? _____

Have you taken any antiviral medication within the last two weeks? ____

Have you used any creams or put any medicine on the cold sore? ____

When was the first cold sore symptom? _____

Appendix C

Journal

Day 1

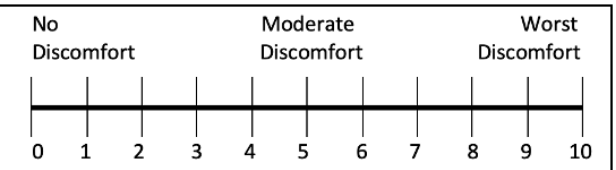
Lesion Size: _____

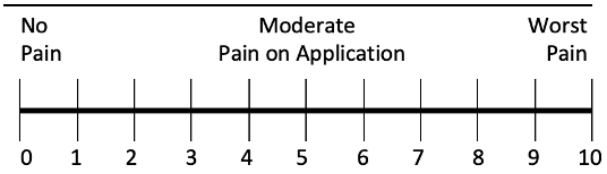
How many applications did you apply today?

_____

Notes: _____

_____





Day 2

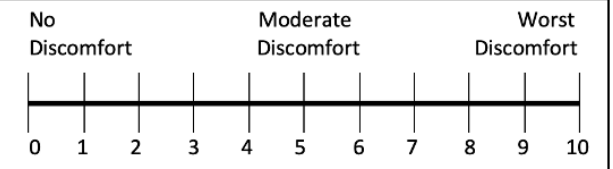
Lesion Size: _____

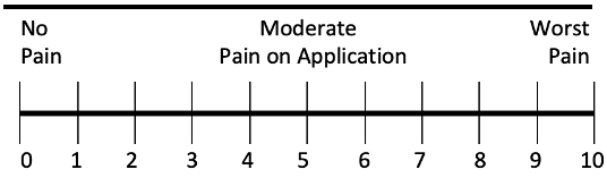
How many applications did you apply today?

_____

Notes: _____

_____





Day 3

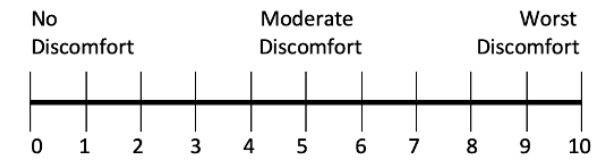
Lesion Size: _____

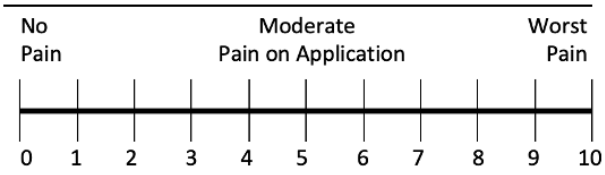
How many applications did you apply today?

_____

Notes: _____

_____





Day 4

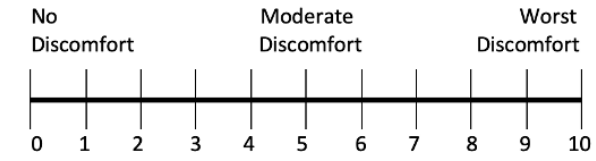
Lesion Size: _____

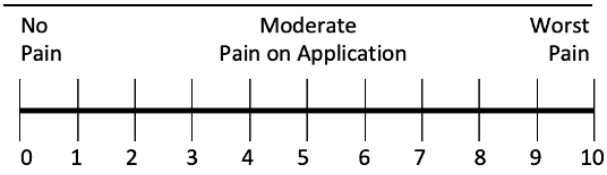
How many applications did you apply today?

_____

Notes: _____

_____





Day 5

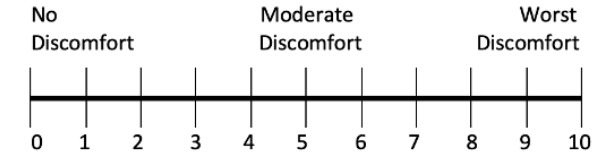
Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____

_____



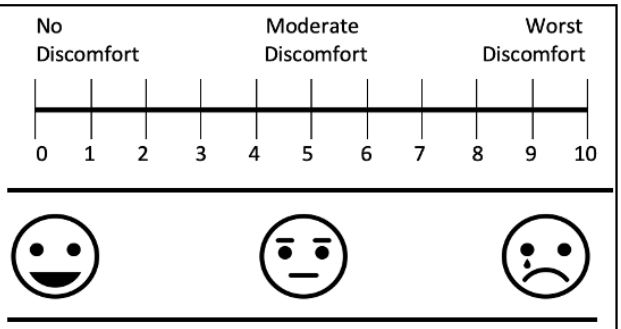
Day 6

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



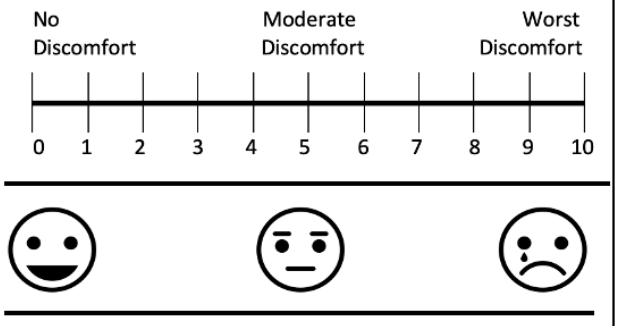
Day 7

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



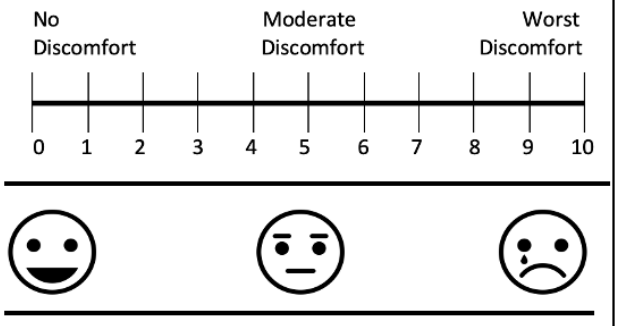
Day 8

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



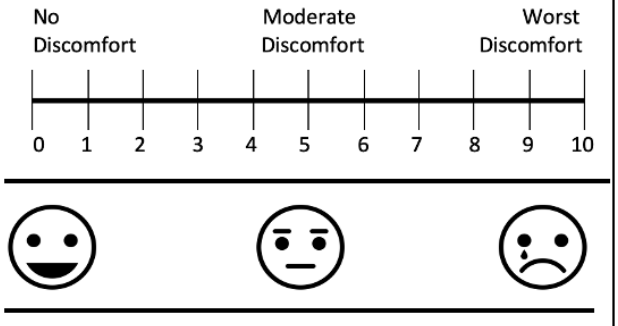
Day 9

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



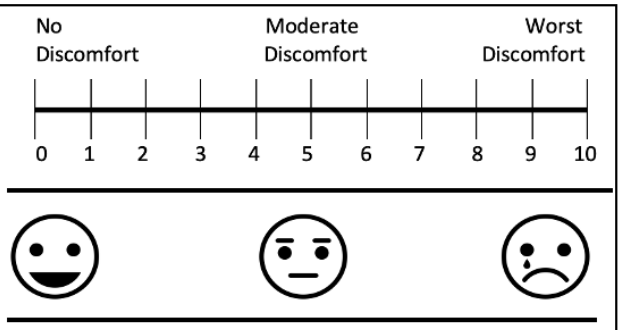
Day 10

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



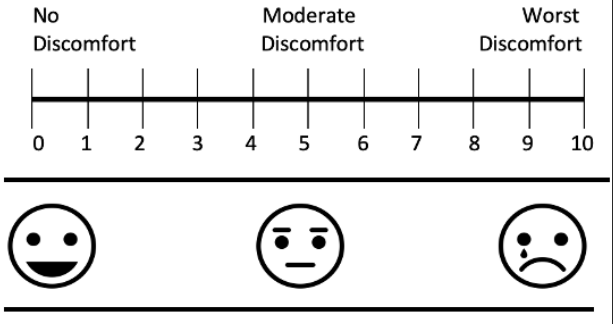
Day 11

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



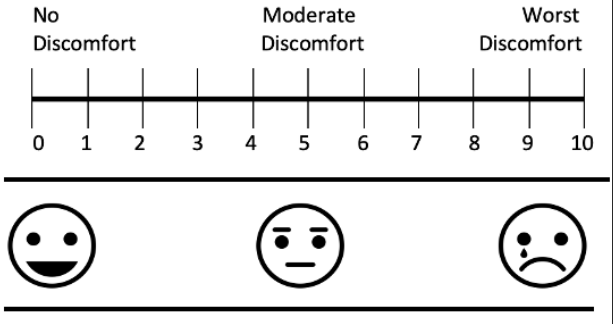
Day 12

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



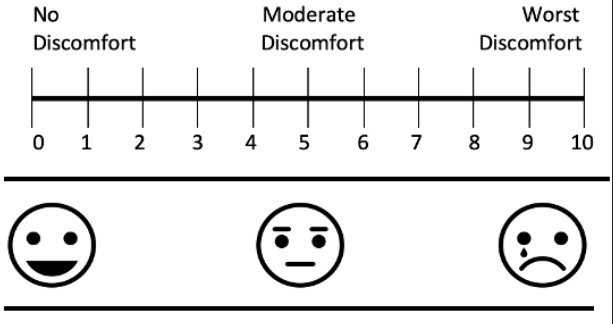
Day 13

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



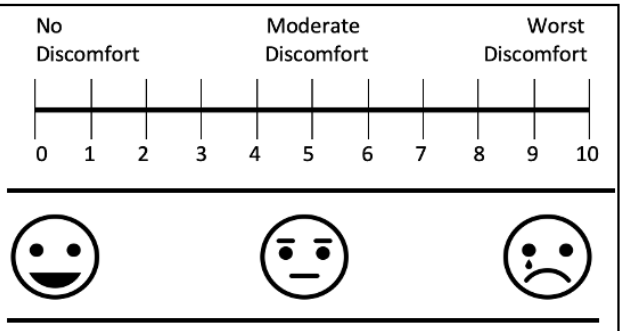
Day 14

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



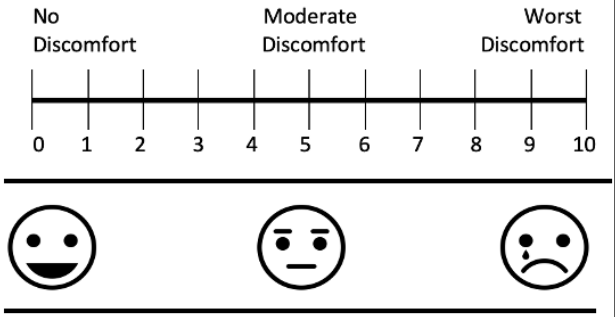
Day 15

Lesion Size: _____

No need to apply any product today. Return to the clinic as soon as the lesion is not visible.

Notes: _____

_____



Congratulations!! You have completed the study! This study will provide valuable information for those individuals suffering from recurrent HSV-1 outbreaks. Thank you for your participation and completing this till the end. Please return this journal to the clinic.

Lip Balm Letter_____

Appendix D

Human Subjects Informed Consent Form

Idaho State University Department of Dental Hygiene

Herpes Simplex Virus-1: A Pilot Study

Amanda Gibbs, RDH, BSDH, MSDH (c)

What is the Research?

You have been asked to participate in a study that is researching a new treatment for Herpes simplex virus-1 (HSV-1), more commonly known as a cold sore. The Human Subjects Committee at Idaho State University has approved this research project. With your participation we will have a better understanding of how cold sores respond to a new treatment.

Procedures

If you agree to participate in this study, you agree to the following procedures:

- Upon agreeing to participate, an informed consent document will be signed and returned to the investigator, and you will receive a copy.
- After the researcher has qualified you to participate, you will be randomly selected to receive either the medication being tested or a substance that does not have any known therapeutic value.
- Keep a daily journal.
- Return to the clinic two times for records and pictures, and to receive or drop off the journal.
- Carry the lip balm with you each day. Administer one drop to the lesion and then hold the tube on the lesion for 20 seconds. Repeat every hour (except at night). After each application, allow time to dry and avoid contact with the lesion. Refrain from picking the scab. Continue to apply hourly for 4 days.
- Measure the size of the lesion with the millimeter ruler you received.
- Record your pain level on the pain scale (after applying treatment).
- Record your discomfort level on the discomfort scale (overall discomfort for the day-not in relation to the application).
- Document how diligent you were at applying the medicament.
- Note any changes or symptoms you are feeling (increase or decrease in itching, swelling, throbbing etc.) or any additional information you would like to add.
- If the lesion has healed (meaning the crust has fallen off) and there is no visible sign of lesion, please call the clinic and return for the final examination and photo.
- A copy of the results of the pilot study will be sent to participants upon request. Data will be reported in group format with no personal identifiers.
- On the lid of the lip balm there is a letter. Please write the letter on the last journal page.

Voluntary Participation

This study is voluntary—you do not have to take part if you do not want to. You may leave the pilot study at any time and for any reason. Participation in this study will not affect any dental hygiene treatment provided at the clinic.

Risks and Benefits

There is a risk you may be in the control group and receive a substance that has no known therapeutic value. This is a very important part of the pilot study as it allows a comparison to the "normal" stages and time frames when no treatment is given. You may receive the treatment, there might be a risk of having a minor reaction to the treatment, such as dryness around the application site. If you are experiencing any adverse reaction, you will be instructed to stop the study immediately and seek medical care. Please avoid ingesting any amount of the content in the tube, as this is not for ingestion purposes. Possible side effects could include diarrhea if large amounts are ingested. Please alert the principal investigator immediately if you are experiencing the above side effect.

There are no personal benefits for taking part in this research. However, the information gained from this study may help researchers learn more about a treatment modality that may shorten the duration, size, pain, and discomfort of HSV-1 lesions.

Privacy and Confidentiality

To protect your confidentiality, all personal identifiers will be destroyed once data is collected from the daily journal. Data collected from this study will be uploaded into Box which is a HIPPA certified electronic storage tool at Idaho State University. Box is password protected and has firewall protection. Only the principal investigator and co investigators will have access to the data collected from the study. The data will be stored and secured in Box for seven years, at that point all material of the study will be destroyed by Idaho State University following university protocol.

Gift Card Drawing

All participants who complete the study will have the choice to be entered into a random drawing for a $50 Amazon gift card. If you choose to do this your phone number will be put in a container and one phone number will be randomly selected to receive the gift card. The winning participant will be notified via text.

Questions

If you have any additional questions about the study, you may contact the primary investigator.

Investigator

Mandy Gibbs, RDH, BSDH, MSDH (c)
(801)450-3509

amandagibbs@isu.edu

Faculty Thesis Co-Chairpersons

Leciel Bono, RDH-ER, MS
Graduate Program Director
Idaho State University
Mail Stop 8048
Pocatello, ID 83209
Email: bonoleci@isu.edu
Phone: (208) 242-8158

JoAnn R. Gurenlian, RDH, PhD
Dental Hygiene Professor
Idaho State University
Mail Stop 8048
Pocatello, ID 83209
Email: gurejoan@isu.edu
Phone: (208)-240-1443

I have read the information in the consent form. I have been given an opportunity to ask questions, and any questions I had have been answered to my satisfaction. I have been given a copy of the informed consent.
I give my consent for the results of the pilot study to be published or discussed using my photos and journal. No information will be included that will reveal my identity.
I HAVE REVIEWED THIS CONSENT FORM AND UNDERSTAND AND AGREE TO ITS CONTENTS.

Printed Name	Signature	Date

Appendix E

Social Media Recruitment

Join us for an innovative research study for a new cold sore treatment. To participate in this exciting new study, contact us immediately if you experience a cold sore between the months of May 2022-October 2023. The trial is for early-stage cold sores (<24hours) so act fast! If you know someone who is prone to cold sore outbreaks, please let them know about this study.

Please contact: Mandy Gibbs, RDH, BSDH (801-450-3509)

Manuscript

Cover Letter

Herpes Simplex Virus-1: A Pilot Study Using Hand Sanitizer

Date

Catherine K. Draper, RDH, MS, FADHA
Managing Editor
Journal of Dental Hygiene
cathyd@adha.net

Dear Ms. Draper,

On behalf of my coauthors, Leciel Bono and Dr. JoAnn Gurenlian, I am submitting this manuscript entitled “Herpes Simplex Virus-1: A Pilot Study Using Hand Sanitizer” for consideration in the *Journal of Dental Hygiene*. This paper represents original research conducted through Idaho State University.

As part of this study, I served as the Principal Investigator, and Ms. Bono and Dr. Gurenlian were co-investigators and thesis advisors. We collaborated on the study design, I was responsible for data collection, and we collaborated on data analysis and manuscript preparation. We each approved of the final submission of the manuscript to this journal.

This study received IRB approval from the Human Subjects Committee at Idaho State University (FY2022-172) and relates to the National Dental Hygiene Research Agenda priority area, **Client level: Oral health care** (new therapies and prevention modalities). Further, the study has been registered in ClinicalTrials.gov. Identifier is NCT06135844. Lastly, the Consolidation Standards for Reporting Trials an Extension to Pilot or Feasibility Trials (CONSORT) checklist was used as a guide for designing and reporting the results of this research study.

We hope that you consider this paper appropriate for review.

Sincerely,

Amanda Gibbs, RDH, MS

Publishable Manuscript

Title Page

Herpes Simplex Virus-1: A Pilot Study Using Hand Sanitizer

Authors:
Amanda, L, Gibbs, RDH, MS
Clinical Instructor, Utah Tech University
email: amandagibbs@isu.edu

Leciel Bono, RDH-ER, MS, Ed.D(c), FADHA
Associate Professor, Graduate Program Director and Interim Department Chair of the Dental Hygiene Department at Idaho State University
email: lecielbono@isu.edu

JoAnn Gurenlian, RDH, MS, PhD, AAFAAOM, FADHA
Director of Education and Research, American Dental Hygienists' Association
Professor Emerita, Department of Dental Hygiene, Idaho State University
email: joanngurenlian@isu.edu

Address correspondence to:

Leciel Bono, RDH-ER, MS, Ed.D(c), FADHA
Associate Professor, Graduate Program Director and Interim Department Chair of the Dental Hygiene Department at Idaho State University
email: lecielbono@isu.edu

Conflict of interest declaration. The authors have no conflicts to declare.

IRB: FY2022-172

NDHRA priority area: **Client level: Oral health care** (new therapies and prevention modalities).

Abstract.

Purpose: Herpes Simplex Virus type 1 (HSV-1) is a highly contagious virus that manifests as a painful lesion and recurrences can be distressing to patients. The purpose of this pilot study was to determine if the use of a 70% ethanol alcohol hand sanitizer alters the duration, size of the lesion, level of pain upon administering treatment, and overall daily discomfort during outbreak.

Method: This study was a double-blind randomized controlled trial (RCT) using 70% ethanol alcohol hand sanitizer for the experiment and medical grade mineral oil for the control group. The treatment and the control were dispensed in lip gloss applicators for applying medicament. Data was collected through the initial examination, a daily journal, photographs, and a re-examination day. Descriptive statistics and the independent sample *t*-test were used to analyze data (p=0.05).

Results: A total of 20 individuals completed the research study: 10 in the experimental group and 10 in the control group. The mean duration of HSV-1 lesions for the control group was 10.3 days while the mean duration of the HSV-1 lesions for the experimental group was 7.6 days. The mean size of lesions for the control group was 4.87mm; the mean size for the experimental group was 4.25mm. The mean pain score for the control group was 1.08 and the mean pain score for the experimental group was 2.74. The mean discomfort score for the control group was mean was 1.33 while the mean discomfort score for the experimental group was 1.72. There was no statistically significant difference between the experimental and control groups in terms of duration, size of lesions, pain, and discomfort; therefore, the null hypothesis was not rejected.

Conclusion: Additional research is needed to determine if 70% ethanol alcohol is an effective agent in the treatment of HSV-1.

Keywords. Herpes simplex virus, HSV-1, duration, size, level of pain, and discomfort

NDHRA Statement. This study supported the NDHRA priority area, **Client level: Oral health care** (new therapies and prevention modalities).

Introduction:

Herpes Simplex Virus-1 (HSV-1), more commonly known as a cold sore or a fever blister, is a highly contagious virus. An estimated 40-80% of adults and children in the United States have had at least one HSV-1 infection.[1] Many different components can contribute to HSV-1 such as injury or trauma to the lip, sunlight, and stress.[1] HSV-1 can be spread by touching the infected area and self-inoculating or by spreading the virus to others through direct contact.[1] This highly contagious virus manifests as an orofacial lesion that begins as an erythematous base of papules, progresses to vesicles within hours of initial appearance (considered the most contagious stage), and then ends in ulcerated crusts.[2] HSV-1 is also associated with epithelial and stromal keratitis, encephalitis, eczema herpeticum, herpetic whitlow, and has detrimental effects on immunocompromised individuals.[3-6]

The HSV-1 is considered a large virus (150-200nm diameter), belongs to the Herpesviridae family, and is an enveloped double-stranded DNA virus.[6-8] Multiple stages occur during the HSV-1 infection process.[8] The stages begin with viral entry, viral gene expression, viral DNA synthesis, and reproduction of infected host cells or assembly of progeny virion. With the viral DNA entering the nucleus, viral gene transcription begins. HSV-1 establishes a latent infection in the host often lasting a lifetime. Many viral infections constantly replicate, however during HSV-1's latent stage, no viral progeny (or very little) is produced.[8] The latency site is located in the sensory neurons in ganglion tissue.[8,9]

Although HSV-1 is found to be most contagious in the vesicle stage, further research has found asymptomatic shedding (HSV present without the presence of a lesion) leading to increased transmission period.[10,11] In a study by Ramchandani et al[10] eight immunocompetent participants with a history of symptomatic HSV-1 lesions underwent examinations five times a week for a total of five weeks. During this examination, samples were taken from 12 different orofacial sites (gingiva, left nares, right nares, pharynx, tongue, left palate, right palate, left upper lip, right upper lip, left lower lip and right lower lip). With a total of 2,626 swabs collected

(about 334 swabs per person), asymptomatic shedding was found on 27.1% of the days. Symptomatic shedding (HSV-1 lesion present) was found on four of eleven days or 36.4%.[10] With transmission rate at its highest when the HSV-1 lesion is present, it is important to find a treatment that will decrease the duration of the outbreak.

HSV-1 has been difficult to treat. Currently there is no cure available, and the virus is building resistance to antiviral medications.[11] Treatments for HSV-1 lesions may be administered through oral medication, topical cream or gel, a patch that adheres to the lesion, photodynamic therapy, amino acid, local anesthetic, or laser therapy.[12-15] Some treatments are over-the-counter while others need a prescription or are an in-office therapy.

There are several variables to consider when determining the best treatment route for HSV-1 lesions such as whether the lesion is primary or recurrent, what the patient's preference is, or whether the patient is immunodeficient.[16] Primary HSV-1 lesions are most commonly treated with oral antiviral medications whereas recurrent HSV-1 lesions are treated with topical antivirals in conjunction with oral antivirals.[16-18] The HSV-1 recurrent infection is usually mild, but the illness can be uncomfortable and disfiguring, leaving a psychological impact that should not be underestimated especially among young patients with multiple recurrences.[19]

A recent prospective, controlled, randomized assessor-blind trial study by Boes et al[12] compared three products (acyclovir cream 5%, acyclovir 5% patch, and a denatured alcohol and zinc serum) with healing time, reaction rate, reaction quality, and a patient questionnaire when used for the treatment of HSV-1 lesions. Testing 180 participants, the denatured alcohol-zinc serum demonstrated the highest measurements for all three of these features; however, this serum also showed the most intolerances such as dried lips and redness on the participant questionnaire.[12]

In a randomized, placebo-controlled, double-blind, patient-initiated study by Hull et al[17] an oral medication (valacyclovir) in conjunction with a topical steroid (clobetasol propionate) was compared to an oral and topical placebo. This study demonstrated that aborted lesions

significantly increased while classical lesion, size, and healing time of classical lesions significantly decreased. These results suggested that the combination of valacyclovir and clobetasol propionate is safe and effective for HSV-1 lesions. The authors indicated that this study supports the theory that corticosteroids can be used as a new therapeutic treatment for HSV-1 lesions. The authors also recognized the need for further research for the use of corticosteroids as a treatment option for HSV-1 lesions.[17]

A recent study by Sauerbrei[20], established that an inactivation effect on enveloped viruses (such as the HSV-1) occurred when ethanol alcohol was used at 60%-80%. This type of compound has microbial effects against enveloped and non-enveloped viruses when used as a hand disinfectant.[21] Ethanol alcohol was tested for toxicity levels as it is absorbed through the skin and/or inhalation of the fumes to determine the safety of its use. The findings of this study demonstrated the effectiveness ethanol alcohol has when used as a virucidal agent and demonstrates the safety of its use.[21] This raises the question if ethanol alcohol would have a virucidal effect on an HSV-1 lesion.

Finding a treatment that will minimize the highly contagious stage would help reduce the spread of the virus. One possible option is 70% ethanol alcohol hand sanitizer which has become a popular disinfectant known for its powerful virucidal and bactericidal effects.[22] Ethanol alcohol is the main ingredient in hand sanitizer and in concentrations of 60%-80%, has been shown to kill the HSV-1 virus.[22] More research is needed to determine the efficacy of the use of 70% ethanol alcohol hand sanitizer as an HSV-1 treatment option. Thus, the purpose of this pilot study was to determine if the use of a 70% ethanol alcohol hand sanitizer alters the duration, size of the HSV-1 lesion, level of pain, and discomfort during treatment.

The following research question guided the conduct of this study: Is there a statistically significant difference in the duration, size of the lesion, level of pain, and level of discomfort for individuals in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used a medical grade mineral oil? The null

hypothesis for this study was: There is no statistically significant difference in the duration, size of the lesion, level of pain, and level of discomfort for individuals in the experimental group who used 70% ethanol alcohol hand sanitizer on their lesion versus those in the control group who used a medical grade mineral oil.

Methodology

IRB Approval and Research Design. This double-blind randomized controlled study was approved by the Institutional Review Board (IRB-FY2022-172). This study has been registered in ClinicalTrials.gov. Identifier is: NCT06135844.

Twenty kits were created, one for each participant. Ten lip balm applicators were filled with 70% ethanol alcohol hand sanitizer (experimental group) and the other ten lip balm applicators were filled with medical grade mineral oil (control group). These lip balm applicators provided a “touch-free” application, limiting self-inoculation and spreading. The applicators were free from any labeling except a single letter “A” (70% ethanol alcohol hand sanitizer), or “R” (medical grade mineral oil) located on the lid to ensure participants were blind. Each lip balm was placed in a paper sack along with paper laminated millimeter ruler and a packet of instructions for the participants to follow. The packet gave the participants daily instructions, contained a space for a daily journal, and provided a place to put the assigned letter (R or A).

Sampling. Study participants consisted of a convenience sample of local community members from Southern Utah, Pocatello Idaho, and Long Beach California who were experiencing early stages of an HSV-1 lesion. For the purpose of this study participants needed to be in the early prodromal stage of an HSV-1 outbreak (less than 24 hours from initial symptom), with the visible manifestation of a lesion,18 years or older, capable of following daily treatment instructions, willing to complete a daily journal, willing to come to the assigned clinic for the initial examination and final examination. Exclusion criteria included individuals who were: immunocompromised, pregnant, taking any antiviral medication within the last two weeks,

and using any antiviral creams in the last 10 days. Recruitment for participants was achieved using social media (Facebook and Instagram).

Research Assistant Training. Five individuals completed a training course via Zoom led by the primary investigator. During this course, research assistants were calibrated on how to give instructions to participants and the data collection. The research assistants were a key component in keeping the primary investigator and co-investigators blind. Once trained, research assistants were given multiple experimental and controlled group kits to the qualified participants.

Protocol and Procedure. Participants began treatment as soon as they were approved, the consent form was signed, and the instructions were completed. After approval, participants met with the research assistant for the initial examination. Each participant was randomly assigned to either the experimental or controlled group and given a daily journal for recording data. For participants in the experimental group, research assistants were instructed to administer a fresh container of 70% ethanol alcohol into the lip balm applicator before participants arrived that day. Participants' name, contact information, age, gender, and a photo of the lesion were collected. Every day the participants recorded in their daily journal the lesion size, pain, discomfort, and any notes the participant wanted to add about the lesion or the process (Figure 1). The duration was determined when the crust of the lesion had fallen off and the lesion was fully healed. Once healed, the participant was required to return to the clinic for a concluding photograph taken by the research assistant and return the daily journal.

The size of the lesion was measured daily by the participant using millimeter markings on a laminated ruler provided in the kit. Participants were given instructions on how to measure the lesion using this ruler. Pain and discomfort were measured by the participants daily using a Visual Analog Scale (VAS). The discomfort scale referred to their overall discomfort from the lesion that day, whereas the pain scale was used after the medication was applied to determine if there was any corresponding pain with the medication.

The VAS measurements began with zero meaning no discomfort or pain and ended with ten meaning worst discomfort or pain. The VAS has been widely used to record patient's pain progression and for diverse types of conditions including chronic pain, cancer, and ambulation. This scale was completed by participants who marked on the line the point they feel represents their perception of their current state. The VAS takes less than one minute to complete and is easy to use with minimal training. Values of reliability have been shown to be between r=0.94 - 0.99.[23,24] For construct validity, correlations range from 0.71-0.78 and 0.62 -0.91.[25]

Instructions for application were apply every hour (waking hours) for the first 4 days (about 12 applications a day) or until the lesion is gone. Participants were instructed to continue the journal and discomfort measurements until the healing of the lesion. Once the lesion was healed, participants were instructed to contact the research assistant for a final examination and photo. At the closing of the trial, all photos and documents were charted, analyzed, and compared. The primary endpoint for this study was the duration of an HSV-1 lesion. The secondary endpoint was a measurement for size, pain, and discomfort.

Descriptive statistics and the independent sample *t*-test were used to analyze data from the two groups. Significance was set at p=0.05. The Consolidation Standards for Reporting Trials an Extension to Pilot or Feasibility Trials (CONSORT) checklist was used as a guide for designing and reporting the results of this research study.[26]

Results

A total of 20 individuals completed the research study: 10 in the experimental group and 10 in the control group. One participant in the control group did not report pain level; all other data were reported correctly and were included in the final data analysis. Most participants were female (n=16, 80%) while 4 (20%) were male. The ages of participants ranged from 20-69 with an average age of 40.80 years. The majority (n=9, 45%) of participants were from Utah, 8 (40%) were from Idaho, and 3 (15%) were from California.

Photographs were used to document the initial presentation of the HSV-1 lesion and the resolution of the lesion for each study participant. Figure 2 represents these photos for a participant in the experimental group. Figure 3 provides photos for a participant in the control group. The mean duration of HSV-1 lesions for the control group was 10.3 days while the range of duration was 2 to 24 days. The mean duration of the HSV-1 lesions for the experimental group was 7.6 days with the range of duration from 2-13 days. The independent sample t-test was 1.12 and p-value = 0.28. Therefore, there was no statistically significant difference between the use of 70% ethanol alcohol hand sanitizer and the medical grade mineral oil. The null hypothesis was not rejected.

Size of the HSV-1 lesions were measured by millimeters. The range of size of lesions for the control group was 2 to 8.57mm and the mean size was 4.87mm. The range of size of lesions for the experimental group was 0.5-10.45 mm and the mean size was 4.25mm. The independent sample t-test was 0.48 and p-value =0.63 indicating no statistically significant difference was found between the experimental and control groups. Therefore, the null hypothesis was not rejected.

Pain was measured using the Visual Analog Scale (VAS) upon administration of the medicament. The mean pain score for the control group was 1.08 and the range was 0-4.25. The mean pain score for the experimental group was 2.74 and the range was 0.5-6.5. The independent sample t-test was 1.89 and the p value = 0.77. There was no statistically significant difference between both groups and the null hypothesis was not rejected.

Discomfort of the lesion was measured using the VAS on a daily basis until the lesion was healed. The range of discomfort for the control group was 0.5-2.09 and the mean was 1.33. The range of discomfort for the experimental group was 0-3.77 while the mean was 1.72. The independent sample t-test was 0.89; p=0.38. There was no statistically significant difference between the experimental and control groups; therefore, the null hypothesis was not rejected.

Discussion

Findings of this study revealed three key factors. First, one purpose of a pilot study is to evaluate the feasibility of the protocol and procedures.[26] This study demonstrated that the protocol was appropriate and manageable. Participants were compliant with the application of the products and recorded duration, size, pain, and discomfort using the daily journal. There did not appear to be issues with following the instructions provided even though the study lasted over two weeks and even as long as 20 to 24 days for some participants. The protocol appeared to be safe and no harm to the participants was apparent throughout the study.

The second factor was the statistical result. Because the sample size for the pilot study was small, no statistical significance was noted for any of the variables studied: duration, size, pain, and discomfort. While this result was anticipated, replication of the study with a larger sample size might reveal different findings. It is interesting to note that even with the small sample size, the experimental group showed a shorter healing time. One possible explanation is the antimicrobial effect of the 70% ethanol alcohol hand sanitizer to the HSV-1 lesion.[22]

Further, pain measurement was reportedly more pronounced in the experimental group perhaps associated with the 70% ethanol alcohol content of the hand sanitizer being applied to an ulcerative lesion.[27] Although higher pain was expected due to the alcohol content in the experimental group, a disadvantage of using 70% ethanol alcohol hand sanitizer as a treatment option would be if the pain exceeded compliance. Of the 10 participants in the experimental group, no one experienced severe pain to terminate the study or recorded severe pain on the VAS scale to be significantly different than the control group.

There are limited studies that utilize an alcohol-based product as part of the study protocol. In comparison to this pilot study, Boes et al[12], utilized denatured alcohol and zinc in comparison to an antiviral cream and patch to evaluate HSV-1 healing time, reaction rate and reaction quality. HSV-1 symptoms and features were also tested. Outcomes showed that the denatured alcohol and zinc product had favorable results in terms of reaction rate and quality, lesion protection, esthetics, and relief of discomfort; however, healing time was not statistically

significant compared to the antiviral cream and patch. Additional studies are needed to further evaluate the efficacy of alcohol-based products on HSV-1.

The participants demonstrated a high level of compliance with the study. Researchers have documented psychosocial behaviors that help with patient adherence when treatment protocols are recommended.[28-30] Optimism and hope about treatment outcomes is a key factor in guiding patient adherence because it lends itself to motivation and value of achieving health or treatment goals.[29] Participant adherence in this study may have been influenced by the desire to shorten the duration of the HSV-1 lesion. Many viral lesions in this study were located on the vermillion border of the lip, thus were highly visible. In addition, lesions of this type created discomfort for most participants. Psychological stress and a negative mood about the HSV-1 lesions may have also influenced adherence. A study investigating the relationship of perceived psychological stress, negative mood, and the recurrence of HSV-1 demonstrated that participants who had more frequent outbreaks of HSV-1 were more likely to experience these factors.[31] Although our study did not investigate stress or mood with HSV-1 lesions, this cyclic pattern may have been a contributing factor to patient adherence to the protocol as participants may have been motivated to find a solution to break the cycle.

This study is not without limitations. The primary limitation is the small sample size as results cannot be generalized to the population at large. In addition, the smaller sample size did not permit an evaluation of an estimated effect size. Another limitation of this study is access to early therapy. Whitley[32] stressed the importance of starting treatment early. For this study participants had to meet up with the research assistants, this could have delayed the starting of treatment. Other study methods have been able to send kits home with willing participants who are prone to reoccurring HSV-1 lesions which allowed patient-initiated therapy giving the lesion little time to progress.[17,18,32] Future recommendations include replicating this study with a larger sample size to see if there is a statistical difference between groups and whether the results represent a true result, a false positive result, or a false negative result. Another

recommendation would be to take photographs of the lesion every other day for visual comparison for size and duration of lesions.

Conclusion

HSV-1 continues to be a common contagious virus that affects many persons. Various treatment modalities are used in the management of this virus. A randomized controlled clinical trial was conducted as a pilot study to determine if 70% ethanol alcohol could be beneficial as a treatment modality for HSV-1. Parameter studies included duration, pain, discomfort, and size of the lesion. Participant compliance was high; however, study findings did not show statistical significance between the experimental and control groups. Future studies should include a larger sample size and earlier treatment therapy to determine if statistical differences between groups can be measured and if differences represent a true result.

Disclosures: The authors have no conflicts to declare.

Acknowledgments: The authors wish to acknowledge Kaitlin Liebert, RDH, MS, Camille Biorn, RDH, MS, Peggy Lelesi, RDH, MS, who served as Research Assistants for this study as well as the individuals who served as study participants.

References:

1. Mahoney J. Cold sores. In: Auday BC, Buratovich MA, Marrocco MA, et al. editors. Magill's medical guide. 7th ed. Hackensack (NJ): Salem Press. 2014. p.506-507

2. Richardson VN, Davis SA, Gustafson CJ, et al. Patterns of disease and treatment of cold sores. J Dermatolog Treat. 2013 Dec;24(6):439-443.

3. Farooq AV, Shukla D. Herpes simplex epithelial and stromal keratitis: an epidemiologic update. Surv Ophthalmol. 2012 Sep;57(5):448-62.

4. Greenberg MS. Herpesvirus infections. Dent Clin North Am. 1996 Apr;40(2):359-368.

5. Sarid R, Klepfish A, Schattner A. Virology, pathogenetic mechanisms, and associated diseases of Kaposi sarcoma-associated herpesvirus (human herpesvirus 8). Mayo Clin Proc Digit Health. 2002 Sep;77(9): 941-949.

6. Szczubiałka K, Pyrć K, Nowakowska M. In search for effective and definitive treatment of herpes simplex virus type 1 (HSV-1) infections. RSC Adv. 2016 Jan;6(6):1058-1075.

7. Duarte LF, Farías MA, Álvarez DM et al. Herpes simplex virus type 1 infection of the central nervous system: insights into proposed interrelationships with neurodegenerative disorders. Front Synaptic Neurosci. 2019 Feb;13(46):1-23.

8. Taylor TJ, Brockman MA, McNamee EE, et al. Herpes simplex virus. Front Biosci. 2002 Mar;7(4):752-764.

9. Quinn JP, Dalziel RG, Nash AA. Herpes virus latency in sensory ganglia—a comparison with endogenous neuronal gene expression. Prog Neurobiol. 2000 Feb;60(2):167-179.

10. Ramchandani M, Kong M, Tronstein E et al. Herpes simplex virus type 1 shedding in tears, and nasal and oral mucosa of healthy adults. Sex Transm Dis. 2016 Dec;43(12):756-760.

11. Bergmann M, Beer R, Kofler M et al. Acyclovir resistance in herpes simplex virus type I encephalitis: a case report. J Neurovirol. 2017 Apr;23(2):335-337.

12. Boes H, Goulioumis V, Wechsler A et al. Clinical study on the effectiveness of three products in the treatment of herpes simplex labialis. Sci Rep. 2020 Apr;10(1):1-9.

13. Singh BB, Udani J, Vinjamury SP et al. Safety and effectiveness of an L-lysine, zinc, and herbal-based product on the treatment of facial and circumoral herpes. Altern Med Rev. 2005 Jun;10(2):123-127.

14. Silva-Alvarez AF, de Carvalho AC, Benassi-Zanqueta É et al. Herpes labialis: A new possibility for topical treatment with well-elucidated drugs. J Pharm Sci. 2021 Oct;110(10):3450-3456.

15. Ramalho KM, Cunha SR, Gonçalves F, et al. Photodynamic therapy and acyclovir in the treatment of recurrent herpes labialis: A controlled randomized clinical trial. Photodiagnosis Photodyn Ther. 2021 Mar;33:102093.

16. Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections: an evidence-based review. Arch Intern Med Res. 2008 Jun;168(11):1137-1144.

17. Hull C, McKeough M, Sebastian K et al. Valacyclovir and topical clobetasol gel for the episodic treatment of herpes labialis: a patient-initiated, double-blind, placebo-controlled pilot trial. J Eur Acad Dermatol Venereol. 2009 Mar;23(3):263-267.

18. Spruance SL, McKeough MB. Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet radiation-induced herpes simplex labialis: a pilot study. J Infect Dis. 2000 Jun;181(6):1906-1910.

19. Hobbs MR, Jones BB, Otterud BE et al. Identification of a herpes simplex labialis susceptibility region on human chromosome 21. J Infect Dis. 2008 Feb 1;197(3):340-346.

20. Sauerbrei A. Bactericidal and virucidal activity of ethanol and povidone-iodine. MicrobiologyOpen. 2020 Sep;9(9):1-27.

21. German Association for Applied Hygiene (VAH). As a biocidal active substance, ethanol is indispensable for hygienic hand disinfection (2020). [Internet]. Bonn: Institut für Hygiene und Öffentliche Gesundheit der Universität Bonn. [cited 2023 Nov 8]. Available from: https://vah-online.de/files/download/vah-mitteilungen/VAH_Ethanol_biocide_29Oct2020_2.pdf

22. Centers for Disease Control and Prevention. Chemical disinfectants: Guideline for disinfection and sterilization in healthcare facilities (2008). [Internet]. Atlanta: Centers for Disease Control and Prevention. [cited 2023 Nov 8]. Available from: https://www.cdc.gov/infectioncontrol/guidelines/disinfection/disinfection-methods/chemical.html

23. Ferraz MG, Quaresma MR, Aquino LR, et al. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol. 1990 Aug; 17(8):1022-1024.

24. Gallagher EJ, Bijur PE, Latimer C, et al. Reliability and validity of a visual analog scale for acute abdominal pain in the ED. Am J Emerg Med. 2002 Jul; 20(4): 287-290.

25. Downie WW, Leatham PA, Rhind VM, et al. Studies with pain rating scales. Ann Rheum Dis. 1978 Aug; 37(4):378-381.

26. Lancaster GA, Thabane L. Guidelines for reporting non-randomized pilot and feasibility studies. Pilot Feasibility Stud. 2019 Dec;5(1):1-6.

27. Slotosch CM, Kampf G, Löffler H. Effects of disinfectants and detergents on skin irritation. Dermatitis. 2007 Oct;57(4):235-241.

28. Carver CS, Scheier, MF, Segerstrom, SC. Optimism. Clin Psychol Rev. 2010 Nov;30(7):879-889.

29. Carver CS, Scheier MF. On the Self-Regulation of Behavior. Camb.: Cambridge University Press; 1998. Oct 28.

30. Nsamenang SA, Hirsch JK. Positive psychological determinants of treatment adherence among primary care patients. Prim Health Care Res Dev. 2015 Jul;16(4):398-406.

31. Faulkner S, Smith A. A prospective diary study of the role of psychological stress and negative mood in the recurrence of herpes simplex virus (HSV1). Stress Health. 2009 Apr;25(2):179-87.

32. Whitley R. New approaches to the therapy of HSV infections. Herpes. 2006 Aug 1;13(2):53-55.

Figure 1: Daily Participant Journal with Visual Analog Scale

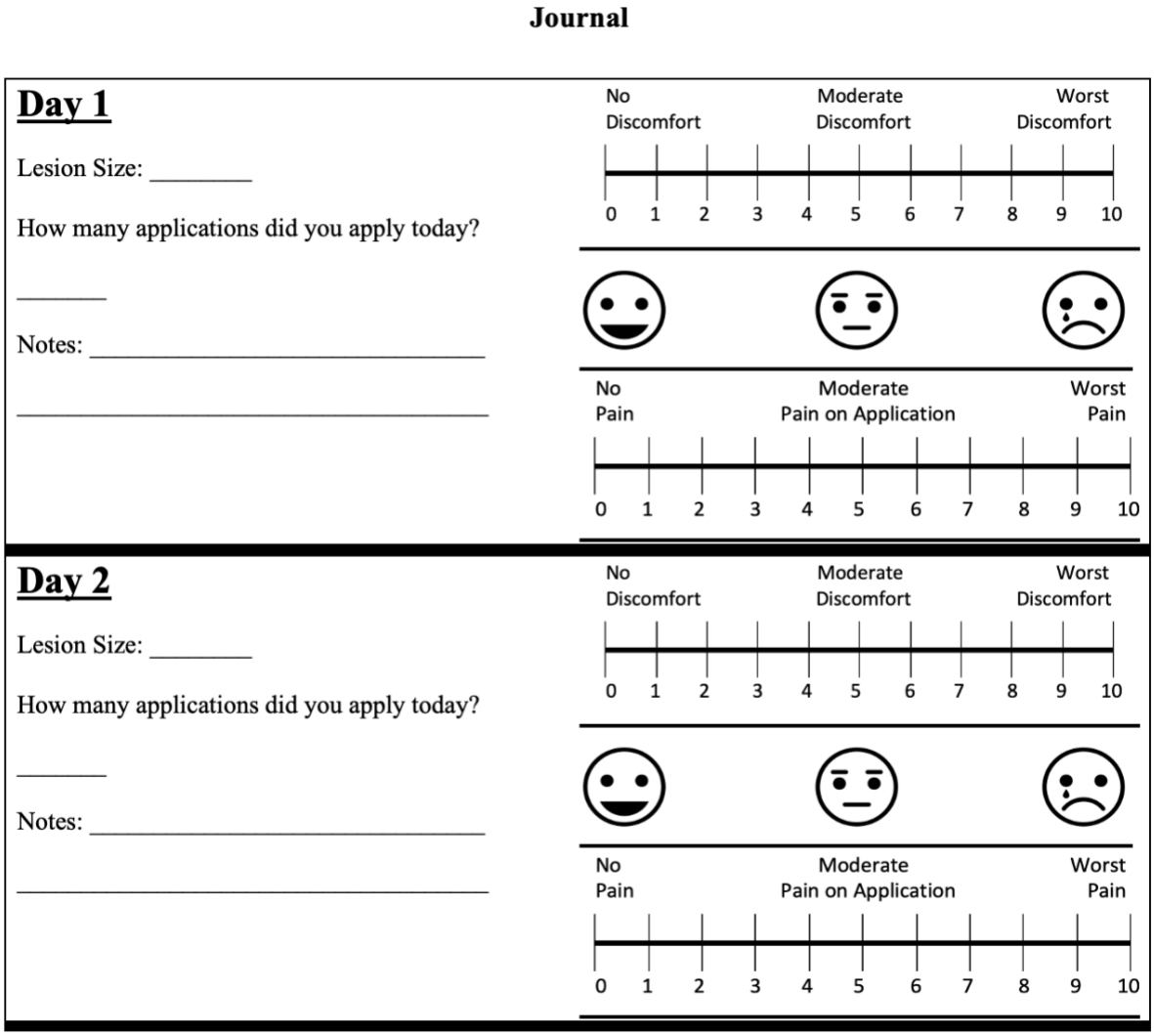


Figure 2: Initial and Final Photos of Participant in Experimental Group

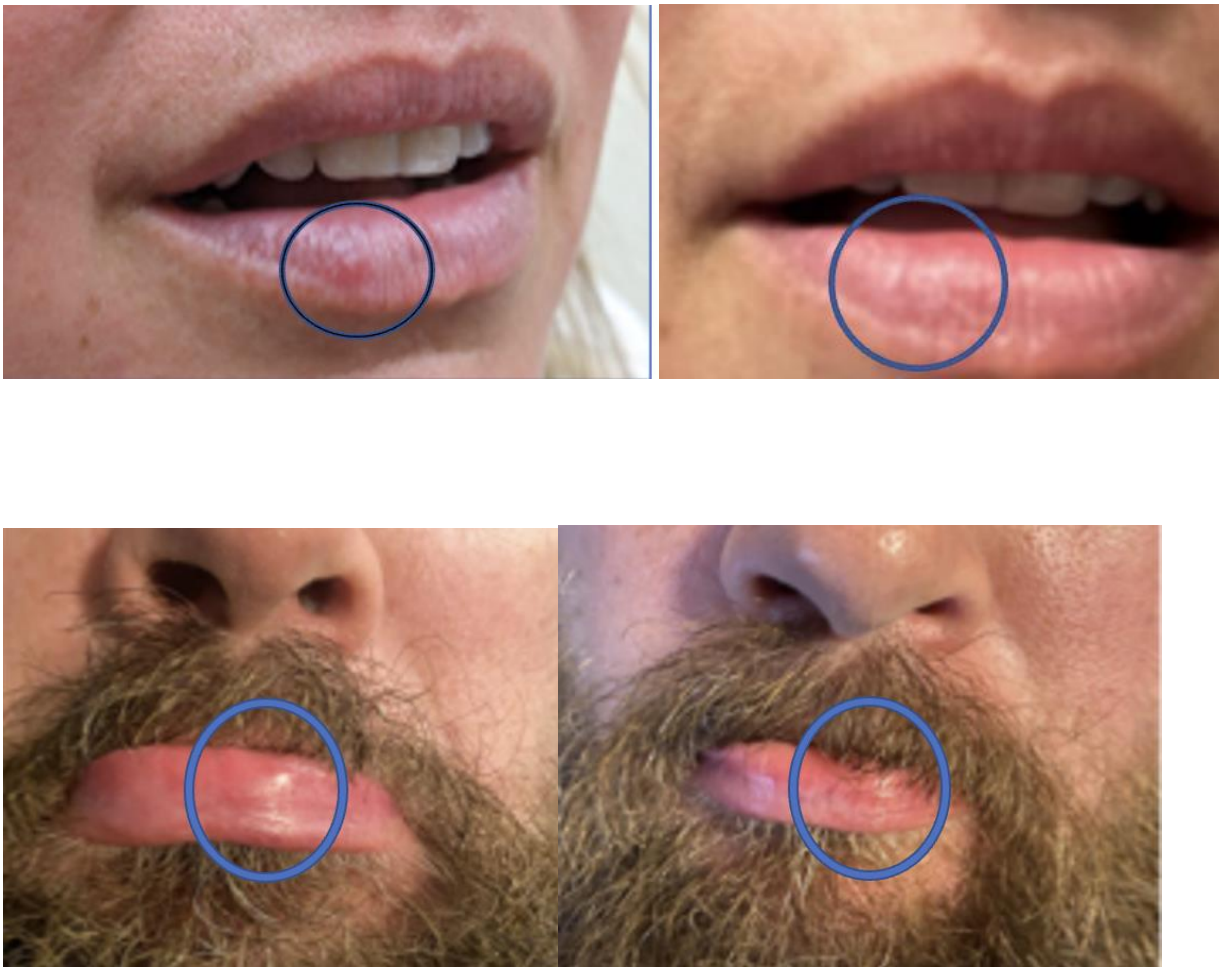


Figure 3: Initial and Final Photos of Participant in Control Group