USE OF TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS TO REDUCE PAIN IN ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS

Ishraq Alshanqiti

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Committee:

Stuart Taylor

Michael Martin

Douglas Ramsay

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Abstract

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Ishraq Alshanqiti

Chair of the supervisory committee:

Dr. Stuart Taylor

Oral Medicine

Background: Lichen Planus (LP) is a chronic inflammatory disorder demonstrating some immune pathology. It is a cell-mediated immune condition of an unknown etiology. Oral Lichenoid Lesions (OLL) have been viewed both as a separate condition from OLP and as a variation of OLP. Available treatments for OLP are not curative and many of them have potentially significant side effects. Although topical Steroids are considered the first line of treatment, recent systematic review found that there was no evidence shows that one steroid is more effective than another.

Objective: The aim of this study was to conduct a crossover clinical trial to examine the efficacy of a topical non-steroidal anti-inflammatory agent (ibuprofen) over placebo in reducing pain in patients with Oral Lichen planus (OLP) and Oral Lichenoid Lesions (OLL).

Methods: A four-week randomized, double blind, cross-over, placebo-controlled trial was planned. Potential participants who had symptomatic forms of OLP and OLL with pain levels equal to or greater than 3 out 10 on a 10cm Visual Analog Scale (VAS) were screened through the Oral Medicine patient registry at the University of Washington. Based on a coin toss, Placebo (drug A) was chosen for the first block of two participants. At first visits the participants received two bottles; each bottle had an individual label marked either “A” or “B” for active medication and placebo respectively. The coding which identified the contents of A and B was sealed by the pharmacy and was kept with one of the committee members as well as with the pharmacy. One of

the bottles contained the suspension of the topical NSAID (100 mg per 5 ml concentration of ibuprofen). Another placebo suspension was also compounded with the same taste but without the active ingredient. The participants were asked to record their baseline score of spontaneous pain on a horizontal 10 cm VAS before commencing the use of the provided rinses. Subjects were asked to record their pain level also at day 4 and day 7. All participants were instructed to use the first suspension four times a day for 7 days. The primary study endpoint was the change in pain severity score from Baseline to day 4 and day7.

Results: At baseline, the participants using the bottle B first (active drug) reported a mean score of 50.8 ± 16.6 on the VAS. Those who used the bottle A (Placebo arm) first reported a mean VAS score of 55.9 ± 19.23. A t-test comparing mean scores showed that the mean pain level at baseline for both groups was not significantly different (P=.144). VAS scores for the placebo drug decreased by a mean of 6.4mm from baseline to the end of the drug use (49.3mm to 42.9mm). For the active drug, the VAS scored decreased by 12.3mm (56.3mm to 44.0mm). A paired samples t-test showed near significance (P=0.096) was observed for the active medication (bottle B) between days 0 and 7. A linear regression showed that the percent change from days 0 to 7 for the active medication group was near-significant (p=.108), even when controlling for both order and the baseline VAS score.

Conclusion: Our results tend to support the validity of an approach to the treatment of inflammatory conditions of the oral cavity, based on using topical NSAIDs

According to the findings of the present study, topical NSAIDs may help to reduce pain caused by OLP and OLLs.

Acknowledgement

I would like to sincerely thank my research committee members, Dr. Taylor, Dr. Martin, and Dr. Ramsay, for their patience and support as I overcame the numerous challenges I faced throughout my research.

I would like to dedicate this work to my family—to my father, who has always believed in me and my potentials; to my mother, who is my best friend and my backbone; she taught me how to be the best version of myself; to my husband, who has always made me feel safe and loved and has inspired me to reach my full goals; to my children, Tamim and Talah, who had no idea why they had to move to a different country, learn a different language, and leave everything behind and yet were resilient throughout their adjustment process and have learned to love their new place. Sorry, Tamim and Talah, for not being around all the time, and yet you have supported and loved your mom no matter what.

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INTRODUCTION

Lichen planus (LP) is a mucocutaneous disorder in which oral involvement may precede the appearance of other symptoms or lesions at other locations. The etiology of LP is not known clearly, but at present, it is linked to autoimmune dysregulation.

Oral lichen planus (OLP) is a common chronic autoimmune disease associated with cell-mediated immunological dysfunction. Symptomatic OLP is painful, and its complete healing is rare. Current treatments for LP and lichenoid mucositis are usually directed toward reducing their symptoms (Thongprasom, Carrozzo et al. 2011).

Patients' lives can be severely affected by the pain caused by OLP. Because of its unclear etiology, treatment is usually symptomatic. The principal goals of current OLP therapy are the resolution of painful symptoms, resolution of oral mucosal lesions, reduction in the risk of oral cancer, and maintenance of good oral hygiene. Several topical drugs have been suggested to treat this condition, including steroids, calcineurin inhibitors, retinoids, and ultraviolet light phototherapy. Although topical steroids are the mainstay of current management strategies, there use is limited because possible adverse reactions that include secondary candidiasis, nausea, refractory response, mucosal atrophy, delayed healing, and systemic absorption. Some of these side effects can affect a patient's quality of life significantly (Savage and McCullough 2005).

Numerous possible therapeutic strategies have been recommended in OLP cases that are refractory to steroids. The miscellaneous treatment regimens include tacrolimus, pimecrolimus, thalidomide, low-level laser therapy, photodynamic therapy, and surgical excision. However, weak evidence supports the effectiveness of any of these modalities (Yang, Wu et al. 2016).

The proposed clinical trial will assess the effectiveness of topical non-steroidal anti-inflammatory drugs (NSAIDs) compared with the placebo for patients with OLP and oral lichenoid mucositis.

BACKGROUND AND SIGNIFICANCE

1. Lichen planus (LP)

1.1 Oral lichen planus (OLP) and its diagnosis

The term "lichen planus" (LP) is derived from the Greek word "leichen," meaning tree moss, and the Latin word "planus," meaning flat. In 1869, Wilson first described the condition of LP as a chronic disease affecting the skin, scalp, nails, and mucosa, with a possible rare malignant transformation (Farhi and Dupin 2010).

LP is a chronic inflammatory disorder demonstrating some immune pathology. It is a cell-mediated immune condition of an unknown etiology, in which T lymphocytes accumulate beneath the epithelium of the oral mucosa and increase the rate of differentiation of stratified squamous epithelium, resulting in hyperkeratosis and erythema with or without ulceration.

The prevalence of OLP has been reported as 1.27 % and is greater in women aged 30 to 60 years (McCartan and Healy 2008).

Whereas in the majority of instances, cutaneous lesions of LP are self-limiting and cause itching, oral lesions in OLP are chronic, rarely undergo spontaneous remission, are potentially

premalignant,(Fitzpatrick, Hirsch et al. 2014) and are often a source of morbidity. Furthermore, the symptoms of oral lesions, unlike those of cutaneous lesions, are difficult to manage palliatively (Eisen, Carrozzo et al. 2005).

OLP usually has recognizable and distinctive clinical features and a characteristic distribution. It may manifest in one of the following clinical forms: reticular, erythematous (atrophic), and erosive (ulcerated, bullous). Whereas reticular lesions occur as isolated lesions and are often the only clinical manifestation of the disease, erythematous lesions are accompanied by reticular lesions, whereas erosive lesions are accompanied by reticular and erythematous lesions in almost all cases (Scully, Eisen et al. 2000).

1.1.1 Histological presentation

LP is studied microscopically by routine hematoxylin and eosin (H & E) staining and direct immunofluorescence study (DIF). Under H & E staining, OLP presents with hyperkeratotic, thin, irregular saw tooth-like or normal stratified squamous epithelium with liquefactive degeneration of the basal cell layer. The lamina propria (the area in the connective tissue directly under the epithelium) characteristically contains a band of inflammatory cells chiefly made up of lymphocytes arranged in a linear fashion. Civatte bodies usually present in the lamina propria and juxtaepithelial area. Eosinophils seldom appear in the sub-epithelial infiltrate. Other characteristics of OLP include increased numbers of granulated mast cells in areas of basement membrane degeneration, increased periodic acid–Schiff (PAS), positive basement membrane thickness, and a well-mixed sub-epithelial infiltrate containing lymphocytes arranged in a linear fashion in the lamina propria (connective tissue adjacent to the epithelium). Connective tissues increase vascularity (Scully and Carrozzo 2008, Mravak-Stipetic, Loncar-Brzak et al. 2014).

DIF is the best method that oral pathologists have been using for the confirmation of OLP. DIF shows a linear pattern of fibrin and shaggy fibrinogen deposits at the epithelial basement membrane. It can also show cytoid bodies in the absence or presence of fibrinogen. Either or both findings indicate OLP activity (Mravak-Stipetic, Loncar-Brzak et al. 2014, Alrashdan, Cirillo et al. 2016).

1.2 Oral lichenoid mucositis

Oral lichenoid lesions (OLLs) have been viewed both as a separate condition from OLP and as a variation of OLP. It is the name given to lesions that present in a very similar manner to OLP clinically and histologically, but they often appear in response to inciting factors, such as medications and restorations (Mravak-Stipetic, Loncar-Brzak et al. 2014, Kamath, Setlur et al. 2015).

1.2.1 Clinical presentation

Similar to OLP, OLL can present with the classic Wickham striae. These lesions can also present with erosive, erythematous, and bullous patterns. However, OLL lesions are typically associated with an inciting agent. Oral lichenoid Lesions (OLLs) are considered variants of OLP. They may be regarded as a disease or an exacerbation of an existing OLP. OLLs have been associated with numerous medications and dental materials, although only some of these have been experimentally confirmed. OLLs also tend to occur on less well-established sites, such as the gingiva, lips, and palate, in addition to well-established sites, such as the buccal mucosa and the tongue. In the confirmation of the causal effect of a suspected inciting agent, withdrawal of the drug or replacement of the restoration with another material may result in lesion regression (Payeras, Cherubini et al. 2013, Kamath, Setlur et al. 2015).

1.2.2 Histological presentation

In most cases, OLLs are indistinguishable from idiopathic OLP, clinically or histologically. However, OLLs are characterized by focal parakeratosis, interruption of the granular layer, and many cytoid bodies without increased PAS-positive basement membrane thickness. A diffuse, deep, and perivascular infiltrate containing lymphocytes, neutrophils, and a substantial number of plasma cells and eosinophils appears in the lamina propria and superficial submucosa without increased vascularity (Mravak-Stipetic, Loncar-Brzak et al. 2014, Kamath, Setlur et al. 2015).

1.3 Treatment for oral lichen planus (OLP) and oral lichenoid lesions (OLLs)

Available treatments for OLP are not curative, and many of them have potentially significant side effects. Therefore, the current objective of OLP management is to prevent and screen for malignant transformation and alleviate symptoms in the long term. Whenever drug-induced OLLs are alleged, the suspected drug should be withdrawn. Any source of oral irritation or mechanical trauma, such as sharp cusps, rough dental restorations, and ill-fitting prostheses, should be identified and removed because they may exacerbate OLP lesions through the Koebner phenomenon. Oral hygiene is of paramount importance. Importantly, some patients report a decline in oral hygiene procedures as a result of the soreness associated with OLP lesions, particularly when the gingival mucosa is involved, thus producing a vicious circle. Psychological support is often important because of the chronic and painful nature of OLP. Discontinuing alcohol and tobacco use may require long-term specialized medical care (Eisen, Carrozzo et al. 2005, Al-Hashimi, Schifter et al. 2007).

Although topical steroids are considered to be the first line of treatment, we only identified

one recent study that compared steroids (clobetasol propionate 0.05%) to the placebo in topical OLP treatment; they found that the symptoms improved (100%) after four months of use, despite the presence of some adverse effects (Arduino, Campolongo et al. 2018). While conventional therapy has been successful in reducing pain and erythema, it has not been able to completely manage the disease because of its recalcitrant nature. From a recent systematic review, no evidence shows that one steroid is more effective than another. Moreover, from the 28 trials included in this review, the wide range of interventions compared suggests insufficient evidence to support the effectiveness and superiority of a specific treatment (Thongprasom, Carrozzo et al. 2011).

2. Non-steroidal anti-inflammatory drugs (NSAIDs)

Prostaglandins (PGs) are a group of hormone-like molecules formed from arachidonic acid. They are mediators of many critical physiological responses, including blood clotting, ovulation, bone metabolism, and kidney function (Dubois, Abramson et al. 1998). The production of PGs increases dramatically during inflammation (Cao, Matsumura et al. 1999). PGE2 is the most abundant and potent PG produced during inflammation. PGE2 has also been shown to be an important immunomodulatory for the cytokine profiles secreted by T and B cells (Snijdewint, Kaliński et al. 1993).

NSAIDs have long been used to treat fever and inflammatory diseases, such as arthritis. Previous work showed that all NSAIDs inhibit local PG production (Tomlinson, Ringold et al. 1972). Traditional NSAIDs, such as aspirin, ibuprofen, and indomethacin, can inhibit the activity of both COX isoforms. However, although they are very effective in addressing inflammation, they can cause side effects. COX is the rate-limiting enzyme in the production of PGs. COX catalyzes the oxidation of arachidonic acid to PGH2, which is subsequently isomerized and reduced to the major biologically active eicosanoids, PGE2, PGF2a, PGI2 and thromboxane A2. The array of PGs

produced varies, depending on the downstream enzymatic machinery present in a particular cell type.

2.1 Topical use of non-steroidal anti-inflammatory drugs (NSAIDs)

Topical analgesic drugs are used for a variety of painful conditions. Some of these are acute, typically strains or sprains, tendinopathy, or muscle aches. Others are chronic, typically osteoarthritis of the hand or knee or neuropathic pain. A recent Cochrane review shows that some formulations of topical diclofenac and ketoprofen are useful in acute pain conditions, such as sprains or strains (Derry, Wiffen et al. 2017).

Although topical anesthetics and cycloplegics have not demonstrated significant improvements in either healing rates or pain control, topical NSAIDs have been proven to reduce pain symptoms in corneal abrasion cases. The use of topical NSAIDs in the standard management of corneal abrasions can therefore be supported (Thiel, Sarau et al. 2017).

2.1.1 Topical non-steroidal anti-inflammatory drug (NSAID) use in oral mucosa

Topical NSAIDs are used to relieve aphthous ulcer pain. A randomized, double-blind, single-dose study of 60 healthy adults with aphthous ulcers investigated the following three different treatment groups: 3% diclofenac in 2.5% hyaluronan, 2.5% hyaluronan alone, and 3% viscous lidocaine alone. The study found a 48% overall reduction in pain ($p<0.01$) observed 10 min after gel application; however, no significant difference was found between the three topical agents. A 35% to 52% pain reduction ($p <0.01$) was reported 2 to 6 h after the application of diclofenac in hyaluronan, whereas hyaluronan gel alone and viscous lidocaine failed to produce significant reductions in visual analog scale (VAS) scores (Saxen, Ambrosius et al. 1997).

In another study, indomethacin was used to alleviate pain in cancer patients with oral stomatitis. The study found that pain associated with stomatitis caused by chemotherapy and radiotherapy was reduced from 10 to 4.7 after the application of indomethacin-containing spray (Momo 2015).

Significance

According to the published literature, topical NSAIDs have never been used to control the pain caused by OLP and OLLs. We hypothesize that using NSAIDs will result in less side effects and better outcomes, especially with the OLP type, which has not been managed well with other treatments of this condition.

Research Question/Hypothesis

We tested the hypothesis that topical NSAIDs reduce the pain in patients with OLP and OLL.

Overall Objective

a. We conducted a cross-over clinical trial to examine the efficacy of a topical NSAID (ibuprofen) over placebo in reducing pain in patients with OLP and OLLs.

Specific Aims

1- Compare the effect of topical ibuprofen versus placebo in reducing pain in patients with OLP and OLLs in three subgroups evaluated at the University of Washington's Oral Medicine Clinical Services (UWMC OMCS) and who were diagnosed with the following:

A. Classic OLP lesions based on clinical diagnosis and histological findings on biopsy (biopsy-confirmed OLP [BCOLP])
B. OLP lesions based on clinical diagnosis only without biopsy confirmation (non-biopsy-confirmed OL [NBCOLP])
C. OLLs

2- Examine in two treatment conditions the effect (correlation) of pain levels with demographic and medical history factors, including the following:

- Age
- Gender
- Race
- Duration of primary chief complaint (in months before the first test)
- Pain intensity of oral mucosal lesion
- Current medical conditions
- Current prescription drugs
- Current over-the-counter (OTC) drugs

PARTICIPANTS AND METHODS

Protocol Proposal

A four-week randomized, double blind, cross-over, placebo-controlled trial was planned. Ethical approval was obtained from the Institutional Review Board (IRB) at the University of Washington before the start of the study, participants agreed to participate in this study had to sign a

written informed consent. The present trial was also registered (#NCT03509675). The research was conducted in accordance with the ethical principles stated in the World Medical Association's Helsinki Declaration.

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

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

Population and Study Sample

Potential participants were screened through the Oral Medicine patient registry at the University of Washington. Prospective patients aged 18–80 were examined by the attending at the Oral Medicine Clinical Services (OMCS) faculty. All potential study participants with a clinical diagnosis of symptomatic oral lichenoid mucositis with or without a biopsy were identified. Individuals were eligible for inclusion if they met the following criteria:

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

The exclusion criteria were as follows:

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

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

Sample Size and Sample Selection

The most similar study to the present one was done by Saxen et al., in which a 45% change in VAS scores between the treatment groups was found. With the assumption of a 45% difference in VAS scores, a standard deviation of 0.69, a two-sided significance level of 0.05, and a statistical power of 80%, a sample size of 36 was calculated. When accounting for the effect of a cross-over trial and analyses, a sample size of 36 should be able to show significance with a change in VAS scores between 25% and 30%, significantly less than that found in the work of Saxen et al.

Collection of Data

The data collected included the following:

- VAS at baseline, end of day 4 and following the end-of-the week application of the active intervention and the placebo
- Gender
- Race and ethnicity
- Duration of the primary chief complaint
- Medication trials for the condition

- Current medical conditions
- Current prescription drugs
- Current OTC drugs
- Known allergies to drugs or food substances
- Clinical diagnosis of the disease
- Classification of the OLP (if noted): reticular, erythematous, erosive, bullous

Topical Formulation

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

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

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

Assessment

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

Intervention

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

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

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

spontaneous pain level on the VAS. After the first week, they discontinued any treatment for 7 days (wash-out) before starting the second suspension.

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

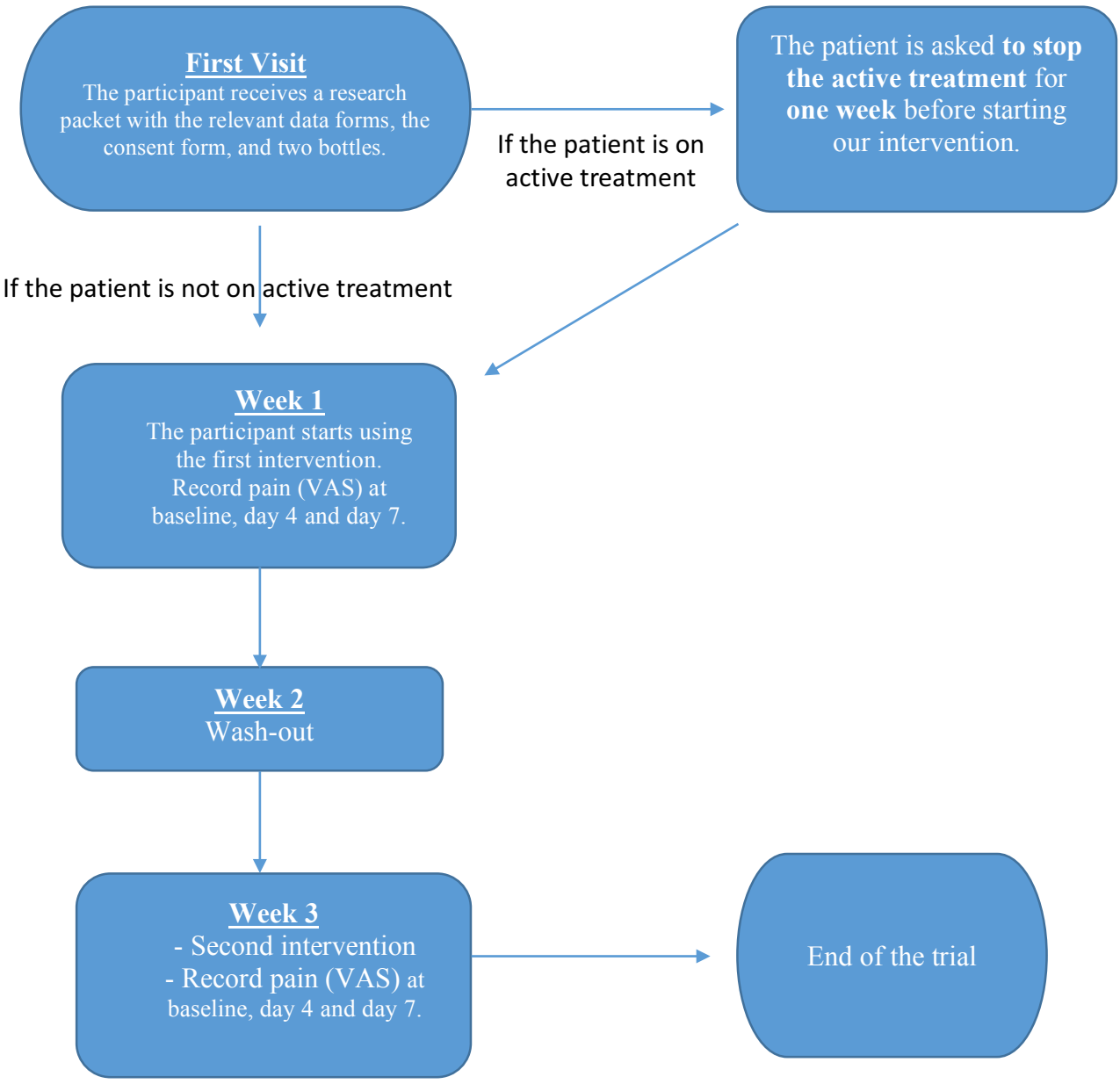

Figure 1 Flow diagram showing the process of the intervention.

Data

We protected the patients' information by assigning each individual with a study number that was correlated with the medical record number on a master list. The master list was secured in a password-protected file on a password-protected computer stored in a locked office. The collected data were stored separately. The list was not placed on a portable device. Only the research committee members and the personnel required for the statistical analysis had access to the files. The study data will be kept indefinitely but will only be linked until December 31, 2019. Only the investigators will have access to the identifiable data, unless otherwise required by law.

Data Analysis Strategies

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

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

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

Ethics and Human Participant Issues

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

RESULTS

A total of 170 patients were assessed for eligibility through the Oral Medicine Clinical Services at the University of Washington. Ninety-eight of the patients did not meet the criteria for inclusion, because ninety-three had pain less than 3 out of 10 cm on the VAS score, 3 did not speak English, 1 subject had history of asthma and 1 had a history of gastrointestinal ulceration. Seventy-two met the inclusion criteria to be included in the trial. Forty-nine declined to participate in the study. Twenty-three participants were enrolled after they signed the consent form. A total of 10 participants dropped out, whereas the remaining 13 completed the protocol, except for one patient who completed one bottle only. Figure 2 reports the flow diagram of the subjects' recruitment process.

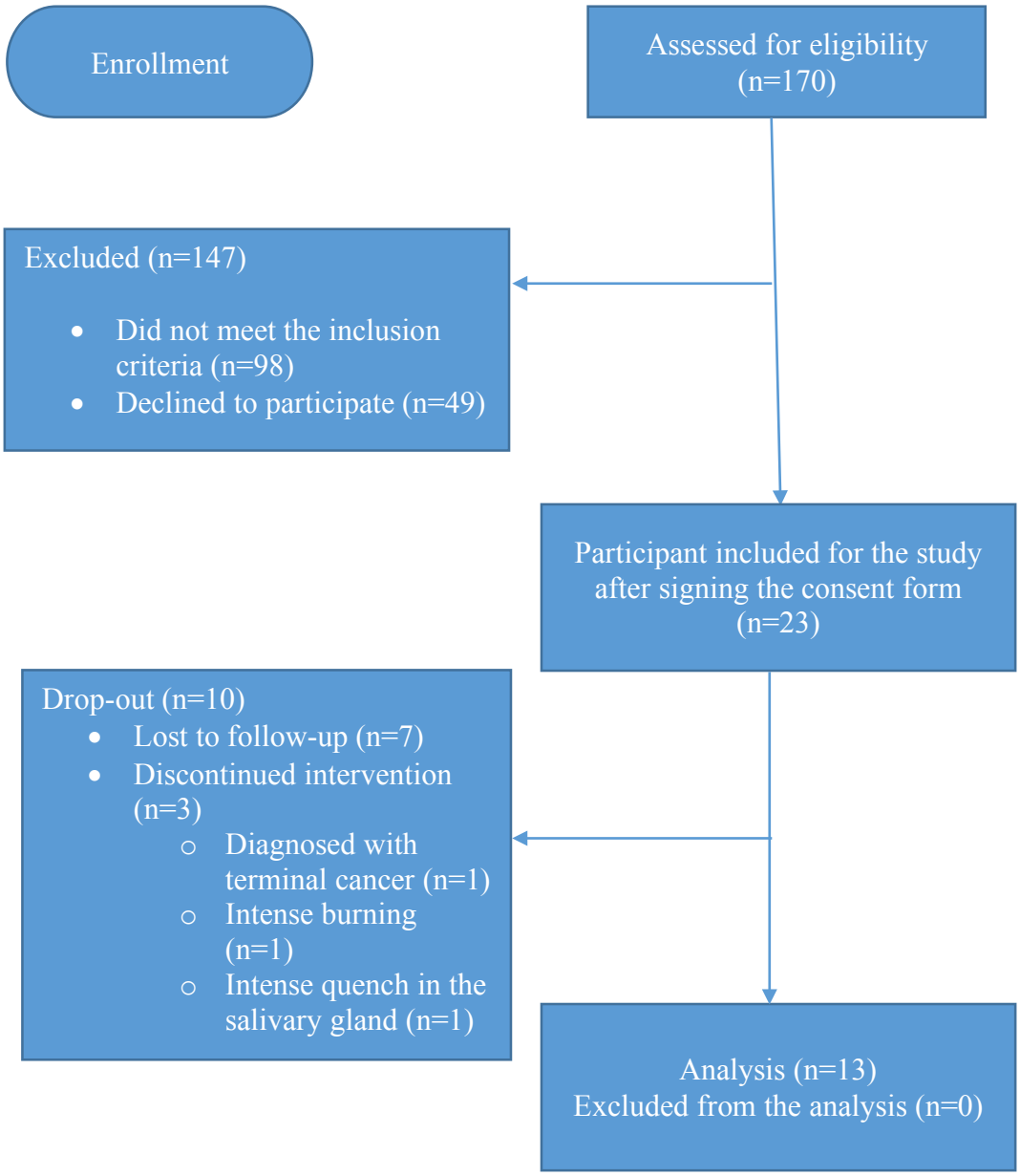

Figure 2 Flow diagram showing the number of patients for enrollment, treatment, and inclusion in the final analysis.

Table 1 describes the subjects' characteristics. The mean age of the participants was 66.9 years (min, 33.0; max 80.0). The mean symptom duration was 30.0 years with a maximum of 48.0 years and a minimum of 9 months.

Participant ID	Age (months)	Race	Condition duration (months)	Treatment trials	Medical conditions	Current prescription medication	Current over-the-counter (OTC)) medication	Clinical diagnosis of the condition	First bottle
001	Female/960	White	576	Chlorohexidine, Dexamethasone, Triamcinolone Acetonide	Diabetes, obesity	Metoprolol, Simvastatin, Glyburide, Basaglar kwikpen	Allertec	OLP	Placebo (A)
002	Female/686	White	18	Prednisone, Dexamethasone	Obesity, hemicrania continua, sinusitis, bronchitis, asthma, chlolethiasis, AMA ng cholangiopathy	Atorvastatin, Levothyroxine, Indomethacin, Topiromate, Ursodiol, Triamcinolone, Clobetasol	Vitamin D	OLP	Placebo (A)
003	Female/840	White	180	Medrol dose pack, Betamethasone, Clobetasol	Hearing loss, sinusitis	Lipitor, Enalapril	Multivitamin, Co Q 10, fish oil, calcium, B complex, Aleve	OLP	Active medication (B)

Participant ID	Age (months)	Race	Condition duration (months)	Treatment trials	Medical conditions	Current prescription medication	Current OTC medication	Clinical diagnosis of the condition	First bottle
008	Female/780	White	120	Prednisone, Triamcinolone, Dexamethasone, Azathioprine	Thyroid problem, arthritis, cataract, hypertension, high cholesterol, bronchitis, sinusitis	Levothyroxine, Benazepril, Simvastatin, Clonazepam, Celecoxib, Carafate, Pantoprazole, Pseudoephedrine HCL, Hydrocodone-Acetaminophen, Gabapentin, Dexamethasone	Omega-3 , calcium, vitamin C, vitamin D, magnesium, iron, primrose oil, potassium, Aller-Tec	OLP	Active medication (B)
009	Male/NA	NA	48	NA	Asthma, bronchitis	Beclomethasone Dipropionate Inhaler	None	OLP	Placebo (A)
011	Female/876	NA	168	Dexamethasone, Prednisone, Azathioprine, Amitriptyline, Doxepin oral solution, Triamcinolone, Clobetasol, Naltrexone	History of right breast cancer, arthritis, Bell's palsy, thyroid problem, bronchitis, bladder problem	Doxycycline, Nabumetone, Levothyroxine, Prednisolone, Metprolol, Etedolac	Multivitamin, NaturesPlus Source of Life, Kal D-3	OLP	Active medication (B)

Participant ID	Age (months)	Race	Condition duration (months)	Treatment trials	Medical conditions	Current prescription medication	Current OTC medication	Clinical diagnosis of the condition	First bottle
015	Female/840	White	18	Dexamethasone, Medrol dose pack, Tacrolimus, Magic mouthwash	Hypertension, cataract	Lisinopril	Muscadine grape seed, multivitamin, essential fatty acids	OLP	Active medication (B)
016	Female/840	White	24	None	History of skin cancer, hypertension, cataract, arthritis	Lisinopril, Amlodipine, Trazodone,	Women's multivitamin, fish oil, glucosamine chondroitin, aspirin, turmeric, curcumin	OLP	Active medication (B)
017	Female/900	White	98	Dexamethasone	Diabetes, high cholesterol, Arthritis, Back pain, History of breast cancer, Sinusitis, Thyroid problem	Levothyroxine, Losartan, Amlodipine, Aspirin, Oxybutynin, Metformin, Glipizide, Simvastatin, Omeprazole, Nortriptyline, Clonidine, Hydrocodone acetate, Insulin, Fluticasone, Saline sinus rinse, Remeron	L-Lysine, Nystatin	OLP	Placebo (A)

Participant ID	Age (months)	Race	Condition duration (months)	Treatment trials	Medical conditions	Current prescription medication	Current OTC medication	Clinical diagnosis of the condition	First bottle
018	Female/864	White	144	Dexamethasone	Migraine, depression, anxiety	Trileptal, Lexapro, Premarin, Provera	Centrum silver, B complex, omega 3	OLL	Placebo (A)
019	Female/396	Asian or Pacific Islander	84	Clobetasol	Diabetes, thyroid problem, headaches, back pain	Metformin, Levothyroxine, Glipizide, Invokana, Atorvastatin, Sitagliptin	Vitamin D, parental vitamins	OLP	Active medication (B)
020	Male/900	White	9	Medrol dose pack, Clobetasol Ointment	Hearing loss, visual loss, history of cancer, back problem, hepatitis, hepatocellular carcinoma	Naproxen, Tramadol, Losartan, Omeprazole, Escitalopram,	Baby aspirin, vitamin E, fish oil, multivitamin	OLP	Active medication (B)
021	Male/828	Asian	244	Doxepin solution, Halcinonide, Prednisone, Dexamethasone, Triamcinolone	Diabetes, thyroid problem, high cholesterol, heart disease, genetic disease	Lovastatin	None	OLP/OLL	Placebo (A)

Table 2 The clinical characteristics of our 13 participants diagnosed with OLP or OLL. Age is presented in months. NA=not available

Baseline Comparisons

At baseline, the participants using the bottle B first (active drug) reported a mean score of 50.8 ± 16.6 on the VAS. Those who used the bottle A (Placebo arm) first reported a mean VAS score of 55.9 ± 19.23.

A t-test comparing mean scores showed that the mean pain level at baseline for both groups was not significantly different (P=0.144). See Figures 3 and 4.

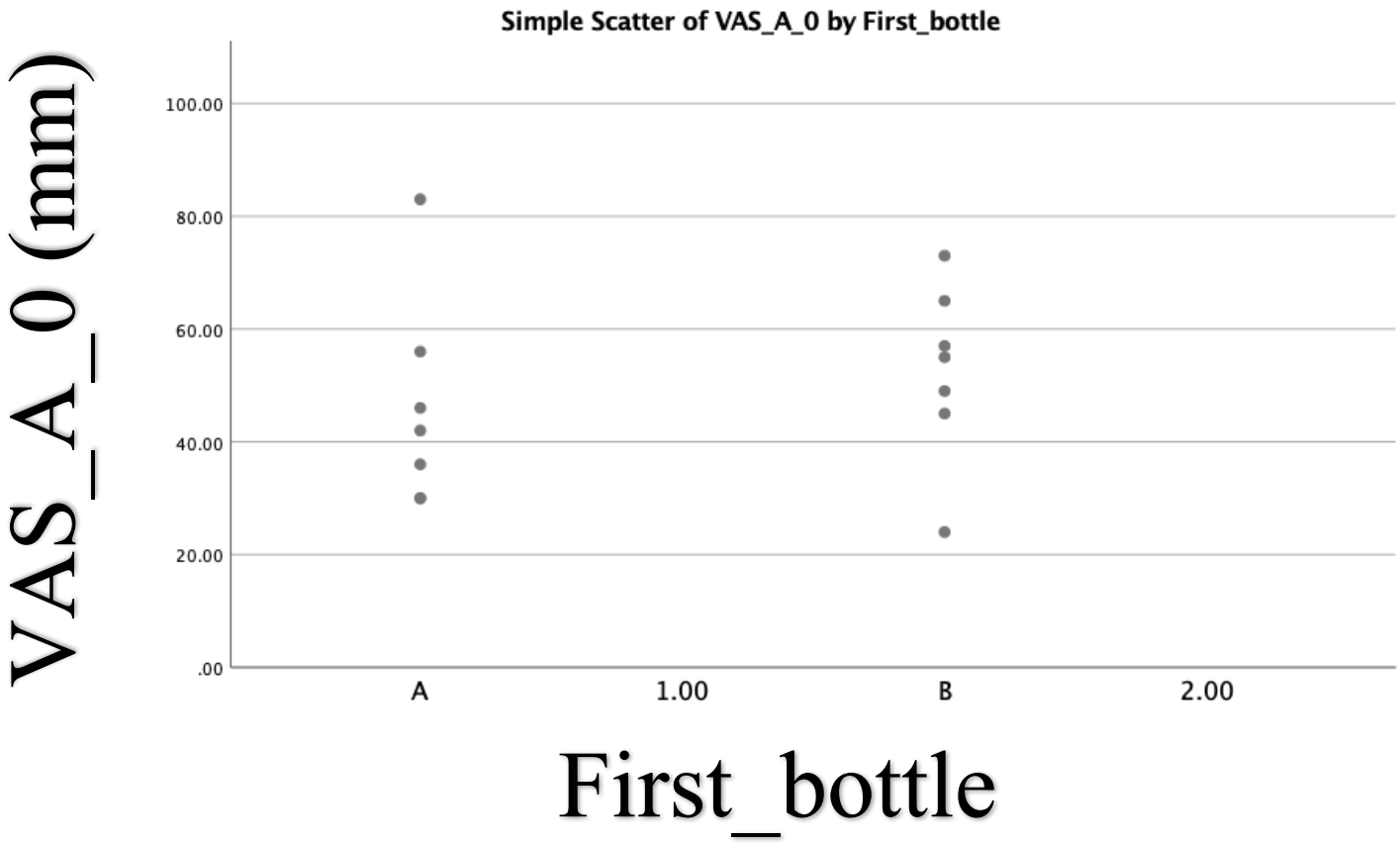

Figure 3 shows the pain level for bottle A (Placebo) depending on which bottle was first.

Figure 4 shows the pain level for bottle B (active medication) depending on which bottle was first.

One-way ANOVA showed that the groups did not have different baseline VAS scores based on age (active: P=0.77; placebo; P=0.74). The baseline VAS scores were not affected by the duration of the chief complaint when the participants used the placebo (P=0.36). However, the duration of chief complaint could be a factor that affected the baseline scores when the participants used active medication (P=0.062).

Drug effect

When looking at the VAS scores themselves for the two drugs, regardless of use of order, the VAS scores for the placebo drug decreased by a mean of 6.4mm from baseline to the end of the drug use

(49.3mm to 42.9mm). For the active drug, the VAS scored decreased by 12.3mm (56.3mm to 44.0mm).

A paired samples t-test showed no significant difference in the mean values between days 0 and 4 or for the values between days 0 and 7 for the placebo arm (bottle A). No significant difference was observed in the mean values between days 0 and 4 for the active medication group (bottle B), but near significance (P=0.096) was observed for the active medication (bottle B) between days 0 and 7. See Table 3.

		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
					Lower	Upper			
Pair 1	VAS_A_0 - VAS_A_4	-.38462	10.26757	2.84771	-6.58925	5.82002	-.135	12	.895
Pair 2	VAS_A_0 - VAS_A_7	6.42857	15.31070	4.09196	-2.41156	15.26871	1.571	13	.140
Pair 3	VAS_B_0 - VAS_B_4	8.90909	20.58861	6.20770	-4.92253	22.74071	1.435	10	.182
Pair 4	VAS_B_0 - VAS_B_7	12.33333	23.47662	6.77712	-2.58300	27.24966	1.820	11	.096

Table 3 t-test showing the difference in mean values between day 0,4 and 7.

A linear regression showed that the percent change from days 0 to 7 for the active medication group was near-significant (p=.108), even when controlling for both order and the baseline VAS score. Figures 5 and 6 show visually the change in VAS scores from baseline to day 7 for both drugs A (placebo arm) and drug B (active drug) for each participant. The baseline scores are shown in blue for day 0, and green for day 7.

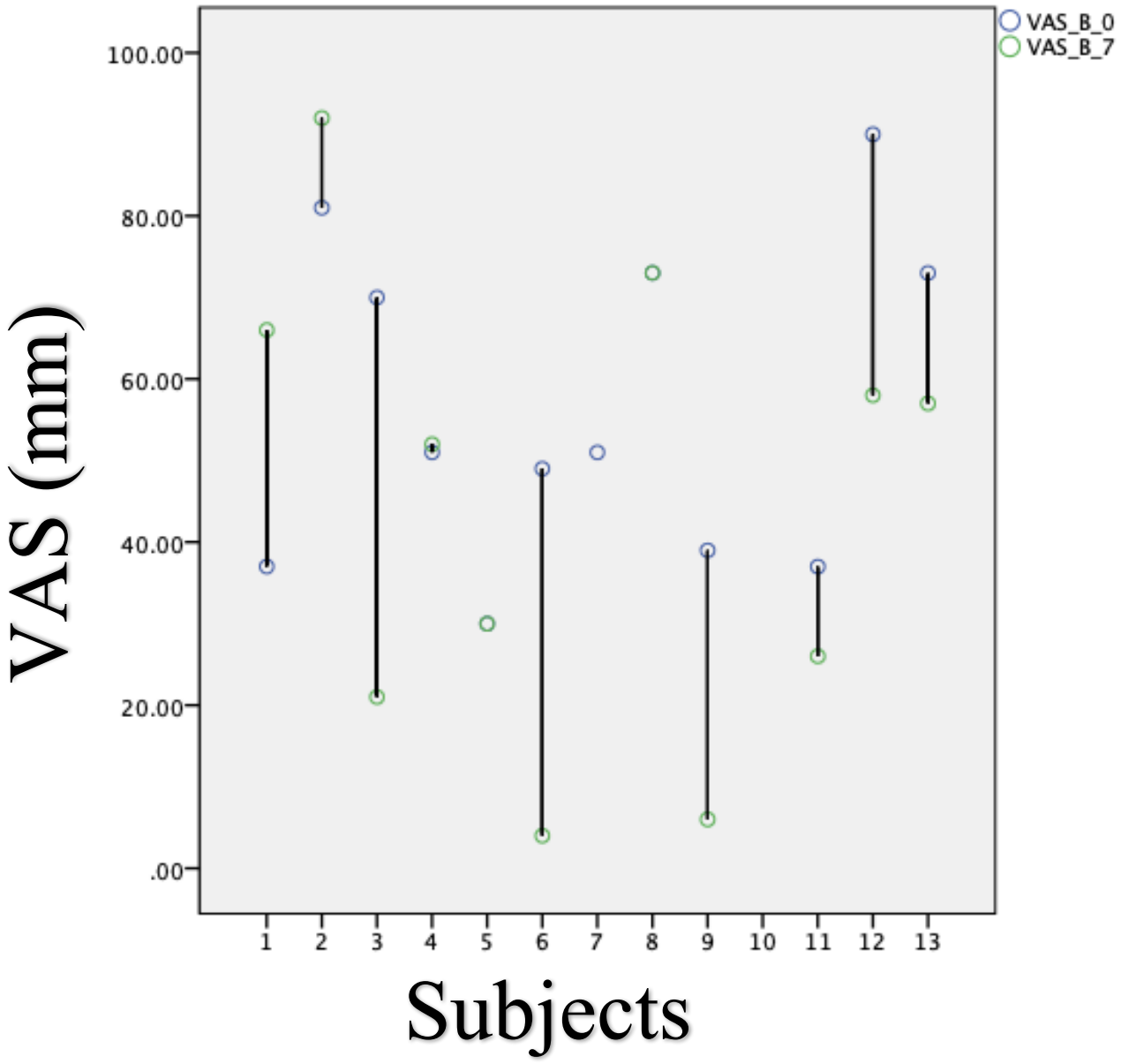

Figure 5 showing the change from days 0 to 7 for the active medication group (bottle B).

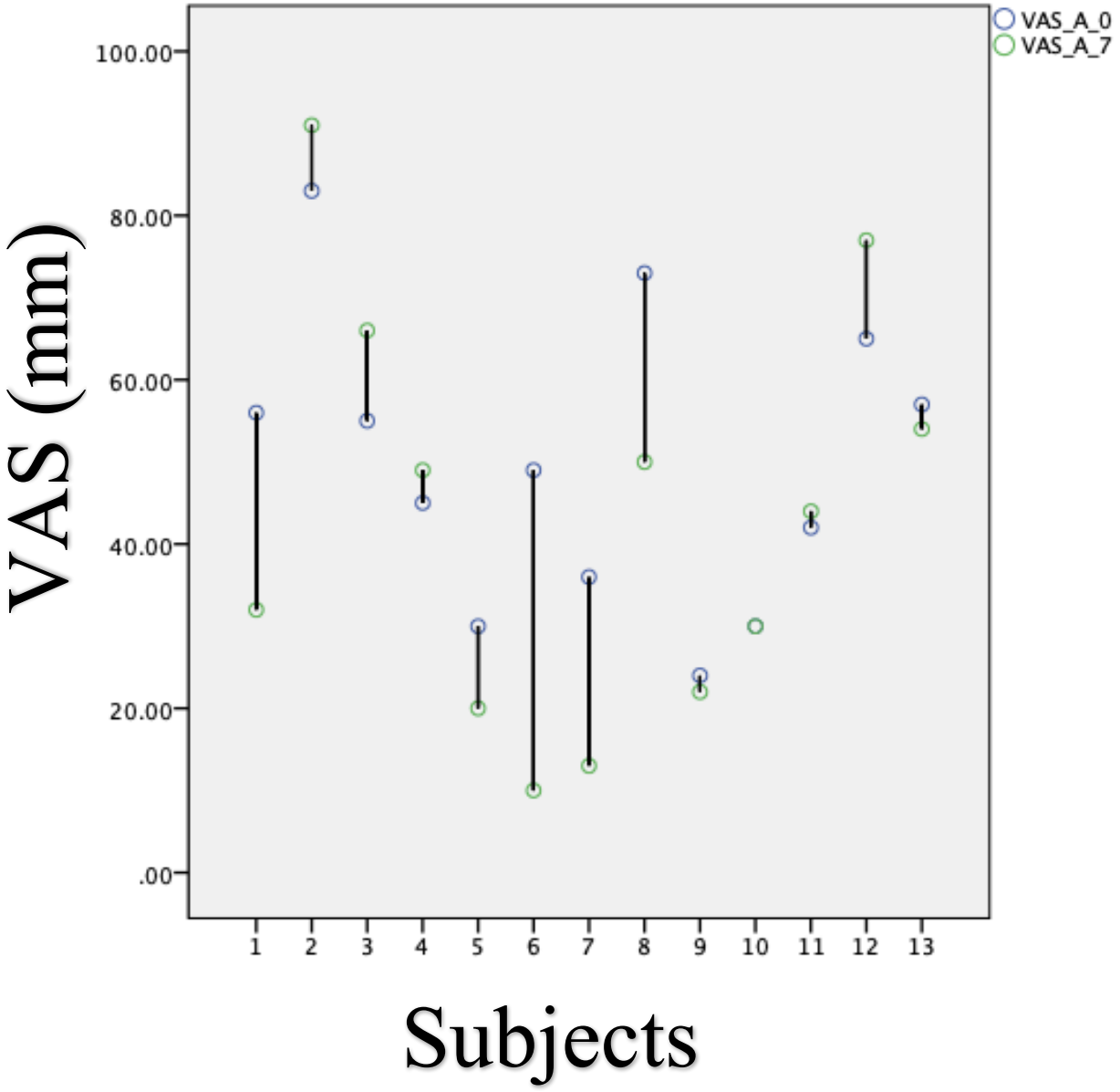

Figure 6 shows the change from days 0 to 7 for the placebo (bottle A).

Order effect

Using linear regression, it was found that the VAS scores on day 7 for both A (placebo arm) and B (active drug) were not affected by which bottle was used first (for placebo, P=.560; for active, P=.453).

Regression analyses indicated that for bottle A (placebo arm) for percent change in VAS score from days 0 to 7, there was no order effect depending on which drug was used first (P=.652). However, when comparing percent change from days 0 to 7 and controlling for which bottle was used first, an order effect was found (P=.042). If the first bottle used was A (placebo arm), the percent change for the second bottle B (active drug) was -11.1%, signifying a reduction in pain of 11.1%. While if the first bottle was B (active drug), the percent change for the active medication was 43.13%, indicating an increase in pain by 43%.

Parametric Analysis

In addition, using parametric analysis, a Wilcoxon Signed Rank test comparing the percent change for the active medication for day0-day7 to percent change for the placebo for day 0-day7, no significant difference was seen between placebo and active drug (P =0.37). see figure 4

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The median of differences between changeA0A7 and changeB0B7 equals 0.	Related-Samples Wilcoxon Signed Rank Test	.374	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table 4 Showing that no significant was seen between placebo and active drug.

DISCUSSION

Patients with a symptomatic form of OLP suffer from pain and burning that can be debilitating. Its management is problematic and is often aimed at palliation rather than cure; numerous systemic and topical agents have been used with different outcomes. Weak evidence for the effectiveness of any treatment for oral OLP has been described (Cheng, Kirtschig et al. 2012). However, the usual prescribed treatment for OLP and OLL, is a topical steroid. Topical steroid therapy, while often effective, can also be ineffective in some cases of unresponsive lesions. They also have potential side effects, including predisposing the oral cavity to fungal infections.

According to the results of this study, we observed near-significant pain reduction (p=0.096) with the use of a topical NSAID compared with a placebo. In another study a more-significant but similar reduction in pain of the oral mucosa was observed with stomatitis patients using a topical NSAID (indomethacin spray). Pain associated with stomatitis was reduced after application of the spray from 10 to 4.7 on a 0-10 Visual Analog Scale (VAS) on 23 patients (Momo 2015). Another recent trial by (Serafini, Trevisan et al. 2012), compared a mouth wash formulation of diclofenac

epolamine (diclofenac/n-(2-hydroxyethyl) pyrolidine; DHEP) with a commercially available mouthwash containing diclofenac. They found significantly greater proportion of patients treated with DHEP were free of pain and inflammatory symptoms at day 3 compared with diclofenac mouth wash (40% vs 20% of patients; $p<0.05$). These studies show potential advantages for treating inflammatory condition using oral topical NSAID's.

According to the published literature, the use of topical NSAIDs has never been used to control the pain caused by OLP and OLLs. Moreover, our findings are in agreement with previous studies on NSAID topical used for oral mucosal inflammatory and irritating lesions. In an open label clinically study in patients who underwent oral or periodontal surgery, 7 days treatment with diclofenac 0.074% mouth wash twice a day significantly reduced the intensity of spontaneous pain compared with baseline.(Tramèr, Bassetti et al. 2001)

Additionally, we found an order effect in the amount of pain control achieved by the active medication. If the first bottle used was A (placebo arm), the percent change in pain scores for the second bottle B (active drug) was -11.1%, indicating a reduction in pain of 11.1%. While, if the first bottle used by a patient was B (active drug), the percent change for the active medication was 43.13%, indicating an increase in pain by 43%. This could be due to the nature of the chronicity of the condition with relapses and remission (Eisen, Carrozzo et al. 2005). A longer study trial of a month for each medication may have shown better results. It also may be due to the carry over effect which is common weakness for crossover design. What we believed may have occurred is that when subjects used the first bottle they had a memory or an effect from their previous steroid treatment. So when they used the medication first, they marked their pain level aggressively than what they used before but when they used the active medication second they marked their pain level less as the effect of steroids had faded.

Another explanation for this order effect might be that we used A and B labeling for the interventions. Individuals working with this model in the future should consider the use of an individual bottle coding system. That would have helped to prevent both the investigators and the participants from predicting which bottle contained the active medication. However, we found that the percent change from days 0 to 7 for the active medication group was near-significant (p=.108), when controlling for both the order of use and the baseline VAS score.

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Although NSAIDs are considered to be associated with OLL, we only used them topically and found no difference in the reporting of adverse events between the placebo and active medication groups (Al-Hashimi, Schifter et al. 2007).Treatment was generally well tolerated and no clinically relevant adverse events (AEs) were recorded.

Strengths and Limitations

To our knowledge, this is the first double-blind, cross-over, placebo-controlled clinical trial designed to measure the effectiveness of topical NSAIDs in reducing the pain associated with OLP and OLLs. Moreover, local tolerance also appeared to be good, with no adverse effects (AEs) on the oral mucosa even with four times daily rinses for 7 days.

The limitations of this study are as follows: (1) An inadequate sample size may have prevented us from observing a significant pain reduction. We hypothesized that the use of relatively safe medication could serve as an option for patients suffering from symptomatic OLPand OLL; (2)

even though the participants were asked to discontinue using any steroid medication systemically or topically, some were using polypharmacy with other types of analgesics, which could have affected the results; and (3) using labeling crossover study design could have made our study subject to an order effect.

Along with these data, and despite some limitations in our research such as the small sample size and the order effect of our drug deliveries, our results provide an option for the use of a local NSAIDs treatment with specifically (ibuprofen mouthwashes) in the management of pain associated with OLP or OLL conditions affecting patients quality of life. Such an approach can help provide an alternative medication to patients either suffering from the side effects of topical steroids or if their conditions are resistant to the treatment of steroids. In our study, treatment was not associated with NSAID-related AEs such as gastrointestinal events.

CONCLUSION

Patients with severe oral lichen planus refractory to standard topical treatment currently have limited options of therapy suitable for long-term use. NSAID had shown promise in improving pain in oral lesions such as aphthus ulceration, stomatitis in cancer patients undergoing radiotherapy and chemotherapy and patient having periodontal surgery. Our results tend to support the validity of an approach to the treatment of inflammatory conditions of the oral cavity, based on using topical NSAIDs. According to the findings of the present study, topical NSAIDs may help to reduce pain caused by OLP and OLLs. These findings warrant further investigation in a larger sample of patients, over a longer period of time.

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APPENDIX (A)

Study Tracking Form

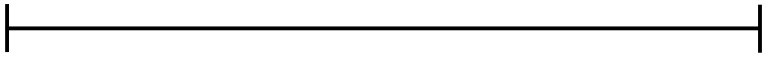
Participant ID#: Date:

Bottle #:

- Pain intensity:

Immediately before the 1st time you use the first study drug

- Please rate the strength of the pain you are experiencing by making a vertical mark on the line below. Place your mark at a place on the line that correspond to how intense your pain.

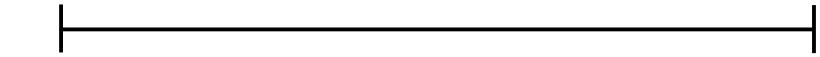


Not Intense — Extremely intense

Please use 5 ml of the suspension 4 times a day and by rinsing for 1 minute then spit out without swallowing. Try not to eat or drink for 20 minutes after each application. Check the boxes for every application of the medicine.

		Before Breakfast	Before Lunch	after Dinner	Before Bed
❖ Day (1)	Date:				
Please check a box after each Application of the medication		☐	☐	☐	☐
❖ Day (2)	Date:	Before Breakfast	Before Lunch	after Dinner	Before Bed
Please check a box after each Application of the medication		☐	☐	☐	☐
❖ Day (3)	Date:	Before Breakfast	Before Lunch	after Dinner	Before Bed
Please check a box after each Application of the medication		☐	☐	☐	☐
❖ Day (4)	Date:	Before Breakfast	Before Lunch	after Dinner	Before Bed
Please check a box after each Application of the medication		☐	☐	☐	☐

- Pain intensity:
  - Please rate the strength of the pain you are experiencing by making a vertical mark on the line below, **at the end of day (4)**. Place your mark at a place on the line that correspond to how intense your pain



Not Intense — Extremely intense

- Day (5) Date:

Before Breakfast	Before Lunch	after Dinner	Before Bed
Please check a box after each Application of the medication				

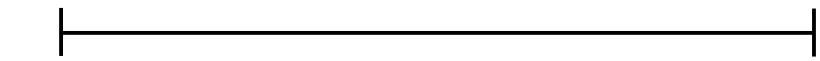
- Day (6) Date:

Before Breakfast	Before Lunch	after Dinner	Before Bed
Please check a box after each Application of the medication				

- Day (7) Date:

Before Breakfast	Before Lunch	after Dinner	Before Bed
Please check a box after each Application of the medication				

- Pain intensity:
  - Please rate the strength of the pain you are experiencing by making a vertical mark on the line below, **at the end of day (7)**. Place your mark at a place on the line that correspond to how intense your pain



Not Intense — Extremely intense

APPENDIX (B)

University of Washington consent form

Consent Form

Use of Topical Nonsteroidal Anti- inflammatory to Reduce Pain for oral Lichen Planus patients

Researchers:

Dr. Stuart Taylor DMD, MSD — Clinical Assistant Professor, Oral Medicine — stuartt@uw.edu

Dr. Michael Martin DMD, MPH, MA, MSD, PHD — Professor, Oral Medicine — mickeym@uw.edu

Dr. Douglas Ramsay DMD, PhD, MSD — Professor, Oral Health Sciences — ramsay@uw.edu

Ishraq Alshanqiti — Oral Medicine Resident — ishraa@uw.edu (206) 229-9037

Rashmi Mishra — Oral Medicine Resident — mishrar@uw.edu (832) 552-6199

Researchers' statement

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

PURPOSE OF THIS STUDY

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

STUDY PROCEDURES

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

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

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

At the beginning of week #3, before using the **second suspension**, please mark your level of pain on the sheet and for each usage you will place a check in the corresponding box on the form. By this week, you will start the second bottle and use it four times a day and again check the box on the form for each application. At the end of days 4 and 7 you will mark your pain level on the form again and your participation in the treatment part of the study will conclude at the end of day 7. Following this, **we would like to see you again for a 15 minutes**, no charge visits in which we will evaluate you again and receive the forms from you.

RISKS, STRESS, OR DISCOMFORT

Discontinue the standard care of treatment:

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

Adverse Reaction from the suspensions:

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

Privacy

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

Unknown risks:

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

ALTERNATIVE FOR TAKING PART IN THIS STUDY

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

BENEFITS OF THIS STUDY

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

CONFIDENTIALITY OF REASERCH INFORMATION

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

OTHER INFORMATION

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

Subject statement

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

Printed name of subject signature of subject Date

Copies to: Researcher
Subject

APPENDIX (C)

(Data extraction sheet)

<table>
<tr><td colspan="3">Use of Topical Non-Steroidal Anti- Inflammatory to Reduce Pain in Oral Lichen Planus and Oral Lichenoid Lesions.</td></tr>
<tr><td colspan="3">PI: Ishraq Alshanqiti</td></tr>
<tr><td colspan="2">ID #</td><td></td></tr>
<tr><td colspan="2">Age</td><td></td></tr>
<tr><td colspan="2">Gender</td><td></td></tr>
<tr><td colspan="2">Race</td><td></td></tr>
<tr><td rowspan="3">A
VAS Length:
Code #</td><td>Baseline</td><td></td></tr>
<tr><td>Day 4</td><td></td></tr>
<tr><td>Day 7</td><td></td></tr>
<tr><td rowspan="3">B
VAS Length:
Code #</td><td>Baseline</td><td></td></tr>
<tr><td>Day 4</td><td></td></tr>
<tr><td>Day 7</td><td></td></tr>
<tr><td colspan="2">Duration of primary chief complaint</td><td></td></tr>
<tr><td colspan="2">Medication trials for the condition</td><td></td></tr>
<tr><td colspan="2">Current medical conditions</td><td></td></tr>
<tr><td colspan="2">Current prescription drugs</td><td></td></tr>
<tr><td colspan="2">Current over-the-counter drugs</td><td></td></tr>
<tr><td colspan="2">Known allergies to drugs or food substances</td><td></td></tr>
<tr><td colspan="2">Clinical diagnosis of the disease</td><td></td></tr>
<tr><td colspan="2">Classification of Oral Lichen Planus (if noted) (reticular, Erythematous, Erosive, Bullous)</td><td></td></tr>
<tr><td colspan="2">First Bottle</td><td></td></tr>
<tr><td colspan="2">Notes</td><td></td></tr>
</table>