EFFECT OF FLUDROXYCORTIDE AND IMIQUIMOD CREAMS ON THE TREATMENT OF ACTINIC CHEILITIS: A RANDOMIZED CLINICAL TRIAL

SUMMARY

1 BACKGROUND

Cheilosis or actinic cheilitis is a potentially malignant inflammatory condition of the labial vermilion, which occurs most frequently in the lower lip. It was first described by DuBrevilh in 1886[1] and it is estimated that 95% of vermilion labial carcinomas originate from this lesion.[2] Actinic cheilitis has a greater probability of malignant transformation than actinic keratosis,[3] because labial vermilion has thinner epithelium and keratin layer, it has less melanin and less sebaceous and sweat gland secretion than the skin.[4] In addition, the risk of metastasis of lip carcinomas is four times higher than that of skin carcinomas.[5]

The main etiological factor of actinic cheilosis is exposure to ultraviolet solar radiation (UV), especially type B (UVB), due to its greater potential for epithelial penetration when compared to type A (UVA).[2,6] This condition preferentially affects fair-skinned individuals, who are more susceptible to UV radiation damage. It is more frequently diagnosed in male, who work under constant sun exposure such as rural workers and fishermen. The lower lip is the preferred location, as it is more exposed to solar radiation compared to the upper lip. Although this condition can affect individuals of all age groups, it is most often seen after 50 years old due to its slow progression, delay in diagnosis (because it is painless), and accumulation of sun damage over time.[7,8] Actinic cheilosis has high prevalence in the population of southern Brazil due to the tropical climate of the region and European descent of a large part of the population.[9] It is believed that other minor risk factors such as smoking and alcoholism participate in the progression and severity of these injuries.[10]

Clinically, there are two forms of actinic cheilitis: acute and chronic. The acute manifestation occurs more manly in young patients, after excessive exposure to solar

radiation. The lips are dry, pale, scaly and erythematous. In chronic lesions, many alterations are irreversible, a dry and atrophic lip is observed, with areas of dyschromia, and there may be leukoplakia and chronic ulcers. Loss of the mucocutaneous junction of the lip is typically seen. The presence of erosions, persistent ulcerations and stiffening may be indicative of progression to labial carcinoma. Actinic cheilosis is usually asymptomatic, but in some cases patients may report a burning sensation, numbness and pain.[2,9,11]

The follow-up of patients with chronic actinic cheilitis and performing incisional biopsies in more severe clinical conditions is essential to avoid their malignant transformation.[2] The histopathological presentation of the lesions varies from an atrophic stratified squamous epithelium with hyperkeratosis, to varying degrees of dysplasia or even invasive squamous cell carcinoma. There is an infiltrate of chronic inflammatory cells and basophilic alterations of the lamina propria (solar elastosis) induced by ultraviolet radiation.[12] Epithelial atypia can be classified as mild, moderate or severe, according to the cellular alterations.[5] Carcinoma in situ and even invasive carcinoma can be found in the histopathological examination of patients with a clinical picture of actinic cheilosis.[2] The diagnosis of this condition is based on a set of factors, which include demographic findings, clinical presentation and histopathological confirmation of epithelial changes. From the diagnosis, the prognosis can be established and appropriate treatment can be planned.[8,13]

Early diagnosis of actinic cheilitis and patient follow-up are essential, as it is not possible to predict which cases will undergo malignant transformation over time. In addition, patients should be instructed to apply sunscreen on a daily basis and modify their sun exposure habits to prevent further damage. The choice of the most appropriate therapeutic option depends on the clinical severity of the lesions and the

epithelial alterations observed in the histopathological examination.[2,11] The treatment goals are to prevent the development of squamous cell carcinoma, improve lip esthetics and reduce the discomfort caused by erosions lips, crusts and roughness. Different therapeutic modalities are described in the literature. Actinic cheilitis can be treated clinically with topical application of 5-fluorouracil, trichloroacetic acid, imiquimod, ingenol mebutate, fludroxycortide, or diclofenac sodium. Other treatments include cold scalpel surgical excision (vermilionectomy), CO2 or Er:YAG laser vaporization, cryosurgery, electrodissection, and photodynamic therapy (PDT).[3,9]

Imiquimod is a topically applied drug with antineoplastic properties that acts as a modifier of the immune response. It was approved by the Food and Drug Administration (FDA) and is currently available in a cream formulation at concentrations of 5% and 3.75%.[14-16] Imiquimod is a heterocyclic, mononucleoside amine that increases innate and acquired immunity, resulting in immunomodulatory, antiviral and antitumor effects. This substance stimulates the immune reaction by inducing, synthesizing and releasing cytokines, which increases cellular immunity, inducing indirect anticancer activity. This drug can also directly stimulate the apoptosis of neoplastic cells by stimulating cell death receptors.[14-16] Systemic absorption of imiquimod after application to the skin or pseudomucosa is considered insignificant.[16] There is evidence of the efficacy of this substance in the treatment. of actinic keratosis and in several dermatological conditions, however, there are only a few case series and a clinical trial that report its use in the treatment of actinic cheilosis.[14-16] Husein-ElAhmed et al.[17] selected 30 patients with actinic cheilosis, from of which 10 received imiquimod therapy. Complete response to treatment was achieved in five (50%) of 10 participants treated with this drug. Adverse effects completely disappeared in all

patients, regardless of the therapy used. Adverse effects of imiquimod application include erythema, scaling, crusting, edema, blistering, and ulceration.

Fludroxycortide is a topical corticosteroid with anti-inflammatory, vasoconstrictor and antipruritic properties, commonly used in the treatment of skin inflammation and allergies. This drug reduces edema at the site of inflammation, as well decreases as the formation, release and activity of pro-inflammatory substances. Despite being a widely known substance, there are few studies in the literature that explain its pharmacokinetics and pharmacodynamics, and only one previous clinical trial investigated its effects on actinic cheilitis.[18] Bezerra et al.[18] selected 23 participants with actinic cheilosis, of whom 15 received treatment with fludroxycortide. At the end of the study, five patients showed complete remission of the clinical characteristics of the lesions, seven showed partial improvement and only three showed no changes in the clinical aspect. No side effects have been reported with the use of this substance.

Due to the aggressiveness of some therapeutic interventions for actinic cheilosis, causing considerable discomfort to patients, the development of effective alternatives for the treatment of these lesions is of great interest. Currently, there is no universally accepted therapeutic approach that is considered the gold standard. In this context, the present study aims to evaluate and compare the effect of fludroxycortide and imiquimod creams in the treatment of actinic cheilosis through clinical analysis. In addition, possible long-term relapses will be evaluated.

2 OBJECTVE

2.1 Main Objective

To evaluate and compare the topical effect of fludroxycortide 0.125 mg/g and imiquimod 5% creams in the treatment of actinic cheilosis through clinical analysis and digital photographs.

2.2 Specific Objectives

- To evaluate the effect of topical application of fludroxycortide cream 0.125 mg/g in the treatment of actinic cheilitis.
- To evaluate the effect of topical application of 5% imiquimod in the treatment of actinic cheilitis.
- Compare and effect of both treatments using clinical analysis and digital photographs.
- Compare adverse effects of both therapies.
- Evaluate patients' satisfaction and tolerability to both treatments.

3 MATERIALS AND METHODS

3.1 Ethical Aspects

The research project was approved by the Scientific Committee of the School of Health and Life Sciences of the Pontifical Catholic University of Rio Grande do Sul (PUCRS) and by the Research Ethics Committee of the same institution.

After being clarified about the research objectives and procedures, participants who agree to participate must read and sign the Free and Informed Consent Form (APPENDIX A).

3.2 Outline

This is a prospective, randomized, comparative and blinded clinical trial.

3.3 Sample

Forty participants of both sexes, white, aged at least 30 years, diagnosed with actinic cheilosis on the lower lip will be selected. This lesion is characterized by labial dyschromia (changes in lip color), dry and scaly areas, erosions, ulcerations, leukoplasic areas and loss of the labial mucocutaneous junction. According to these changes, cheilosis will be classified in different degrees, adapted from the study by Lima et al.[9]

- Grade I - presence of dyschromic areas and/or loss of delimitation between labial vermilion and adjacent skin;

- Grade II – presence of dyschromic areas and/or loss of delimitation between labial vermilion and adjacent skin associated with areas of dryness and scaling;
- Grade III – presence of thin whitish plaques with a smooth surface, associated or not with the alterations present in grade II cheilitis;

  Grade IV – presence of thick whitish plaques with a rough surface and/or erosions and ulcers, associated or not with the alterations present in grade II cheilitis

Patients will be randomly assigned to two groups. The randomization process will be carried out using the Research Randomizer platform, available through the website: www.randomizer.org.

1. **Fludroxycortide Cream 0.125 mg/g Therapy Group (Drenison®):** 20 participants treated by topical application of fludroxycortide cream.
2. **Imiquimod Cream Therapy Group (IG):** 20 participants treated by topical application of Imiquimod cream.

The sample size was based on previous studies in which participants with actinic cheilosis were treated with Fludroxycortide 0.125 mg/g (Drenison®) and Imiquimod 5%.[17,18]

3.3.1 Inclusion Criteria

Individuals will be included to participate in the study:

- Patients with actinic cheilosis classified as grades III or IV, as previously described.
- Over the age of 30 years.
- White skinned.

3.3.2 Exclusion Criteria

Participants who:

- Have other lesions in lip vermilion in addition to solar cheilitis.
- Are immunosuppressed such as transplanted or infected with HIV.
- Have had any type of treatment for actinic cheilosis in the last six months (except with sunscreen and lip balms).
- Have a known allergy to imiquimod.
- Have a known allergy to fludroxycortide.
- Are pregnant or breastfeeding.
- Have a suspicion of malignancy and, after partial biopsy, receive a histopathological diagnosis of carcinoma in situ or invasive squamous cell carcinoma.
- Have a history of radiotherapy in the head and neck region.
- Present any condition that may compromise their collaboration in the study.

3.4 Procedures

3.4.1 Interview and Physical Exam

During the anamnesis, the patient's identification data, profession, medical history, medication use, family history, smoking and drinking habits and history of sun exposure will be recorded in an individual form (APPENDIX B).

Extraoral and intraoral physical examination will be performed. Participants in both research groups will receive instructions for the daily use of lip sunscreen (SPF

30) and to avoid excessive exposure to the sun. In addition, they will be recommended to avoid the consumption of tobacco and alcohol. These patients will be monitored periodically at the Service of Stomatology of Hospital São Lucas, PUCRS.

Standardized digital photography will be performed to record lip changes. The patient's head must be positioned so that the Frankfurt horizontal plane is parallel to the ground and the edges of the photograph, the midsagittal plane must be perpendicular to the ground and parallel to the vertical edges of the photograph. The photos must be taken horizontally and must include only the patient's upper and lower lips centered on the image. The mouth should be slightly closed at rest, without maximum dental intercuspation. The light should be natural and without flash. To improve the visualization of the lesions, a cotton roll can be used, placed between the lower teeth and the labial mucosa.

3.4.2 Incisional Biopsy and Patient Management

In cases where there is a clinical suspicion of malignancy, an incisional biopsy will be performed. If the histopathological diagnosis is carcinoma in situ or invasive squamous cell carcinoma, the participant will be excluded from the sample and referred for treatment, which is part of the routine care of the Stomatology Service of Hospital São Lucas, PUCRS.

If, at the end of the study, the greater efficacy of one therapeutic approach is confirmed in relation to the other, patients who participated in the research in the group with less efficacy will be submitted to treatment with the therapy performed in the other group, if they so wish.

If, at the end of therapy, there is no clinical resolution of the condition and the participants remain with grades III and IV actinic cheilitis, an incisional biopsy or surgical excision of persistent lesions can be performed. After the end of the research, all participants will continue to be followed up at the aforementioned Stomatology Service.

3.4.3 Therapy with Fludroxycortide or Imiquimod Creams

All products used by participants during the treatment period will be provided free of charge by the researcher. Fludroxycortide (Drenison®) will be used in the form of a cream, at a concentration of 0.125 mg/g, three times a day for a period of six weeks. Patients will be instructed to avoid direct sun exposure after administration, not to eat or drink for one hour after drug application, and to use lip sunscreen (SPF 30) throughout the day.

Participants in the imiquimod group will be instructed to apply a thin layer of 5% imiquimod cream once a day, three days a week (Monday, Wednesday, Friday), for six weeks. Patients will be instructed to avoid direct sun exposure after administration, not to eat or drink for one hour after drug application, and to use lip sunscreen (SPF 30) throughout the day. Participants in both groups will be examined on days 0, 7, 15, 45, 60, 90, 120, and 180 of the study. At each appointment, a new photographic record of the lesions will be carried out.

A quantitative scale described by Rosen et al.[19] will be used to assess adverse effects. Six reactions are observed on this scale: erythema, desquamation, crusting, edema, vesiculation/pustulation and erosion/ulceration. Local adverse reactions will be identified and allocated according to severity on a numerical scale from 0 to 4.[19]

To assess the patient's tolerability and satisfaction with the substances, a three-question questionnaire will be applied at the end of the treatment. The scores of the two responses related to patient satisfaction will be added together and the following classification will be established: scores from 0 to 8 will correspond to a low degree of satisfaction, scores from 9 to 15 to an intermediate degree and scores from 16 to 20 to a good degree of satisfaction to the treatment. The patient's tolerability response score, which asks whether the product causes irritation to the lips, will be classified as follows: from 0 to 3, low tolerability, from 4 to 7, intermediate tolerability, and from 8 to 10, good tolerability to the treatment (APPENDIX C).

3.5 Data Analysis

A previously calibrated researcher will blindly evaluate the photographic images before treatment (day 0), at the end of treatment (45 days), 90 and 180 days after the beginning of the study and will assign a classification referring to the clinical degree of the disease (Grade I, Grade II, Grade III and Grade IV). In addition, a score regarding clinical improvement/worsening of the lip after treatment will be established by the investigator according to the following criteria:

1 - Complete improvement (absence of clinical signs of the disease);

2 - Partial improvement;

3 - No change;

4 - Worsening of the clinical presentation.

In the follow-ups of 90 and 180 days, when the treatment is already completed, possible relapses will be evaluated, thus being able to estimate the durability of the therapeutic effect.

To compare the clinical scores of classification of cheilosis between the groups, as well as its improvement after treatment, the Wilcoxon and Mann Whitney tests will be applied. To compare the results of patient satisfaction with treatment, the Student's t test will be used. For statistical analysis, SPSS 17.0 and R 3.5.1 or higher software will be used. Values of $p \leq 0.05$ will be considered significant.

4 RESEARCH RELEVANCE

The study proposes two therapeutic approaches for patients with actinic cheilosis, a potentially malignant condition of the labial vermilion. According to the results obtained, it is possible that both treatments can contribute to the management of these lesions, preventing their progression to squamous cell carcinoma of the labial vermilion, in addition to preserving and maintaining the aesthetics of this anatomical region.

5 BUDGET

Item	Products	Amount	Dose	Unit Value	Total Value
1	Fludroxicortida Cream (Drenison®)	60	0,125 mg/g	R$ 30,00	R$ 1800,00
2	Imiquimod Cream	180	50 g	R$ 20,00	R$ 3600,00
3	Filtro Solar Labial – FPS 30	24	5 g	R$ 15,00	R$ 360,00
TOTAL					**R$ 5700,00**

Research costs will be the responsibility of the researchers.

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Prof. Fernanda Gonçalves Salum

Responsible Researcher

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Maiara Jochims Fumagalli

Associated Researcher

6 CHRONOGRAM

ACTIVITIES/MONTH	JAN 2022	FEB 2022	MAR 2022	APR 2022	MAY 2022	JUN 2022	JUL 2022	AUG 2022	SEP 2022	OCT 2022	NOV 2022	DEC 2022	JAN 2023	FEB 2023	MAR 2023	APR 2023	MAY 2023	JUN 2023	JUL 2023	AUG 2023	SEP 2023	OCT 2023	NOV 2023	DEC 2023	JAN 2024	FEV 2024	MAR 2024	APR 2024
Screening																												
Randomization																												
Experimental Treatment																												

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APPENDIX A

FREE AND INFORMED CONSENT FORM

We, Maiara Jochims Fumagalli and Fernanda Gonçalves Salum, responsible for the research, EFFECT OF FLUDROXICORTIDE AND IMIQUIMOD CREAMS IN THE TREATMENT OF ACTINIC CHEILITIS: A RANDOMIZED CLINICAL TRIAL, are inviting you to participate as a volunteer in this study.

This research aims to clinically evaluate the effect of topical application of fludroxycortide and imiquimod creams in the treatment of actinic cheilitis, a lesion that occurs on the outer part of the lips and is caused by lifelong sun exposure.

We believe that this research is important because actinic cheilitis is classified as a potentially malignant disorder, so its treatment is essential. For its realization you will be randomly assigned and receive one of the treatments below:

- Fludroxicortide (Drenison®) will be used at a concentration of 0.125 mg/g, three times a day for a period of six weeks. Patients will be instructed to avoid direct sun exposure after administration, not eat or drink for one hour after application, and use lip balm (SPF 30) throughout the day. At the end of the treatment you will answer a questionnaire to evaluate your satisfaction with the treatment. Some side effects may occur with this medication, such as: local irritation, erythema (reddish discoloration of the lip) and edema (increase in volume or swelling).

- Imiquimod will be used by topical application of a thin layer of 5% imiquimod cream once a day for three days a week (Monday, Wednesday, Friday) for six weeks. Patients will be instructed to avoid direct sun exposure after administration, not to eat or drink for one hour after drug application, and to use lip sunscreen (SPF 30) throughout the day. Some adverse effects are expected with the use of this medication, such as: erythema (lip may become red), scaling, crusting, edema (increase in volume or swelling), vesiculation (vesiculation) and ulceration (sore formation). Adverse effects, when observed, last a maximum of 7 days.

You must attend follow-up appointments, which will be held at 0, 7, 15, 45, 60, 90, 120 and 180 days after starting treatment. At each appointment, your lip will be examined and a photograph will be taken so that we can compare the evolution of the case.

Researcher's Rubric Participant's Rubric

The following discomforts or risks may occur: Both treatments may result in side effects such as: erythema (lip may turn red), scaling, crusting, edema (increase or swelling), vesiculation (vesicle formation) and ulceration (wound formation). You have the right to claim compensation for any damage that you can see as a result of your participation in the study.

The benefits that we expect from the study in both treatments are the improvement of the clinical picture or the total remission of the lesions, if they are used correctly. All substances necessary for treatment will be provided to participants free of charge. If, at the end of the study, one of the treatments provides better clinical results than the other, the patients who participated in the research in the group with the lowest efficacy will be treated with the most effective therapy, if they wish.

It is important to clarify that, if you decide not to participate, there are other types of treatment indicated for your case.

During the entire research period, you have the right to clarify any doubts or request any information about the study, simply by contacting Maiara Jochims Fumagalli, on the phone (51) 999780226, or Fernanda Salum, on the phone (51) 981829945 at any time.

In case of any problem related to the research, you will be entitled to free assistance that will be provided by the researchers, in the Stomatology Service of Hospital São Lucas of PUCRS.

You have guaranteed your right to refuse to participate or to withdraw your permission, at any time, without prejudice or retaliation, for your decision.If for any reason you incur transportation and/or food expenses arising from your participation in this study, you will be adequately reimbursed by the researchers.

The information of this research will be confidential, and will be disclosed only in scientific events or publications, with no identification of the participants, except among those responsible for the study, ensuring the confidentiality of their participation.

If you have any doubts about your rights as a research participant, contact the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (CEP-PUCRS) at (51) 33203345, Av. Ipiranga, 6681/building 50 sala 703, CEP: 90619-900, Bairro Partenon, Porto Alegre – RS, e-mail: cep@pucrs.br, Monday to Friday from 8:00 am to 12:00 pm and from 1:30 pm to 5:00 pm. The Ethics Committee is an independent body made up of professionals from different areas of knowledge and members of the community. Its responsibility is to ensure the protection of the rights, safety and well-being of participants through review and approval of the study, among other actions.

Researcher's Rubric Participant's Rubric

By signing this consent form, you do not waive any legal rights you would otherwise have. Do not sign this consent form unless you have had the opportunity to ask questions and have received satisfactory answers to all of your questions. If you agree to participate in this study, you will initial all pages and sign and date two original copies of this consent form. You will receive one of the copies for your records and the other will be filed by the person responsible for the study.

I, _____
after reading (or listening to the reading) of this document and having had the opportunity to talk to the researcher in charge, to clarify all my doubts, I believe I am sufficiently informed, making it clear to me that my participation is voluntary and that I may withdraw this consent at any time without penalty or loss of any benefit. I am also aware of the research objectives, the procedures to which I will be submitted, the possible damages or risks arising from them and the guarantee of confidentiality and clarification whenever I wish.

In view of the above, I express my spontaneous agreement to participate in this study, authorizing the use, sharing and publication of my data and information of a personal nature for this specific purpose.

_____
Signature of the research participant or their legal representative

_____
Signature of a witness

DECLARATION BY THE PROFESSIONAL WHO OBTAINED THE CONSENT

I fully explained this clinical study to the participant or to their caregiver. In my opinion and that of the participant and caregiver, there was sufficient access to information, including risks and benefits, for an informed decision to be made.

Date:_____ _____
Signature of the researcher

_____
Name of the Investigator

APPENDIX B

PATIENT EXAMINATION FORM

IDENTIFICATION DATA:

Name: _____

Race: _____Sex: _____Occupation: _____

Phones: _____ Birth Date: __ __/__ __/19__ __

Interview

1. Medical History:

_____

_____

2. Medications you use continuously:

_____

3. Smoker ( ) Yes ( ) No
4. Alcoholic ( ) Yes ( ) No
5. Habit of taking Chimarrão ( ) Yes ( ) No
6. Sun exposure history ( ) Yes ( ) No

PHYSICAL EXAM:

1. Changes in lip vermilion

_____

_____

2. Clinical classification of the lesion:

( ) Grade I ( ) Grade II ( ) Grade III ( ) Grade IV

FOLLOW UP:

Assessment of patient tolerability and satisfaction according to the questionnaire:

( ) 0 a 9, low degree of satisfaction;
( ) 10 à 19, intermediate grade;
( ) 20 à 30, good patient acceptance of the proposed treatment.

FINAL CLINICAL ANALYSIS:

1 ( ) Complete improvement (absence of clinical signs of the disease);

2 ( ) Partial improvement (change to a less advanced degree of disease);

3 ( ) No change;

4 ( ) Worsening of the clinical presentation (clinical change to a more advanced degree of disease).

3. Clinical classification of the lesion:
( ) Grade I ( ) Grade II ( ) Grade III ( ) Grade IV

- 60 DAYS

1. Clinical classification of the lesion:
( ) Grade I ( ) Grade II ( ) Grade III ( ) Grade IV

- 180 DAYS:

2. Clinical classification of the lesion:
( ) Grade I ( ) Grade II ( ) Grade III ( ) Grade IV

APPENDIX C

ASSESSMENT OF PATIENTS TOLERABILITY FOR TREATMENT

Mark the questionnaire below with a score from 0 to 10 considering:

0 = Minimum score of agreement with the statement

10 = Maximum score of agreement with the statement

QUESTIONNAIRE:

1. My lip lesions got better with this product:

0	1	2	3	4	5	6	7	8	9	10

Minimum agreement — Maximum agreement

2. This product does not irritate the lips:

0	1	2	3	4	5	6	7	8	9	10

Minimum agreement — Maximum agreement

3. I am satisfied with this product:

0	1	2	3	4	5	6	7	8	9	10

Minimum agreement — Maximum agreement