Efficacy of an Aloe Vera, Chamomile, and Thyme Cosmetic Cream for the Prophylaxis and Treatment of Mild Dermatitis Induced by Radiation Therapy in Breast Cancer Patients: a Controlled Clinical Trial Study (Alantel Trials)

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EFFICACY OF AN ALOE VERA, CHAMOMILE, AND THYME COSMETIC CREAM FOR THE PROPHYLAXIS AND TREATMENT OF MILD DERMATITIS INDUCED BY RADIATION THERAPY IN BREAST CANCER PATIENTS: A CONTROLLED CLINICAL TRIAL STUDY (ALANTEL TRIALS)

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Abstract

• **Background**: Dermatitis is a skin condition caused by multiple causes, including radiotherapy treatment. Pharmacological treatments can become chronic and are not exempt from side effects. The latest recommendations of the American Academy of Dermatology establish the use of natural, nourishing, and moisturizing cosmetic products as prevention and the first therapeutic step for dermatitis. Alantel® is a cream developed to reduce redness and irritation and promote the local immune system, combat immunosenescence, as well as promote the healing of epidermal lesions. The objective was to evaluate the effect of a cream (Alantel) based on natural products at high concentrations for the preventive and curative treatment (early stages) of radiation-induced dermatitis in patients with breast cancer.

• **Methods**: Our protocol is a experimental, prospective, double-blind, multicenter, controlled clinical trial with two parallel arms. The experimental group will be treated with Alantel while the control group will receive a placebo. Radiotherapy oncology professionals will recruit a total of 88 patients (44 per comparison group) with breast cancer who will receive radiotherapy oncology treatment for 15 days, and they will be randomly assigned to the experimental or control group. Selected patients will be followed for four visits by Primary Care physicians for up to one week after completion of radiotherapy. The main study variable will be the incidence rate of mild post-radiation dermatitis. An intention-to-treat analysis will be performed, applying a comparison test for independent means and proportions. A bivariate and multivariate analysis will also be developed to check the treatment effect, adjusting for predictive sociodemographic and clinical variables.

• **Discussion**: The purpose of this clinical trial is to evaluate the effect of a cream already marketed (Alantel) based on natural products at high concentrations for the preventive and curative treatment (early stages) of radiation-induced dermatitis in patients with breast cancer. The COVID19 pandemic has influenced by delaying the start of the study. One of the main limitations of this study will be the time required to recruit the patients from the planned sample, given that the selection criteria are restrictive and, although the study is multicenter, recruitment is carried out through a single service on radiotherapy oncology.
Keywords
Chamomile, aloe vera, thyme, prophylaxis, dermatitis, radiation therapy, oncology, breast cancer

Introduction
Background and rationale
Dermatitis is inflammation of the surface layers of the skin, causing itching, blisters, redness, swelling, and often oozing, scabbing, and scaling. Known causes include dry skin, contact with a particular substance, certain drugs, varicose veins, radiation, etc. Typical symptoms include a red itchy rash, blisters, open sores, oozing, crusting, and scaling. The diagnosis is usually based on symptoms and confirmed by results of skin tests or skin samples, or presence of irritants, drugs or an infection [1]. Regardless of the type or cause, dermatitis is always the manifestation of a skin reaction to a major dryness, scratching, an irritant substance, or an allergen.

According to the MSD manual [1], general treatment of dermatitis includes supportive care of cosmetic type (such as moisturizers, dressings, and antihistamines for itching), topical corticosteroids, and sometimes antibiotics or other drugs, or ultraviolet light therapy. Treatment of dermatitis depends on the cause and the specific symptoms. Depending on the severity of the process, this therapeutic ladder can be gradually climbed to treat the milder symptoms to the more severe and chronic ones.

According to the American Academy of Dermatology [2], the first level of treatment should be non-pharmacological, mainly through moisturizers and “bath therapies” such as neutral, emollient, and moisturizing soaps of natural origin. From this point on, all treatments are based on drugs and not cosmetics, although the latter will serve on the following therapeutic steps to supplement hydration and their effect on irritation and pruritus. Among these natural products are aloe vera and chamomile [3-5]. These agents, qualified as cosmetics, have been used to treat iatrogenic radiation dermatitis to alleviate the symptoms and signs of this condition [6-9]. Other studies report using other cosmetic therapies to relieve symptoms and signs of dermatitis [10,11].

Cosmetics are the first level of treatment required for dermatitis [2]. In the case of radiation-induced dermatitis (RD), several studies report the prevention or treatment of radiation-induced dermatitis with the application of skin products, including aloe vera gel [12], phospholipid-based anionic cream [13], wound healing ointment [14], corticosteroid therapy [15], or hyaluronic acid-based formulation [16]. In addition, washing the skin with soap and water during radiation therapy for cancer treatment may be helpful because it may eliminate germs that cause skin inflammation [17]. To date, however, no standard
therapy or broad consensus on the optimal management of RD in cancer patients is available.

The Radiation Therapy Oncology Working Group has developed a scale of skin lesions after radiation therapy [18]. It comprises 5 degrees scored from less to more depending on severity. Acute or moderate injuries, which would be treatable with cosmetics, include categories 1 and 2: Mild atrophy, mild hair loss, mild depigmentation, patch atrophy, and moderate telangiectasia.

However, we have found few clinical trials to support or demonstrate the efficacy of these cosmetic products in the treatment of RD, so we believe that providing scientific evidence about this is very appropriate and convenient.

Following these clinical protocols [1,2] and the literature review on the effectiveness of cosmetics for hydration and relief of symptoms and signs of RD, we consider it relevant to investigate if a cream containing natural products is effective as a prophylactic procedure in breast cancer patients treated with radiation therapy. We focused on this type of cancer as it is one of the most frequent, and in which more patients could benefit if demonstrated that this product is useful. This could avoid climbing the therapeutic ladder toward treating RD with drugs that may lead to side effects. The current drugs cause a pharmaceutical expense that is mostly unproductive because these alone do not adequately manage nutrition, hydration, or de-epithelialization because they do not have the correct formulation. In addition, these treatments are not exempt from side effects, leading to symptoms continuing in short to medium term.

Objectives

A controlled clinical trial is planned to objectively evaluate the efficacy of a cosmetic cream. The purpose is to demonstrate that a topical preparation based on active ingredients of natural origin (Alantel®, based on aloe vera, chamomile, and thyme), with anti-inflammatory and epithelization properties, is effective (compared to a placebo, a harmless product made up of a moisturizing substance), in prophylaxis or curative treatment of mild RD in radiation oncology used to treat breast cancer patients. We also want to show that this preparation is safe and has no side effects.

As secondary objectives, we consider the following: a) To check whether this preparation can reduce the discomfort caused by inflammation and cell death, which are the cause of the symptoms and morbidity of radiation-induced dermal lesions in radiation oncology; b) To determine the health-related quality of life before and after treatment in women who are prescribed this cosmetic cream compared with women who do not use this cosmetic cream; c) To demonstrate that the coordinated follow-up of this type of patients between Radiation Oncology and Primary Care improves its quality and the health care of these patients.
Trial design

Methods: Participants, interventions and outcomes

Study setting

The Alantel study is designed as a randomised, controlled, multicenter, superiority, double-blind trial, with two parallel groups.

A total of 88 breast cancer patients undergoing radiation therapy will be recruited into the radiation oncology clinic and assigned to the experimental group (EG: Alantel) or the control group (CG: Placebo), with an allocation ratio of 1:1 (see flowchart in Figure 1). Both groups will receive a 15-session (3 weeks) hypofractionated radiation therapy, subject to the usual hygienic recommendations.

Table 1 shows the schedule of the main events of the study, both the recruitment process and the intervention and follow-up and evaluation visits.

The study is carried out at the Radiotherapy Oncology Center of the Reina Sofia Hospital and at five participating Primary Care (PC) Centers, located in Cordoba (Spain), and dependent on the Andalusian Health Service.

Eligibility criteria

- Inclusion criteria: Patients aged 18 years or older diagnosed with breast cancer and who are going to start radiation therapy with a radical intention on the affected breast, by the hypofractionated scheme with integrated boost (40.05 Gy with integrated boost, 48 Gy, in 15 sessions), coming from centers involved in the project or that can be followed up by a participating Primary Care professional and that sign an informed consent.

- Exclusion criteria: Patients with dermal lesions or invasive skin cancer or distant metastases, history of connective tissue disorders, severe mental disorder (dementia, drug addiction, etc.), history of hypersensitivity reaction to any of the ingredients in the study cream, history of severe/extensive burn, moisture, erosion or drainage in the treatment area, or participants involved in other clinical trials within that month.

Fourteen-collaborating clinical researchers, 5 oncologists, 8 physicians of family and a Primary Care Occupational Therapist, will carry out the therapeutic intervention to be tested.

Who will take informed consent

In the informed consent form, recruited patients will be asked if they accept the use of their data if they consent to participate, even if they decide to withdraw.

Interventions

Once the patient has been included in the study and assigned to one of the two groups, the radiation oncologist will collect demographics and existing pathologies and perform an initial assessment of the skin to be irradiated before the start of radiation therapy. She will
administer the patient a Quality-of-Life Assessment Questionnaire (Skindex-29) [21] and inform the General Practice (GP) of the patient's details, identification code, and probable date of initiation of radiation therapy so that the GP can contact the patient prior to the start of the treatment to schedule follow-up visits.

At each follow-up visit after sessions 5, 10, 15, and 1 week after completion of radiation therapy, the GP will perform the following actions:

- Evaluate patients' irradiated skin according to the common toxicity criteria of the cooperative skin group suggested by the RTOG Foundation (https://www.rtog.org)[18].

- Likewise, patients presenting with dermatitis will be asked to assess and quantify the discomfort and pain related to dermatitis symptoms and signs on an analog ordinal scale (from 1 to 10).

- Complete the Skindex-29 Quality of Life Questionnaire [21]–(https://www.bibliopro.org/ buscador/294/cuestionario-dermatologico-de-calidad-de-vida-skindex-29).

- Record Adverse Event (AE): Possible adverse effects will be evaluated and reported during the study, and their causal relationship with the components of the cream will be assessed. If an adverse reaction is found, the researcher will evaluate the intensity and frequency of each episode and decide whether or not additional treatments are needed. These side effects will be notified to the Andalusian Pharmacovigilance Center through the yellow card alert system. If the physician considers it appropriate, the patient will be withdrawn from the study.

Outcomes

All outcomes are described in detail in table 1. Primary outcomes is the incidence of RD.

Additional secondary outcomes include the level of toxicity in patients' irradiated skin will be assessed according to the common toxicity criteria of the cooperative group for skin suggested by the RTOG Foundation (https://www.rtog.org) [18] according to which toxicity is classified into five levels: 0 for no toxicity or no change, 1 for scattered macular or papular rash or erythema that is asymptomatic, 2 for scattered macular or papular rash or erythema with pruritus or other associated symptoms, 3 for symptomatic generalized macular, papular or vesicular rash, and 4 for exfoliative dermatitis or ulcerative dermatitis.

The assessment of discomfort and pain concerning symptoms and signs related to dermatitis is based on the subjective assessment and quantification by the patient on an ordinal scale (range 0 to 10), answering the following question: What score would you rate from 0 (where 0 is the situation where you do not feel symptoms such as pruritus, pain, itching or peeling of the skin) to 10 (where 10 is the situation where you notice the most symptoms) to your skin problem where do you have the lesion?.

Quality of life will be assessed by completing the Skindex-29 questionnaire. Skindex-29 is a self-administered questionnaire to measure the quality of life of patients with skin conditions every 4 weeks, consisting of 29 items. The Spanish version of Skindex-29 has been validated (https://www.bibliopro.org/buscar/294/cuestionario-dermatologico-de-calidad-de-vida-skindex-29)21.
Sample size

Taking as reference values those provided in a previous study [20], the expected occurrence rate of RD (primary outcome variable) would be 46.7% in EG and 78.6% in CG, respectively; with a 1:1 allocation, accepting an alpha risk of 0.05 (5%) and a beta risk of 0.20 (20%), and assuming a follow-up loss rate of 20%, 88 eligible patients (44 in each group) are needed (calculations performed with the Granmo software version 7.12 in: https://www.imim.cat/ofertadeserveis/softwarepublic/granmo/, sample size for two independent proportions).

Recruitment

Patients from both groups will be recruited at the Radiation Oncology Unit of the Reina Sofia Hospital (Cordoba, Spain). They will be followed up by family physicians and a Primary Care Occupational Therapist after sessions 5, 10, and 15 of radiotherapy and one week after the end of the treatment. Those in the EG will be given the test cosmetic cream, while those in the CG will receive a placebo. The placebo cream will be very similar to that of the Alantel, both in color, shape, weight, and smell; the placebo cream will be manufactured by the producing laboratory and will be composed of a moisturizing substance.

Assignment of interventions:

Sequence generation

The participants will be assigned equally to the two study groups using the block randomization procedure, by one of the investigators, an expert in statistics, who will remain blind to the assignment of subjects during the statistical analysis. The random sequence of allocation of eligible patients to EG or CG will be generated using EPIDAT version 4.1. Once this sequence has been generated, the alphanumeric codes will be constructed according to the following order: Number of the recruited patient (01, 02,…); assigned group (A or B); oncologist responsible for the case (1-5); primary care physician (1-9).

Assignment of interventions: Blinding

This is a double-blind study, where neither the investigator responsible for the intervention, nor the patients included in the study, will know at any time whether they receive Alantel cream or placebo. The statistician in charge of the analysis will also remain blind. The product bottles will be similar in appearance, containing the active substances for the EG and a harmless placebo (a moisturizing substance) for the CG. The placebo will be prepared and provided by the company making the Alantel cream.
Data collection and management

The person in charge of monitoring the field work of the study will contact the field researchers, if necessary, to complete the missing data in the data collection forms, under the supervision of the principal investigator, who will not participate in the collection and mechanization of the data. After the trial, patients’ personally identifiable information will be removed and placed in a separate database for statistical analysis. The final data of the trial will be available to the project funder and the Ethics Committee. The personal information of the participants will be stored in a database that will be guarded by the principal investigator throughout the study period, safeguarding it for 5 years, as established by Spanish legislation.

Statistical methods

After the mechanization and filtering of the data, a descriptive analysis will be performed that will include the characteristics of the studied population (sociodemographic variables) and outcome variables using measures of central tendency, dispersion, and position in the quantitative variables; tabulation and calculation of relative frequencies in qualitative variables. The calculation of the main estimators with their corresponding confidence intervals for 95% safety will also be performed. A pre-post-intervention comparative analysis will then be performed with the end-points used; for this we will use means comparison tests for independent samples (parametric, such as ANOVA, if the variables follow a normal distribution -Shapiro-Wilk Test- or non-parametric, such as Friedman's test, if they do not follow it), or proportion comparison test on qualitative variables, such as Pearson's Chi-square test or Fisher's exact test (p<0.05). Finally, the results will be statistically compared between groups using the log-rank test after estimating the survival curve with the Kaplan-Meier method. An intent-to-treat analysis will be performed that will include all participants assessed at least once after randomization. In addition, a per-protocol analysis will be performed, defined as the group of participants who comply with the procedure to be followed, including the use of the substances tested in the study, in at least 80%. Multiple linear regression analysis -dependent variable: VAS), and the survival analysis, by Cox regression -dependent variables: RD or no; RD improvement vs. no improvement and cured vs. non-cured-) will be performed to evaluate the effect of the product, adjusting for the sociodemographic and clinical variables presumably predictive or confounding. Statistical analysis will be performed using SPSS v.17.0 and EPIDAT 4.1 packages.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

The Project Coordination Commission is made up of the management team, which
consists of 6 members who meet every two months to review the status of the trial. It is made up of the main researcher of the project (Dra. Celia Jiménez, epidemiologist), Dr. Luis Angel Pérula (epidemiologist expert in methodology and statistics), Dra. María Espinosa (oncologist from the radiotherapy oncology service) and three family doctors (Dra. Gertrudis Montes, Dr. Juan José Muñoz and Dra. Esperanza Romero).

Important modifications made to the initial protocol will be communicated to the funding body, the Ethics Committee and will be registered in clinicaltrials.gob.

### Adverse event reporting and harms

Possible adverse event (AE) will be evaluated and reported during the study, and their causal relationship with the components of the cream will be assessed. If an adverse reaction is found, the researcher will evaluate the intensity and frequency of each episode and decide whether or not additional treatments are needed. These AE will be notified to the Andalusian Pharmacovigilance Center, as well as the Ethics Committee of the Reina Sofia Hospital, in Cordoba. If the physician considers it appropriate, the patient will be withdrawn from the study.

### Dissemination plans

Study results will be communicated to clinical stakeholders, disseminated in communications at scientific events, and through publications in peer-reviewed scientific journals. The final results will also be disseminated to the health professionals involved in the care of this type of patient through the internal communication channels of the Andalusian Health Service.

### Discussion

The purpose of this clinical trial is to evaluate the effect of a cream already marketed (Alantel) based on natural products at high concentrations for the preventive and curative treatment (early stages) of radiation-induced dermatitis in patients with breast cancer. One of the main limitations of this study will be the time required to recruit the patients from the planned sample, given that the selection criteria are restrictive and, although the study is multicenter, recruitment is carried out through a single service on radiotherapy oncology. The COVID19 pandemic caused the study to be delayed and could not start at the scheduled time. In addition, this influenced the patient recruitment process, given that accessibility to the health system was restricted and the research staff suffered an increase in the demand for care, focusing their efforts on the care of cancer patients with
COVID19.

Trial status
The study was intended to start in 2019, but had to be interrupted due to the COVID19 pandemic. The pilot study was carried out between July and September 2021, the training sessions for field researchers were held in October 2021, and the study is expected to conclude in May 2023. The date recruitment began in November 2021, having recruited 60 patients, and is expected to end in February 2023.

Abbreviations
RD: Radiation-induced dermatitis.
EG: Experimental group.
CG: Control group.
GP: General Practice.
PC: Primary Care.
AE: Advers Event.

Declarations

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Alantel trials Collaborative Group:
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Authors’ contributions
CJG is the Chiev Investigator, junto a LAPT and EVB conceived the study, LAPT, CJG, EVB, MEC, ERR, GMR, and JJMG contributed to study design. LAPT provided methodological and statistical expertise in the design of the clinical trial. LAPT, CJG, MEC, ERR, GMR, and JJMG, developed the study procedures manual, All the authors read and approved the final manuscript.

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Ethics approval and consent to participate
The Clinical Research and Ethics Committee of the Reina Sofia Hospital in Cordoba (Spain) approved the protocol for this clinical trial (reference number 4430, dated 03/12/2019). Signed written informed consent from each participant shall be sought following the general recommendations of the Helsinki Declaration. All participants will be informed about the purpose of the study and the risks and benefits. Confidentiality of the participants' data will be guaranteed at all times under the provisions of Organic Law 3/2018, on the Protection of Personal Data and the Guarantee of Digital Rights, Law 14/2007r, on Biomedical Research, and Regulation 2016/679 of the European Parliament and of the Council on the General Protection of Personal Data about the processing of personal data and the free movement of such data.

Competing interests
Enrique Villegas Becerril claims to be one of the inventors of the Alantel© cream. Authors declare that they have no competing interests.

References


Figure 1. Flow chart of the research phases of the Alnatel study

**Baseline Visit “0”**
Recruitment and screening of patients who meet eligibility criteria.
Request for informed consent.

**Randomized allocation 1:1**
(n=88 patients)

**Experimental Group (n=44 patients)**
Alnatel cream application up to 1 week after completion of radiation therapy

**Visits 1 to 3 (every 5 days):**
Outcome assessment

**Visit 4 (1 week after end of RT):**
Final outcome assessment

**Data collection and analysis**

**Control Group (n=44 patients)**
Placebo cream application up to 1 week after completion of radiation therapy

**Visits 1 to 3 (every 5 days):**
Outcome assessment

**Visit 4 (1 week after end of RT):**
Final outcome assessment

Figure 1
See image above for figure legend

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf
- SPIRITchecklist.pdf