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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 (the Alantel study)

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ABSTRACT

Objectives: Radiation-induced dermatitis (RD) is one of the most common toxicities in radiation therapy (RT) patients. Corticosteroids, immunosuppressants, and natural products (NPs) have been used as treatment. The objective was to evaluate the efficacy of a NPs-based cream (Alantel®) to reduce the incidence of RD in women with breast cancer undergoing RT treatment.
Design: We conducted a controlled, randomized, double-blind clinical trial.
Setting: Radiation Oncology Unit of the Reina Sofía Hospital and 5 Primary Care centers of the Cordoba and Guadalquivir Health District (Spain).
Interventions: Patients assigned to the experimental group (GTA) were treated with Alantel, while those in the control group (GTE) were treated with a moisturizer and emollient cream.
Main outcome measures: The primary outcome variable was the incidence of RD. RD-free time, duration of RD, quality of life, and product safety were also assessed.
Results: Seventy patients were included in the study, 35 in the GTA and 35 in the GTE. The incidence of RD was lower in the GTA (71.4%) than in the GTE (91.4%) after 4 weeks of follow-up (RR = 0.78; NNT = 5; $p < 0.031$). The Skindex-29 questionnaire showed differences in the statement: "My skin condition makes it hard to work or do hobbies" (17.1% in the GTE vs. 2.9% in GTA; $p = 0.024$).
Conclusions: The higher efficacy of Alantel® compared to the control cream in reducing the incidence of RD in women with breast cancer has been demonstrated.

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1. Introduction

Radiation-induced dermatitis (RD) is a common sequel of radiation therapy (RT). Up to 95% of patients will develop moderate to severe skin reactions [1]. According to the American Academy of Dermatology protocols [2], the first level of treatment must be through non-pharmacological interventions (moisturizers, bath therapies: neutral soaps, emollients). In moderate to severe lesions, all treatments are based on drugs, not cosmetics. However, the latter will also be beneficial in the following therapeutic steps to complement the pharmacological treatments, moisturize, and for their effect on irritation and pruritus. Among these natural products (NPs), we found aloe vera and chamomile [3–5].

Rosenthal et al. [1] reported that the incidence of dermatitis, according to the literature, is 85%. This review highlights the role of NPs, including chamomile and aloe, against the appearance of RD. It reports studies finding no differences or improvement after using these NPs in dermatitis management. It is striking that all these references are more than 21–32 years old [6–8], whereas much more recent studies with conclusions contradicting them have been published [9–12]. We found guidelines belonging to our environment recommending the use of these NPs based on the recent literature [2,12,13].

The inconsistent results regarding the usefulness of NPs in preventing RD could lie in the cream formula. According to our literature analysis, these differences could be explained by different NPs concentrations, as shown by our clinical trial and other studies, even compared to the potency given by a corticosteroid in inflammatory diseases in humans and animal models [14–16]. Various origins or concentrations of NPs have been used in the literature. Therefore, the results regarding the presence or absence of efficacy in treating RD cannot be extrapolated. Other studies have reported using other cosmetic therapies to relieve the symptoms and signs of dermatitis [17,18].

Several authors reported the prevention or treatment of RD with the external application of skin products, including aloe vera gel [11], silver sulfadiazine [19], henna ointments or silymarin gel [20], cortisone therapy [21], or hyaluronic acid-based formulation [22]. In addition, washing the skin with soap and water during RT for cancer may be helpful because it may kill the microbes that cause skin inflammation [23]. However, no standard therapy or broad consensus on the optimal management of RD in cancer patients is available to date. The Radiation Therapy Oncology Working Group has developed a scale of skin lesions after radiotherapy [24]. It comprises 5° and is scored from lower to higher severity. Acute or moderate injuries would be treatable with cosmetics; they include categories 1 and 2: Mild atrophy, mild depigmentation, patch atrophy, moderate telangiectasia, and hair loss.

According to the law, no clinical trials are required to market these cosmetic products; therefore, only some trials have been conducted to assess their effectiveness. However, providing scientific evidence about it is appropriate and convenient. It is worth testing if a cream containing natural products is effective as a prophylactic procedure or improves a significant percentage of mild RD. Therefore, climbing the therapeutic ladder toward treatment with drugs can be avoided because plant extracts at the appropriate concentration and origin may be equally effective or better than a topical corticosteroid without the drug side effects [14–16,25]. The purpose of the present study was to demonstrate that Alantel cream, compared with a usual cream, is more effective in preventing the appearance of RD or minimizing its severity or duration in patients with breast cancer. In addition, we aimed to assess the safety of Alantel cream with adequate concentrations so that, as indicated by professional societies, it can be useful for treating mild RD. As secondary objectives, we consider its cost-benefit.

2. Materials and methods

2.1. Study and design

A multicenter, prospective, experimental, randomized, double-blind, controlled trial with two parallel arms was conducted. The patients were randomly assigned to the experimental group treated with Alantel (GTA), or the control group (GTE) treated with moisturizer/emollient. Both groups received a hypofractionated RT of 15 sessions (3 weeks) under the usual hygienic recommendations. The study protocol adhered to the Recommendations for Interventional Trials (SPIRIT Statement) [19], and was registered at ClinicalTrials.gov (NCT04116151). The cream to be tested (Alantel®) is patented (PCT/ES2015/070695).

2.2. Study population and sample

Women diagnosed with breast cancer with an indication of RT in the Radiation Oncology Service of the Reina Sofia Hospital of Cordoba (ROS-RSH) and who were attached to one of the participating Primary Care Centers (PC) in Cordoba (Spain). Fifteen clinicians participated in the research, of which 2 were epidemiologists, 5 were radiation oncologists, 6 family physicians, 1 occupational therapist, and 1 ophthalmologist, creator of the Alantel cream, and with experience in the use of this cream in the treatment of dermal lesions on the eyelids.

- Inclusion criteria: Patients ≥18 years old diagnosed with breast cancer undergoing RT with a radical intention on the affected breast, by the hypofractionated scheme with integrated boost (40.05 Gy with integrated boost of 48 Gy, in 15 sessions), coming from centers involved in the project or that could be followed-up by a clinician working at a participating PC and who signed the informed consent.
- Exclusion criteria: Patients with dermal lesions or invasive skin cancer or distant metastases, history of connective tissue disorders, severe mental disorder, 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.

Taking as reference values provided in a previous study [19], the expected occurrence rate of RD (primary output variable) would be 46.7% in GTA and 78.6% in GTE, respectively, accepting an alpha risk of 0.05 and a beta risk of 0.20 and assuming a follow-up loss rate of 20%, 88 eligible patients (44 in each group) are needed.

2.3. Randomization, allocation concealment and blinding

An expert in research methodology who was not involved in the patients' selection, recruitment, and intervention conducted the randomization. A randomized allocation sequence was generated for eligible patients for GTA or GTE using EPIDAT version 4.2. Then, an alphanumeric code based on the number of the recruited patient, the assigned group, the oncologist in charge of the case, and the PC clinician was assigned to each patient.

The product bottles were similar in external appearance, containing the active substances for the GTA and a moisturizing-emollient cream for the GTE, which was prepared and provided by the same company manufacturing Alantel cream.

2.4. Recruitment

Patients from both groups were recruited at the ROS-RSH, where oncologists assessed whether patients met the selection criteria (baseline visit, V0). Subsequently, a follow-up was conducted by family physicians and a PC occupational therapist after the RT sessions 5, 10, and 15, and one week after the end of treatment (visits 1 (V1), 2 (V2), 3 (V3), and 4 (V4), respectively).

The ROS-RSH professionals provided the patients with cream bottles at V0, following the pre-established randomization scheme. The Alantel cream was given to the GTA, while those patients of the GTE received the cream based on a moisturizing-emollient substance.

2.5. Intervention

Once the patient was included in the study and assigned to one of the two groups, at V0, the clinicians collected demographics and existing pathologies, conducted an initial assessment of the skin to be irradiated before the start of RT, and administered a Quality-of-Life Assessment Questionnaire to the patient (Skindex-29) [26]. Patients were instructed to start treatment with the product according to the following guideline: from two days before the start of radiotherapy and up to one week after the end of it, applying it twice a day, in the morning, at least 2 h before the radiotherapy session and the second, maximum 2 h after the session.

The radiation oncologist also informed the corresponding PC professional of the patient's data, identification code, and the probable date of initiation of the RT, so that the clinician could contact the patient prior to the beginning of the treatment, building trust in the doctor-patient relationship, and schedule follow-up visits.

At each follow-up visit, the responsible PC clinician performed the following actions.

- Evaluated the irradiated skin of patients according to the common toxicity criteria of the cooperative skin group suggested by the RTOG/EORTC Foundation [24].
- Requested patients developing dermatitis to quantify (0–10 points) its effects using an analog ordinal visual scale.
- Evaluated the evolution of the dermal lesion: In case of the appearance of a dermal lesion, the clinician categorized it as 1) remains the same or worsens; 2) partial improvement; 3) total improvement or complete cure.
- Completed again the Skindex-29 questionnaire [26] at the last visit (V4).
- Recorded adverse events (AE): In case of possible AE, these were evaluated and reported during the study, assessing their causal relationship with the components of the creams. If an AE was found, the researcher assessed the intensity and frequency of each episode and instituted treatment if needed. The patient could be withdrawn from the study if the physician deemed it appropriate.

2.6. Study variables

2.6.1. Dependent variables

The dependent primary outcome variable is the incidence of RD throughout the intervention period. As outcome variables, the time to the onset of RD and the duration of RD were also measured. Additional secondary outcomes included the toxicity level in patients' irradiated skin, which was assessed according to the common toxicity criteria of the cooperative skin group suggested by the RTOG Foundation [24]. They classify toxicity into five levels: 0 for no toxicity, 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 compatible with RD was based on subjective perception and quantification by the patient on an ordinal scale (range 0–10), answering the following question: " What score would you give from 0 (0 being the situation where you do not feel symptoms such as itching, pain, stinging or scaling) to 10 (10 being the situation where you perceive the most symptoms) to your skin problem where the lesion occurs?".

In case of the presence of a dermal lesion, 7 pictures of the lesion were taken from each patient at each follow-up visit. The lesion was evaluated and categorized by the clinician responsible for follow-up. The pictures were taken with a mobile phone, and any information that could identify the person had to be deleted, and their communication and storage guaranteed. For this purpose, the location and cloud storage were deactivated, avoiding any feature or character in the image that could identify the person. Once the image was sent through the corporate intranet of the Andalusian Health Service in a password-protected compressed file to the practititoner's corporate computer, the pictures were immediately deleted from the mobile phone.

Quality of life was assessed by completing the self-reported Skindex-29 questionnaire. It consists of 29 items and is specific for measuring quality of life of patients with skin diseases. Its Spanish version has been validated [26].

2.6.2. Independent variables

Age was collected as demographic data of the patients. Clinical data included symptoms and signs in case of development of RD, previous history of similar lesions, presenting other chronic processes, and previous and concomitant treatments.

2.7. Statistical analysis

A descriptive analysis, and the outcome variable analysis were conducted. The main estimators and their corresponding confidence intervals for 95% safety (95%CI) were also calculated. Then, a pre-post-intervention comparative analysis was performed with the end-points used, for which mean comparison tests were used for independent samples (parametric, such as Student's *t*-test or ANOVA for repeated measures, if the variables followed a normal distribution -Shapiro-Wilk test- or non-parametric, such as the Mann-Whitney U or Friedman test, if they do not follow it), or proportion comparison test on qualitative variables, such as the Pearson's chi-squared test. Bilateral contrasts were used ($p \leq 0.05$). Size estimators were used as measures of the effect of the intervention, such as relative risk (RR), absolute risk reduction (ARR), and number of subjects needed to treat (NNT), with their respective 95%CI. The statistical analysis was performed using the SPSS v.17.0 package and an on-line calculator (http://evalmedicamento.weebly.com/calcular/1-calculadora-para-las-medidas-del-efecto-de-resultados-en-salud-variables-dicotomicas).

2.8. Ethical-legal aspects

The Clinical Research and Ethics Committee of the Reina Sofia Hospital in Cordoba (Spain) approved the protocol for this clinical trial (reference 4430). Signed written informed consent was obtained from each participant following the general recommendations of the Helsinki Declaration. All participants were informed about the purpose of the study and the risks and benefits. Confidentiality of the participants' data was always guaranteed 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. The personal data collected from the patients were collected, shared, and kept under restricted access to the researchers responsible for coordinating and monitoring the study, dissociating these data from the clinical information to protect confidentiality before, during, and after the trial.

3. Results

Seventy patients were included in the study, 35 in the GTA and 35 in the GTE. Fig. 1 shows the flowchart of the study. Patients had a mean age of 55.29 ± 11.44 years (limits: 32–79: 95%CI: 52.80–55.78), without statistically significant differences between both groups ($p = 0.159$).

Fig. 2 and Table 1 show the incidence of dermatitis at each follow-up visit by comparison group. Differences between both groups were found

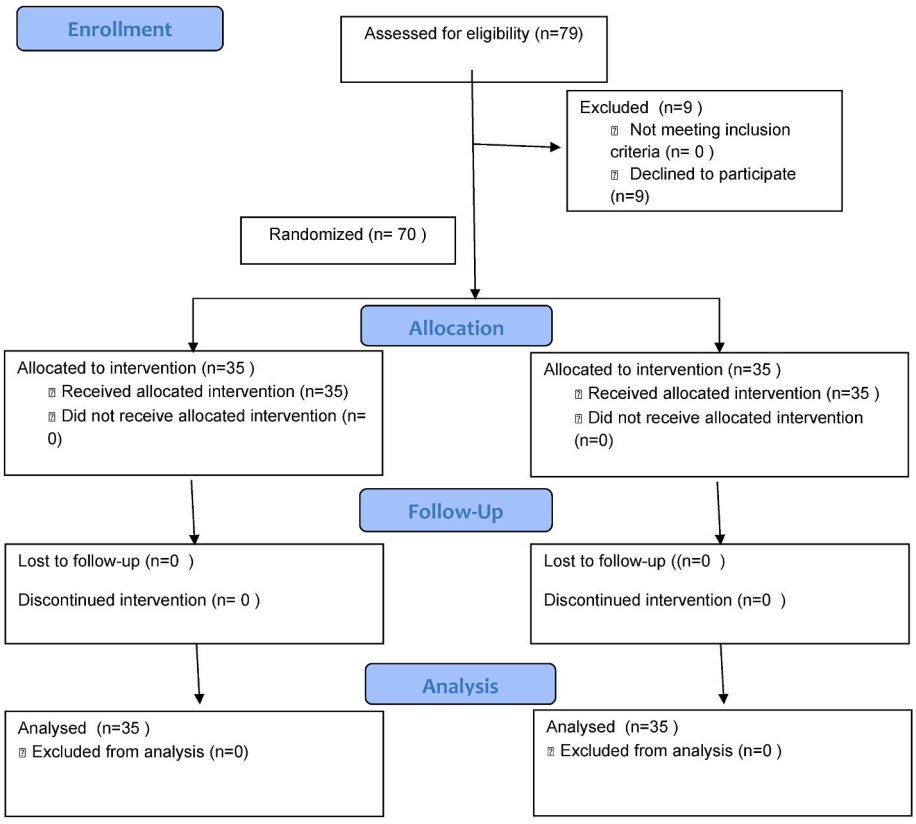

Fig. 1. Flow diagram of Alantel study.

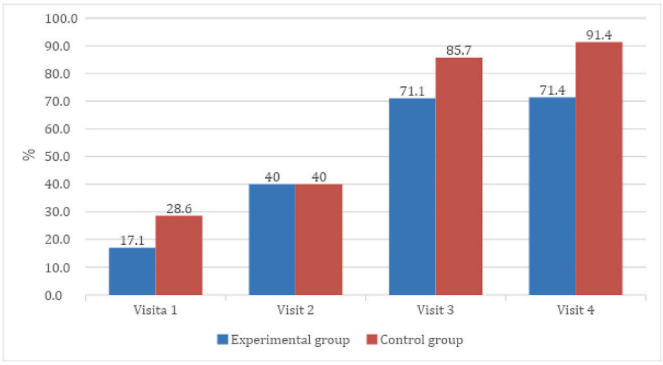

Fig. 2. Incidence of radiation dermatitis at each follow-up visit by comparison group.

in the incidence of RD in V4, at the fourth week of the beginning of the RT sessions, this being 71.4% in the GTA compared to 91.4% in the GTE ($p = 0.031$); as shown in Tables 1 and in the previous visits, the differences were not statistically significant.

It is worth noting from Table 1 the results found in terms of the effect size measures at V4, where the estimated RR was 0.78, the ARR was 20%, and the NNT was 5.

For skin lesions detected or toxicity attributed to oncological RT, 9 (grade 3) were observed at V1, 23 (grade 3) were found at V2, 53 lesions (grade 2: 6, grade 3: 44, grade 4: 3) were found at V3, no significant differences were found between both groups. In contrast, Table 2 shows differences at V4 (χ^2: 8.549; $p = 0.036$), finding a larger number of skin lesions in patients treated with the moisturizer (97.1%) than in those treated with the Alantel cream (74.2%).

Throughout the follow-up period, 10 AE or side effects were found attributable to the creams: 4 were described as stinging or itching, 4 as local redness, 1 as vesicular rash, and 1 like hypoesthesia in the skin. No significant differences were found between groups. No patient required

Table 1
Incidence of dermatitis at each follow-up visit and the effect size of the intervention with the Alantel cream versus the moisturizer cream.

Visit	RD	Group				RR (95%CI)	ARR (95%CI)	NNT (95%CI)	Chi-square (p-value)
		Experimental		Control					
		n	%	n	%				
Visit 1 (5th day)	Yes	6 17.1	29 82.9	10 28.6	25 71.4	0.60 (0.24–1.47)	11.4% (−7.37% a 21.25%)	9 (3 a −14)	1.296 (0.255)
	No								
Visit 2 (10th day)	Yes	14 40.0	21 60.0	14 40.0	21 60.0	1.00 (0.56–1.78)	0% (−21.88% a 21.88%)	NC	0.000 (1.000)
	No								
Visit 3 (15th day)	Yes	25 71.4	10 28.3	30 85.7	5 14.3	0,83 (0,65-1,07)	14,29% (−4.05% a 33.72%)	7 (3 a −25)	2.121 (0.145)
	No								
Visit 4 (22nd day)	Yes	25 71.4	10 28.3	32 91.4	3 8.6	0,78 (0,62-0,99)	20.0% (2.59% a 38.46%)	5 (3 a 39)	4.629 (0.031)
	No								

RD: Radiodermatitis; RR: Relative Risk; ARR: Absolute Risk Reduction; NNT: Number Needed to Treat; 95%CI: 95% Confidence Interval; NC: Not calculable.

Table 2
Level of toxicity due to radiation therapy found at the final visit (fourth week), according to the group.

Level of toxicity and type of skin lesion		Group		Total
		Control	Experimental	
Grade 4: Exfoliative or ulcerative dermatitis	n	2	2	4
	%	5.7	5.7	5.7
Grade 3: Scattered macular or papular rash or erythema with pruritus or other associated symptoms	n	26	20	46
	%	74.3	57.1	65.7
Grade 2: Symptomatic generalized macular, papular, or vesicular rash	n	6	4	10
	%	17.1	11.4	14.3
Grade 1: Scattered macular or papular rash or erythema that is asymptomatic	n	0	0	0
	%	0.0	0.0	0.0
Grade 0: No lesion	n	1	9	10
	%	2.9	25.7	14.3
Total	n	35	35	70
	%	100.0	100.0	100.0

withdrawal from the trial, given the mild AE.

Fig. 3 shows the mean scores obtained with the ordinal scale used to measure the extent to which RD causes discomfort or RT exposure affects the patients symptomatically. The mean values increased from 1 point at V1 to 3 points at V4 ($p < 0.001$), with no significant differences found between groups ($p = 0.677$).

Fig. 4 shows the average durations of RD based on visits and by comparison group. The duration of dermatitis increased significantly ($p < 0.001$) from V1 to V4, with no differences observed between groups ($p = 0.202$). However, it should be noted that the mean duration of dermatitis at V4 was 8.96 ± 4.28 days for the GTA and 10.94 ± 6.28 days for GTE (mean difference: 1.98 days: 95%CI: −0.8 to 4.953; $p = 0.08$).

The mean score at V0 with the Skindex-29 questionnaire was 5.27 ± 7.28 (median: 2; limits: 0–38; 95% CI: 3.52–7.02), while it was 13.57 ± 12.98 (median: 11; limits: 0–59; 95% CI: 10.47–16.67) at V4, resulting in statistically significant mean differences ($p < 0.001$). No differences between groups were found in mean Skindex-29 scores ($p = 0.198$), at V0 and V4 (Fig. 5).

Statistically significant ($0 = 0.024$) differences were found between groups at V4 in the following statement of the quality-of-life questionnaire: "My skin condition makes it hard to work or do hobbies" (Fig. 6).

Finally, regarding the average price of Alantel, this is 14.42 euros for 50 ml. In comparison, that of the moisturizing and emollient cream is 12 euros per bottle; that is, the price of Alantel cream is 2.42 euros higher.

4. Discussion

RD is a condition with incidences of up to 50% of mild degree [27]. Some authors reported that the incidence is 100% for those patients with head and neck cancer, 98% for breast cancer, and 48% for the pelvic region [28]. In our case, the GTE, with a 91.4% incidence of RD, compared to the 71.4% incidence found in the GTA, one week after being subjected to 15 sessions of breast cancer RT. It is important to analyze Fig. 2, which shows that, in all visits (except in V2), the GTA presents a tendency for a lower incidence of dermal lesions than the GTE; however, these differences were not statistically significant. This may be due to the cumulative dose of energy after 4 visits and 15 doses of RT, where the longer period, the higher the accumulated energy and, therefore, the larger the damage and the appearance of the lesion. At that time, prevention and relief of symptoms due to the accumulated energy is most needed, and it is when Alantel has shown to be most effective, decreasing the incidence of lesions by 20% in V4. Although, as we have already pointed out, without reaching a statistically significant p-value, the incidence risk seems to decrease also at V3 by 14.29% in the GTA compared to the GTE. This decrease, directly correlated to time, can be interpreted as the higher the energy that can generate dermal lesions by X and Γ radiation, the higher the effect of Alantel compared to the effect of the emollient cream.

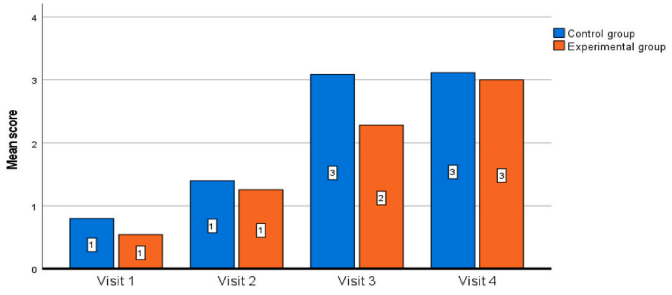

Fig. 3. The extent to which RT caused discomfort or affected patients symptomatically, depending on visits and comparison group.

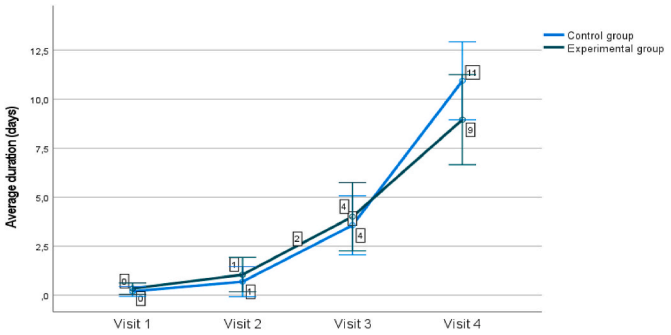

Fig. 4. Average durations of RD based on visits and by comparison group.

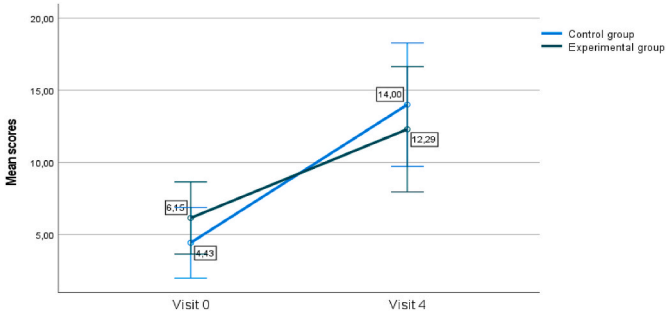

Fig. 5. Patients' quality of life, at baseline and end of the study, according to the comparison group.

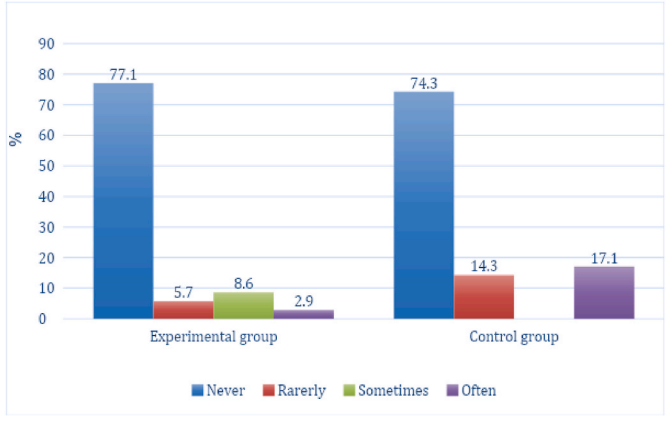

Fig. 6. Distribution of the Skindex questionnaire question "My skin condition makes it hard to work or do hobbies," according to the group, at the final visit.

In addition to this difference in the incidence rate of RD according to the group in the week following the end of RT, the effect size of Alantel was demonstrated, compared with the moisturizer cream, because the RR was 0.78 (which indicates a higher probability of obtaining a protective effect in the GTA than in the GTE), which translates into an ARR of 20% of presenting RD, and an NNT of 5, which is indicating that dermatitis will not appear in one out of five patients who are treated with Alantel. This fact should be considered for the clinical applicability of this adjuvant therapy, which has higher effectiveness than other products.

Regarding data on toxicity or grade of dermal lesions caused by RT, the difference found in the incidence of less severe lesions in the GTA than in the GTE is remarkable. Thus, in the subgroup with grade 3, 26 cases were found in the GTE compared to 20 in the GTA, with a difference in favor of the GTA of 17.2%. In the grade 2 severity lesion group, we found a 5.7% difference. No cases were found with grade 1 severity lesions in none of the groups. It is also noteworthy that 9 of the patients in the GTA presented no lesions (25.7%), and that only one patient in the GTE (2.9%) presented no lesions either.

Our control cream contains beeswax, which has many beneficial and protective effects on the skin, it can even mitigate the unwanted effects of RD [29–37].

The accumulation of RT sessions throughout time is important for successive skin lesions. For this reason, the lesions and duration of the dermatitis were analyzed at each visit. The duration of RD significantly increased from V1 to V4, with no differences found between groups, although the average duration of dermatitis in the GTA and GTE was almost 9 and 11 days, respectively. This means that Alantel could decrease the duration of RD by 2 days on average, although the p-value was 0.08, that is, almost significant.

The completion of questionnaires by patients was proposed to know their quality of life with the applied creams. The mean score obtained at V0 with the Skindex-29 test was 5.27, whereas it was 13.57 at V4, resulting in statistically significant mean differences, i.e., that the overall state of well-being associated with patient dermatitis worsens throughout the 4 weeks, with no differences found between the two groups. The scores of each questionnaire question were also analyzed, finding statistically significant differences between groups in V4 in the following statement: “My skin condition makes it hard to work or do hobbies” in favor of the group treated with Alantel.

These positive results found in this trial with our master formula are due to its properties and concentrations used. As mentioned above, the literature is inconsistent about using natural products in various conditions [14–16,25]. However, we find authors supporting that, at appropriate doses, the therapeutic effect of the elements contained in the ingredients of Alantel is beneficial for treating many diseases. Emodin (present in aloe) stabilizes mast cell degranulation and thus reduces itching and redness in various dermatitis types [38]. Aloe also has anti-inflammatory properties in certain diseases due to the active component α-bisabolol [39,40].

The role of aloe has also been demonstrated as an antibacterial, in wound healing and cell repair [41], and as a powerful antioxidant [42], which has been demonstrated in our case by the decrease in the number of days of duration of lesions, and the incidence of dermatitis. This restorative effect and maintenance of skin stability despite extreme photo-exposure in RT could be due to its immunomodulatory properties [43] when used at adequate concentrations. Cell culture experiments showed that the combined aloe/fibroin gel extract film irradiated with gamma rays promotes the healing of skin wounds by improving cell proliferation and migration, secretion of vascular epidermal growth factor (VEGF), and prevention of cellular senescence [44]. This effect is shown in Table 2 where 9 patients of the GTA had no lesions throughout the 15 RT sessions, and only 1 patient of the GTE had no lesions.

This immunomodulatory, restorative, and anti-senescent effect is due to its activity against cytokines found in cancer lines. In laboratory experiments, different aloe vera phytochemicals have shown promising anticancer activities [45,46] Chamomile, another ingredient of Alantel, has even been postulated as an adjuvant to the usual chemotherapy for tumors by inhibiting cyclooxygenase-2 and, therefore, cancer proliferation [47–49].

The antibacterial effect is essential in a solution whose purpose is the treatment of skin dehiscences. These are a gateway to the body for microorganisms, which can damage the skin locally and induce deterioration and aging, even more when we treat patients who are possibly immunosuppressed by their treatments. Aloe, chamomile, and especially the thymus vulgaris, all ingredients of Alantel, have this bacteriostatic protective effect [42,50,51].

The present trial has demonstrated the benefits of Alantel components. However, the question that arises to the clinician in the decision-making process and the patient is: To what extent are we going to reduce the chances of developing dermatitis if the patient is going to receive RT and uses or not Alantel? As with any other therapeutic intervention, there will always be some uncertainty regarding knowing how many individuals would benefit from Alantel treatment. This uncertainty can be minimized by quantifying it by the NNT, in which the lower the NNT value, the fewer patients we will need to avoid an event. The main difficulty of this estimator is that it is challenging to establish a value of what could be reasonable or clinically reasonable, and it is hard to compare. We want to give as an example the statin therapy for preventing cardiovascular events. CTT et al. [52] obtained a 1-year NNT of 553 and 213 to prevent a major cardiovascular event in patients with CVR $<5\%$ or $\geq 5\%$ to $< 10\%$, respectively. That is, they need to treat 553 patients in one year to avoid a cardiovascular event and 213 patients to avoid a major one. In our case, our NNT is 5, so we can conclude that the answer to the previous question is yes; they are going to substantially reduce the chances of presenting dermatitis based on this data.

If we add to this the low extra cost that would have to bear (2 euros per bottle), which would also be compensated by the expenses that would be saved by not having to treat 1 out of 5 patients, and that the AE were few, of small size and none severe, we consider that the benefits of treating with Alantel, rather than with a moisturizing and emollient substance, are clear.

One of the limitations of this study is that the sample size has been lower than the predetermined (70 vs. 88 patients), although this does not seem to have affected the potency of the study, since the results obtained have been positive. This study began in 2020, at a time when the COVID-19 pandemic implied a large increase in the demand for care and a reorientation of health services toward solving the most priority health problems to cope with the health collapse caused by the pandemic, this caused a slowdown in the recruitment of patients and a higher difficulty in achieving recruitment. In addition, a possible Hawthorne effect [53], inherent bias in this type of experimental studies, in which patients can alter their perception of what happened simply by feeling observed (for example, perception of discomfort or symptoms). We believe this bias has been largely minimized and controlled by the blinding of interventions, both for patients and professionals, as well as those responsible for conducting the statistical analysis. Finally, we think it would have been advisable to have used some method to verify the degree of adherence to the treatment tested, although the professionals asked the patients about this issue, answering most of them affirmatively.

5. Conclusion

We believe that formulas based on plant extracts and essential oils should be included among the various current treatment regimens for RD. However, we should always consider concentrations within therapeutic margins that can establish enough effect for treating the disease but without toxic effects. In our case, Alantel has shown that, unlike other cosmetic remedies, it can achieve differentiating and clinically relevant results for the group treated with this cream compared to the standard therapy.

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CRediT authorship contribution statement

E. Villegas-Becerril: Investigation, Methodology, Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Investigation, Project administration, Supervision. **C. Jimenez-Garcia:** Methodology, Project administration, Writing – original draft, Writing – review & editing, Funding acquisition, Conceptualization, Investigation, Supervision. **L.A. Perula-de Torres:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Investigation, Project administration, Supervision. **M. Espinosa-Calvo:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **C.M. Bueno-Serrano:** Investigation, Writing – original draft, Writing – review & editing. **F. Romero-Ruperto:** Investigation, Writing – review & editing. **F. Gines-Santiago:** Investigation, Writing – review & editing. **M.C. Moreno-Manzanaro:** Investigation, Writing – original draft, Writing – review & editing. **G. Montes-Redondo:** Investigation, Visualization. **M.A. Quesada-Roman:** Investigation, Visualization. **M.C. Linares-Ramirez:** Investigation, Visualization. **J.M. Parras-Rejano:** Investigation, Methodology, Visualization. **N. Muñoz-Alcaraz:** Investigation, Visualization. **M.D. Maestre-Serrano:** Investigation, Visualization. **E.M. Romero-Rodriguez:** Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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