

RADIOCARE®

I. INTRODUCTION

Radiodermatitis are skin lesions caused by ionizing radiation.

Generally, it is known that ionizing radiation, in general terms, can be of several types:

- Alpha: with little tissue penetration however rather destructive using particles produced by isotopes in diagnostic procedures.
- Beta particles, more penetrating and used in superficial radiotherapy.
- Gamma Rays, which are used in diagnostic procedures.
- Orthovoltage, which vary between 800,000 and 400,000 volts and are produced by machines.
- Super voltage: consisting of particles with energy exceeding a million volts, typical of accelerators, specifically the linear particle accelerators.

Ionizing radiation has an additive effect, and can be added to the effect of the actinic radiation. In order to avoid destructive effects on the healthy areas, one must try not to exceed 1000 Rads weekly. The fundamental lesion occurs on the DNA, causing cellular damage, which will give rise to different results, depending on the type of device, the radiation used, the exposure time, the geometry and distribution of the beam, the number of exposures, etc.

The first lesions are produced on the dermal vessels, when reasonable precautions must be taken to avoid radiation accumulations and not to reach a total dermal lesion, with loss of epidermal control by the dermis and the presence of cancerous and precancerous lesions.

Radiodermatitis can be produced by many causes, but fundamentally they can be summarised as:

- Professional radiodermatitis: doctors or healthcare personnel that use X-rays; it has also been observed in workers who use or have contact with radioactive substances (painters of luminous dials, etc.)
- Use of prolonged and frequent radioscopy, especially traumatologists.
- Use of radiotherapy without precise indications, either through erroneous diagnosis, ignorance of the process that is intended to be irradiated.
- Unavoidable adverse effect of handling radiosensitive tumours.

The lesions produced as a consequence of the irradiation are the following:

1. Acute radiodermatitis that, depending on the intensity, is classified as:
 - 3 First degree, with erythema, oedema, pigmentation, alopecia and pain.
 - 3 Second degree, with erythema and blisters that can leave ulcerations and scars, with pain and itching.
 - 3 Third degree, which presents radio necrosis and pain in the periphery of the lesion.
2. Chronic radiodermatitis, which depending on the evolution and progressive accumulation of radiation, the following may appear:
 - 3 A prodromal phase with cutaneous sclerosis, telangiectasis, and disorders in nearby areas with depilation, anhidrosis, asteatosis and even onychopathies if it concerns the hands.
 - 3 Subsequently signs of alarm can appear with evident sclerosis of the area, reticular pigmentation with achromia and hyperchromia, presence of carbon stains and indurations surrounding the epithelium covered with scales, keratomas.
 - 3 Finally, cancerisation of the area can appear, with the appearance of ulcerations and carcinomas on the poikilodermal skin or on the keratomas.

There are special forms of chronic radiodermatitis that should also be considered:

3. Osteoradionecrosis, a very painful and unpleasant experience in the treatment of the dermatophytosis of the scalp.
4. Professional Radiodermatitis, without doubt the most frequently seen at present. The diagnosis is delayed and therefore also its treatment, with advanced carcinomas usually being diagnosed. The presentation is usually on the hands (Roentgen's Hand), with the prodromal phase appearing between 3 to 8 years from the commencement of exposure and the keratomas between 8 and 15 years, with almost immediate ulcers and carcinomas. Although intuition tells us that it should occur in radiologists, it is not normally the case; with the most affected medical specialities depending on their frequency are as following: traumatologists, paediatricians, internists, specialists of the digestive system and general surgeons.

The anatomopathological lesions that are produced can be differentiated in each of the lesions as follows:

- a. Acute Radiodermatitis, like any other type of burn, produces vasodilatation, oedema and epidermal, dermal or deeper destruction. Upon receiving the one time dose, it is not possible for the peripheral structures to be damaged, thereby resulting in the possibility of the "ad integrum" recovery of the first degree acute lesions, with retractile scarring and pigmentation in those of the second degree, while in the third degree the necrosis requires the

extraction of the retractile scar, and grafting, which normally is successful so that the peripheral and deep circulation are usually preserved.

- b. The situation is diametrically different, since the lesion evolution is as following:
- 3 In the first place endarteritis with endophlebitis in the vessels of the hypodermal plexus occurs, with “retrograde venous hypertension” that will cause dilatation of the vessels with the appearance of telangiectasia on the skin surface.
 - 3 Subsequently and with the formation of endovenous thrombus, the vessel walls are destroyed, being included in the dermis, and typical carbon spots (coolspots) with the deposit of free haemosiderin and an intense lymphohistoplasmocitary infiltrate.
 - 3 While the endophlebitis is beginning, progressive sclerosis of the dermis occurs, with atrophy of the surrounding area, observing not only depilation and anhidrosis, but also phenomena of unguinal dystrophies and even anonychia. At that time due to the absolute lack of control of the epithelium, atrophy and acanthosis occurs, on which ulcers, keratomas and carcinomas will be produced.
 - 3 It is important to know that a profound alteration of the collagen takes place, with homogenisation and transformation in collastin, confirming that there is a close relation between the collagen substance and the epithelial tissue so that the collagen lesion is proximate to the epithelial tissue, demonstrating ischemia-reperfusion lesion and of the appearance of oxidant substances in the area of the lesion.

Unfortunately there is no standardised or specific treatment for radiodermatitis from radiation, and although its incidence has decreased with the megavoltage instruments, they can, however, impact the therapeutic program and alter the quality of life of the patients. The usual treatment consists of the use of emollients and/or topical corticosteroids, and on the most severe lesions, surgery to eliminate the necrosis, and grafting.

Therefore, with the need for finding an adequate therapeutic solution for these patients, the incessant search for remedies in this field has resulted in an interesting solution: the use of the Secretion of *Cryptomphalus Aspersa*, a mollusc that during biological alarm responds with a protective mechanism that can be applied to prevent or cure patients affected by radiodermatitis.

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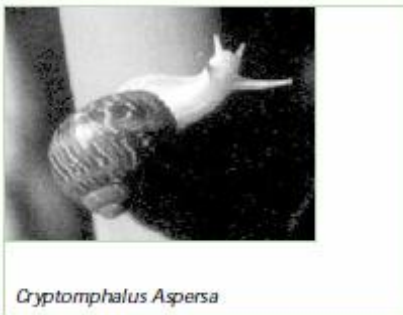
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II. CRYPTOMPHALUS ASPERSA

The *Cryptomphalus Aspersa* (“CA”) is a gastropod (snail), whose origin can be estimated at around 600 million years ago. Its phylogenetic analysis provides very interesting characteristics. The “CA” originally a bivalve shell creature, similar to a mussel currently presents some significant evolutionary differences due to the fact that its viscera experienced a dramatical turn in its evolution, just like the dextrorotatory turns of its shell, which seem to have originated during the creation of the Earth. Although many events caused the extinction of a wide range of species, these caused this creature to be manifested in the form of torsion and dextrorotatory spiralling, which mathematically can be expressed by Archimedes’ spiral.



Cryptomphalus Aspersa

The CA lives for 2 to 5 years; what is therefore very appropriate for experimental research.

Due to its normal secretions, the snail does not characteristically suffer from infections or tumours on its skin or its muscles.

A common characteristic response to a “biological alarm” is through the production of a glycoprotein, an expression of its great phylogenetic memory of its ganglionic brain, as a defence against a so called aggression identified as tremendously injurious for the snail, similar to what resulted as its evolutionary blockage. This glycoprotein is secreted as self-defence and self-protection, and is a different secretion from the one used for its displacements.

The snail has three different types of glands that contribute to its secretion as a protection against the “biological alarm”:

- 3 The Mucous Glands
- 3 The Protein Gland, that serves as a reservoir and that flow into its genital system (it is an alternating rather than a hermaphrodite)
- 3 A strong Salivary Gland

The secretions of these three glands, focus the research related to Radiocare and are the basis for the preparation of the active ingredient called RC316. This active ingredient has been isolated from the *Cryptomphalus Aspersa*, when it is subjected to irradiation with ionizing radiations. The secretion, rapidly and effectively produced, does not become denatured or contaminated.

The *Cryptomphalus Aspersa* is capable of regenerating its skin after thermal aggressions, so that when thermal microburns caused experimentally, it has the capability of rapidly repairing these lesions. Simultaneously there is an increase of the secretion. This remarkable regeneration mechanism is what brought to the possible application to human skin in the cases of lesions produced by ionizing

radiation or by heat. Subsequently it was also demonstrated, that this secretion is a protector and regenerator of the human skin.

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III. THE SECRETION OF CRYPTOMPHALUS ASPERSA

1. Acquisition Method

The extraction procedure is subject to an international patent. The collection on the other hand is different and prior to other patents listed in the bibliography, and which was registered in the United States with patent number USA 5538740 for the active ingredient which is called RC316.

The principles in obtaining the Secretion of the Cryptomphalus Aspersa (“SCA”) are based on subjecting the animal to “biological alarm”, with a new method of collection based on the analysis of the ontogenetic and phylogenetic characteristics of the snail, together with the mathematical analysis of the structure of the shell. An “ad hoc” set of instruments was fabricated in accordance with the specific mathematical-physical formulations what required the reproduction of the cataclysm suffered by living organisms millions of years ago that was memorised in its ganglionic brain. From the radiographic studies, a mathematical analysis was made of the Archimedes’ spiral. This permitted the investigation of its harmonics, and subsequently the subjecting of the snail to “biological alarm” through some artificial conditions contrary to its evolutionary process, mimicking an organism without its shell.

The most essential aspect is that the fine-tuned procedure enables the extraction of a considerable quantity of secretion, without denaturing or contaminating it with other biochemical compounds, and above all maintaining the snail alive. It is far from other extraction methods that use ionizing and ultraviolet radiations, which would denature rapidly the secretion, or physical methods of hyperpressure or grinding that kill the animal and contaminate the secretion.

2. Preservation method

Since the secretion is separated from the animal, it is subjected to many unfavourable contingencies that lead to its denaturation.

The first that must be impeded is its drying; therefore, it must immediately be lyophilised, as this is a very reliable method of preservation: introducing the secretion in an appropriate container, freezing it without the formation of crystals (which would also denature the product), and always working in an abiotic chamber.

3. Structural identification of the secretion

Elementary and fractional purification is carried out by the usual methods. The amino acids observed mostly coincide with those essential for the human survival.

The following tables show the inclusive and separate composition in essential and non-essential amino acids. They are basically those indicated in the following table. The ones indicated with (*) are the essential acids while those without an asterisk are the non-essential ones. See Table 1.

Biologically there is proximity with humans that is shown by the secretion containing 8/10 of the amino acids essential for the human metabolism and survival (lacking methionine and tryptophan), and 8/10 non essential amino acids, but that indeed actively participate in its metabolism (lacking in this case glutamine and asparagine).

Table 1. PRINCIPAL AMINO ACIDS OF RC316

TYPE OF ANIMO ACID	Approximate %	APPRAISAL OF THE AMINO ACIDS
1. With lateral chains	36%	Leucine (*) Valine (*) Isoleucine (*) Glycine Alanine
2. With Hydroxyl groups	11%	Threonine (*) Serine Serine is one of the “active centre” contact amino acids of enzymes as important as Trypsin, Alkaline Phosphatase, Phosphorylase, Phosphoglucomutose and Elastase
3. With SH radicals in their lateral chains	2.5%	Cystine Cystine is a contact amino acid that is found in the “active centre” of six main enzymes (alcohol dehydrogenase, lactodehydrogenase, pyruvate dehydrogenase, ketoglutarate dehydrogenase, glyceraldehyde 3P – dehydrogenase and transaldolase)
4. Dicarboxylic	20%	Aspartic acid Glutamic acid
5. Diaminic	12%	Arginine (*) Lysine (*) Histidine (*)
6. With aromatic groups	10%	Phenylalanine Thyrolysin
7. Imino acids	8.5%	Proline

Methionine (*), tryptophan (+), glutamine and asparagine are absent.

The proportion of essential amino acids (Table 2) and nonessential amino acids (Table 3):

Table 2. ESSENTIAL AMINO ACIDS

Amino acids	RC316 (*)
Aspartic acid	10.7
Serine	5.6
Glutamic acid	9.8
Proline	8.9
Glycine	8.3
Alanine	7.4
Cysteine	2.2
Thyrosine	3.9

(*) Methionine and tryptophan do not exist

Table 3. NONESSENTIAL AMINO ACIDS

Amino acids	RC316 (*)
Threonine	5.6
Valine	5.9
Isoleucine	4.8
Leucine	9.7
Phenylalanine	5.1
Lysine	5.9
Histidine	2.5
Arginine	3.6

(*) Neither glutamine or asparagine exist.

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IV. PHARMACOLOGY OF RADIOCARE

1. Pharmacodynamics

The Secretion of the Cryptomphalus Aspersa (SCA), the active ingredient in Radiocare, has a two-way action mechanism:

- Collagenase against type IV collagen, which facilitates the remodelling of the basal membrane of the skin (denatured collagen is more susceptible to the action of the collagenase, and its activity would remodel the basal membrane of the skin).
- Stimulation of the proliferation of fibroblasts (Fibroblast Growth Factor or FGF) that facilitates the protection and reconstruction of the skin.
- Antioxidant properties of this substance have also been identified recently, due to its Glutathione S-Transferase (GSH-T) and Superoxide Dismutase (SOD).

As previously described, the fundamental lesion that is produced on the skin following irradiation is related to ischemia-reperfusion and to a sudden presence of reactive oxygen species.

The irradiated skin consequently causes the transitory reduction of cell proliferation, which ensures a continual proliferation and preservation of the skin layers. The reaction extent depends to a great extent on the body area, the total volume irradiated, the type of radiation technique and its energy, and the total dose used per session. With conventional radiotherapy (Cobalt) the alterations of the skin reach to its maximum intensity towards the second or third week of treatment, and the dermatitis from irradiation can appear in different degrees according to the presence of erythema, oedema, blisters or cutaneous necrosis. The treatment of these lesions has usually been with the use of different emollients or topical corticosteroids. This accelerated and forced aging process of the skin caused by radiation implies the presence of oxygen free radicals, which has led to a more thorough search for substances that restore the original condition from the preliminary ischemia-reperfusion injury phenomenon.

- Fibroblast Growth Factor: The active ingredient of Radiocare, the SCA, has demonstrated to induce proliferation of human skin fibroblasts of a healthy volunteer donor (F15), expressed as the total number of cells per dish with a feasibility percentage, which is also supported by the fact that by adding other stabilizing elements such as citrate 0.1mM pH 5.0, inositol hexasulphate 1mM and even heparin sodium of low molecular weight 100 UI, the activity increases to values that double the control at the highest SCA concentrations (which were evaluated at 100, 50, 25 and 12.5 mg/ml). This shows the beneficial effect on the regeneration of one of the cells most affected by the aggression, the fibroblasts, since a regenerating activity on them implies a higher replacement and improvement of the skin, as can be seen in the following table.

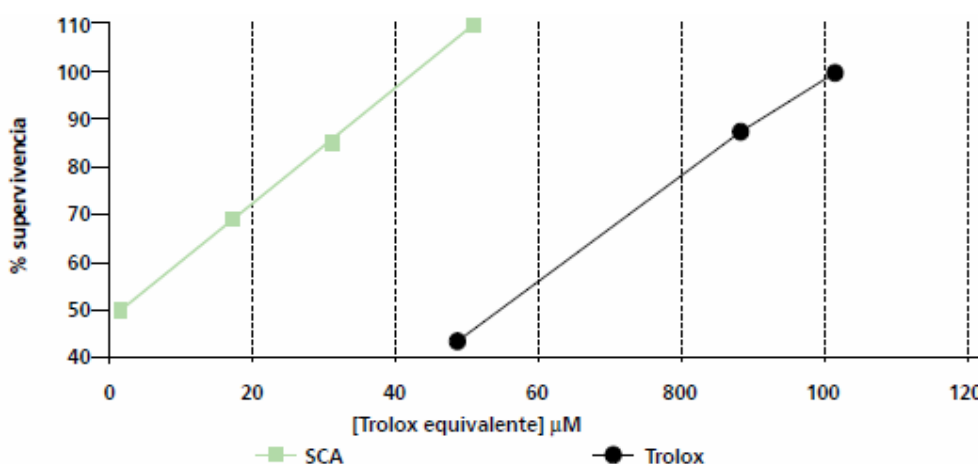
Proliferating activity of fibroblasts in presence of SCA or SCA with additives

CONCENTRATION ($\mu\text{g/ml}$)*	SCA	SCA + citrate	SCA + citrate	SCA + citrate
200	2.3 ± 0.5	3.3 ± 0.8	2.3 ± 0.4	2.0 ± 0.7
100	2.0 ± 0.4	2.3 ± 0.5	2.0 ± 0.7	2.0 ± 0.6
50	1.7 ± 0.4	2.7 ± 0.7	1.7 ± 0.4	1.0 ± 0.2
25	1.5 ± 0.3	2.0 ± 0.4	1.7 ± 0.5	1.0 ± 0.2

The results are presented as a stimulation index = treated cell absorbency/control cell absorbency (average \pm SD). The stimulation index of the control cells without SCA is 1.0 ± 0.2 . * The concentration expressed as mg of protein of SCA /ml.

- **Cytoprotective:** When comparing the cytoprotective action of the SCA (the active ingredient of Radiocare) in terms of its antioxidant capacity with a similar solution of vitamin E (Trolox C) on the F15 fibroblast line subjected to a UVA light source, with irradiation intensity of 1 J/cm^2 , an increase of activity is observed, demonstrated by a higher cellular survival than with the antioxidant of reference at an equivalent concentration when using SCA. This shows the cytoprotective and skin β protecting action of SCA.
- **SOD and GSH β T:** The Superoxide Dismutase activity has been evaluated by measuring the inhibition of the reduction of the cytochrome C produced by the oxygen generated by the xanthine β xanthine oxidase system, and the Glutathione β S β Transferase activity, measuring the capacity of the SCA to conjugate glutathione at $13\text{Cl}32.43\text{d}$ nitrobenzene. According to the results shown in the following table, it can be seen that the active ingredient of Radiocare does not demonstrate xanthine oxidase activity, with a SOD action between 0.03 and 0.005% (p/p) of the protein content, as well as the GSH β T activity shown between 0.5 and 1% (p/p) of the protein content; demonstrating

Test of UVA Protection



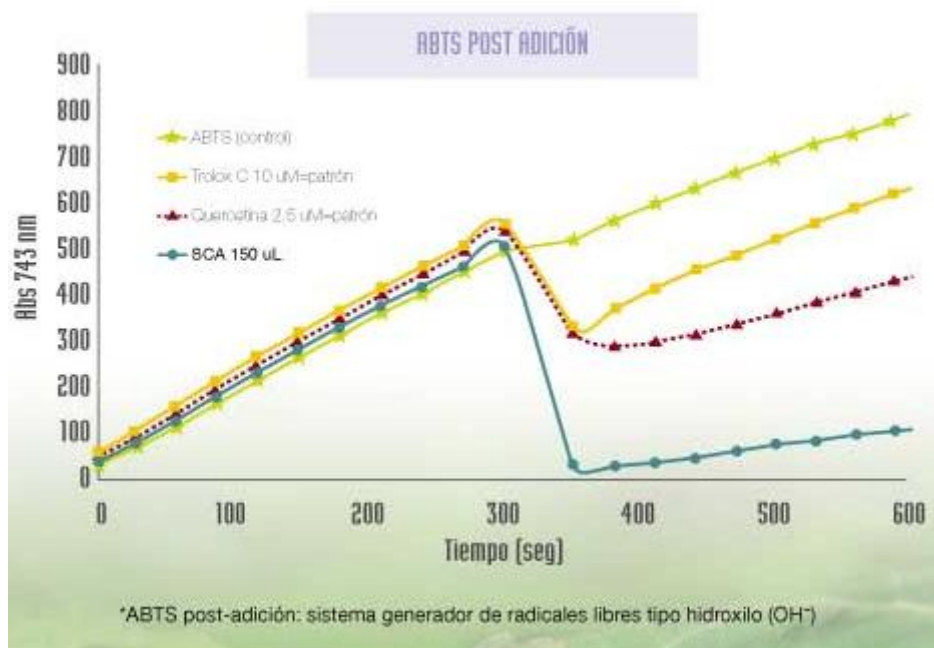
the SOD and GSH3T antioxidant activities in accordance to that described in literature about the presence of these activities in SCA in posthibernation conditions. In addition, these partially explain the skin protective action caused by the secretion. Although the enzymatic levels of SOD and GSH3T are not high, it can be supposed that they have a complementary effect possibly eliminating the superoxide anion, as well as irradiating through the conjugation of oxidized molecules that can be more toxic than the initial oxidizing agent.

GSH3T and SOD Actions found in SCA

Action	U/ml	% mg/mg protein SCA*
GSH3T	1.7 – 3.4	0.5 – 1
SOD	0.7 – 4.1	0.005 – 0.03
50	1.7 ± 0.4	1.0 ± 0.2

*Considering the average action of GSTas 75 U/mg and that of SOD 3,000 U/mg.

- Production of stable radicals (ABTS) and antioxidant capacity: From the following graph it can be demonstrated, that SCA performs as a sequestrate of ABTS radical cation, since an immediate drop in the absorbency resembles to that produced by Trolox C (similar solution of vitamin E, used as an antioxidant reference unit for defining activity units) and quercetin (flavonoid type compound, used as positive control) and as an inhibitor of the production of this radical in this system, since the speed of ABTS production, measured as the absorbency slope compared to time, is less than with the control or the Trolox C, thus, it performs in a similar way to quercetin.



Summarizing, the pharmacokinetic characteristics related to the active ingredient present in Radiocare validate its use for acute radiodermatitis, justified by two factors:

- The cytoprotective effect by the FGF activity, and
- The antioxidant activity encountered: ABTS, SOD and GSH3T, which adds the collagenase effect demonstrated in the active ingredient of Radiocare.

2. The excipient: formulation and galenic characteristics

More than 2,500 formulas were obtained before the formulation of the current one as there was a search after a stabilizing excipient for the active ingredient with the therapeutic properties. Moreover, there was a need for an excipient adapted to the physiopathology of the skin, selecting the compound with the following characteristics:

- High stability level of the active biological product, maintaining the galenic ingredients: A proper excipient was obtained for the optimal preservation of the biological ingredients.
- Similar molecular weight to the body mass of the snail. Only five components intervene.
- The excipient is highly stable, thus protecting the active ingredient.
- Facilitating the penetration acting as a carrier, which is complemented by maximum retention and bioavailability of the active ingredient.
- The excipient does not present toxicity.
- It mildly facilitates with the therapeutic action.
- With regards to the physical effects on the excipient it remains stable at temperature differences (between 320°C and $+60^{\circ}\text{C}$), extreme barometric conditions; it is not disintegrated by the ionizing radiation, making it appropriate for preservation, transport and use in accidents. Therefore it is possible to conclude that the preparation is extremely stable..
- In the excipient, the proportion of the aqueous medium, should not exceed 30%, the proportion of monoalcohols (should not exceed 20%), the concentration of calcium and zinc (should not exceed 1%) and of the monoester octodecanoic acid of the 1,2,3 propanotriol monostearate, must be in balance with the monoalcohol. These elements are all critical for the stability.

- Coadjutant to the active ingredient, the excipient does not to produce alterations of the epidermis and the dermis, thereby maximizing the skin penetration (as a carrier) as is evidenced in the pathological anatomy.
- In addition, it is proven that one of the excipient's properties acts as biological coating, protecting from injuries, and reduces the pain.

During the development of the excipient the original formula was obtained so that it does not exceed five components.

- Aqueous medium. In order to avoid possible contaminations there is no more than 30% of the aqueous medium, presenting the ionic solution of the snail..
- The proportion of monoalcohols. The alcohols used are with the mildest surface activity effect. The small amount of O/W suspension of the formula dictates that the critical point is situated below 20%. The different amounts of diethylene glycols (DEG) derivatives in various molecular weights result in a certain extent of the aqueous medium. The experiment carried out shows that an excess of the aqueous medium hydrolyses the active ingredient, thus degrading it.
- Concentration of calcium ions. In this case it has another objective; for stabilizing the active ingredient.
- Concentration of zinc compounds. It actively stabilizes the formula, and there is no known toxicity of it. The calcium/zinc ratio is not arbitrary in our formula. There is a well defined critical point with respect to the preservation of the active biological ingredient.
- Octadecanoic acid, monoester with 1,2,3 propanetriol monostearate (OAMPM). In this formula the OAMPM concentration is used in a minimal proportion. It assists as a preservative with the monoalcohol, making the use of other toxic preservatives unnecessary. Pharmaceutically it provides stability by means of a light saponification, which helps in the preservation of the active ingredient.

3. Mechanism of action

The effects of Radiocare, discussed in more depth further on, have been demonstrating through the growth induction mature collagen, maintaining the normal keratinisation of the skin, without altering its structure. We conclude that it is an exceptional product take its ability to regenerate skin structures, and furthermore, innovative as there are no current inducers of mature collagen formation.

4. Bacteriology of the active ingredient

As it is a secretion of a live organism originating from the glands of animal snail, it is important to identify the bacterial load and any additional harmful germs. Although the snails are subjected to centrifuging and filtering, bacteria could result in an infectious pathological process to the skin already debilitated. Therefore, the active ingredient was subjected to bacteriological analysis and to purification mechanisms in the Microbiology Laboratories of the Ramon y Cajal Hospital of Madrid. The results of the secretion in natural form comparing to a secretion subjected to slow centrifugation of 500 rpm showed that very few saprophyte germs (non pathogens) were found corresponding to the three colony forming units (Streptococcus faecalis, Acinetobacter anitratus, and Bacillus s.p.) in quantities over 10^5 c.f.u. (Table 1)

Table 1. Quantity of germs

TOTAL LOAD	BACTERIAL SPECIES
More than 10^5 c.f.u./ml	Acinetobacter anitratus
	Streptococcus faecalis
	Bacillus s.p.

c.f.u. = colony forming units

Nonetheless when the biological secretion is subjected without treating the filtration of a microfibre glass filter for clearance, the quantity of bacteria decreased to $3.2 \cdot 10^3$, thus, approximately 70% of the bacteria were eliminated with respect to the previously described basal situation. (Table 2).

Table 2. Decrease in the quantity of bacteria by centrifugation and clearance

TOTAL LOAD	BACTERIAL SPECIES
$3.2 \cdot 10^3$ c.f.u./ml	Acinetobacter anitratus
	Streptococcus faecalis
	Bacillus s.p.

c.f.u. = colony forming units

Filtering with a Millipore filter with a pore size of 0.22 micron following the two previous steps (centrifugation and clearance), result in a purified biological ingredient containing no bacteria. (Table 3).

Table 3. The active ingredient contains no bacteria. Centrifugation with clearance, plus filtering (Millipore filter with 0.22 micra pore size).

TOTAL LOAD	BACTERIAL SPECIES
Less than 1 c.f.u./ml	None

c.f.u. = colony forming units

Additionally, should the above steps be dismissed, and the active ingredient is only subjected to centrifugation to remove impurities (see Table 1) followed by the direct incorporation to the excipient, there are still no bacteria. This is due to the fact that the excipient contains weak surface-active agents, in just a small amount of the aqueous medium, which impedes the proliferation of the bacterial colonies. (Table 4).

Table 4. The active ingredient contains no bacteria

TOTAL LOAD	BACTERIAL SPECIES
Less than 1 c.f.u./ml	None

c.f.u. = colony forming units

Consequently the product, being an active biological secretion contains no bacteria or germs that could make one leery of its use in patients. Any handling other than purely physical ones described herein would denature the active ingredient.

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V. EXPERIMENTAL ANIMAL TREATMENT WITH RADIOCARE

A) In order to evaluate the performance of Radiocare in animals, an experimental model of radiodermatitis was developed in rats, which is as close as possible to the radiodermatitis produced in human beings, through the effect of radiotherapy treatment, and a uniform irradiation protocol was performed for obtaining radiodermatitis in rats through a single hyperdosage of 150 Gy = 15,000 rads, equivalent of a nuclear accident.

For this experiment, Wistar rats were used; their backs were scratched and they were exposed to a dosage of 150 Gy, using an irradiation regime with a Philips RT3100 device with an intensity of 10 mA, a filter of 0.55mm Al and a half-value layer of 0.45mm. Using a localiser of 2.5cm in diameter, 46 kV of energy was applied with a focus-skin distance of 10cm. A single dose of around 15,000 rads was administered.

In this way, a reproducible biological pattern of radiodermatitis was obtained, which allows analyzing possible similarities among the experimental radiodermatitis and the lesions produced in nuclear catastrophes or accidents. It also allows an examination of the effectiveness of a therapeutic product in unfavourable conditions that indicate the highest limit of its therapeutic effectiveness.

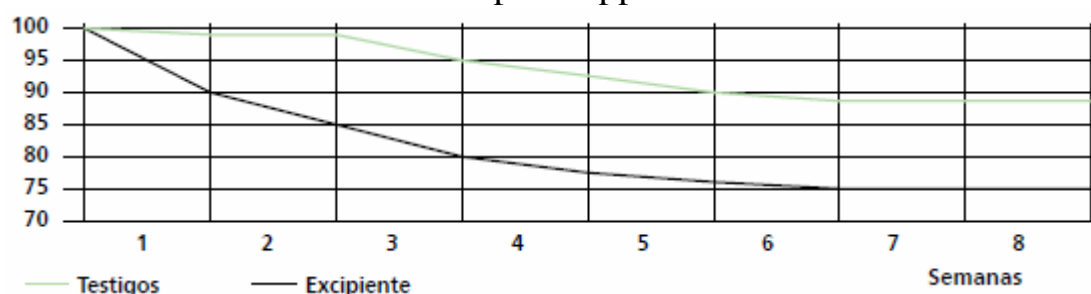
In a study planned for this purpose, we tried to evaluate: the healing over time following the treatment and the decrease of the disease. To accomplish this, 322 Wistar rats were used, of which 104 (32%) were the control group that didn't suffer any treatment (TES), 106 (33%) were animals treated only with the excipient (EXC), and 112 (35%) were treated with Radiocare (PT) and observed for 8 weeks, obtaining extremely interesting and promising results in view of clinical practice:

When the results of the 106 animals treated with the Excipient were compared to the 104 control group (following figure), a difference of 14% was observed between both curves, due basically to the biological coating effect of the excipient, but without statistical significance. Although it can also be stated that the clinical beneficial effect is due to the penetration of the excipient, tenaciously assimilated by the skin (epidermis, dermis, even the subcutaneous cellular tissue), performing as a carrier, thereby increasing the effectiveness of the active ingredient.

Fig. 1. Experimental radiodermatitis.

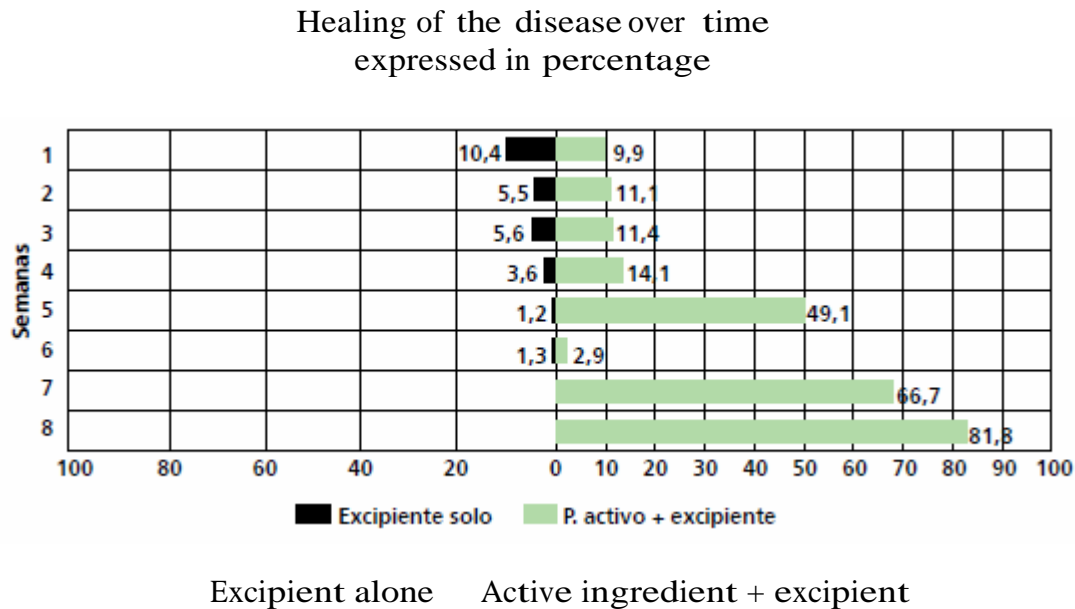
Results in 104 control animals (TES) and 106 animals with the excipient (EXC).

Growth rate of the radiodermatitis in control animals vs. animals with only the excipient applied



By analyzing the weekly healing during 8 weeks in the excipient treated animals and those treated with Radiocare, the data shown in the following figure were obtained.

Fig. 2. Experimental radiodermatitis. Percentage of weekly healing



A significant increase in healing was observed, especially in the fifth, seventh and eighth weeks, as is seen in the percentages of weekly healing with Radiocare compared to the excipient alone. Although it is interesting to note how the start of the healing and tissue regeneration begins after the first week, due to the fact that, in the first place, it is necessary for all the dead and irreparable damaged cells to be eliminated from the skin and this is done in the first treatment period, after which the tissue regeneration and healing actually begins. It is logical that the action of Radiocare is not immediate.

Week after week, it was observed that the percentage of healing in the patients treated with Radiocare increases, from a figure without statistical significance in the first week (9.9% Radiocare versus 10.4% with excipient), until the eighth week in which the percentage of animals that Radiocare heals is 82%.

This observation is reinforced by evaluating the decrease in the lesions comparing the animals treated with the excipient with those treated with Radiocare, measured in terms of increase in the healing throughout the 83week period of treatment.

The animals treated with Radiocare improved progressively in a way that on the ninth week 98% of the animals were cured, that is, did not have radiodermatitis. On the contrary, the animals treated with the excipient alone continued with the disease from the seventh week in 75% of the cases, due to natural properties the process of 25% had been abated.

B) With regards to the effects on the skin of the treated animals, from an anatomopathological point of view, it was observed that under the effects of Radiocare administered in these experiments, the following was demonstrated:

- Treated epidermis recovered its normal thickness (thinner), without wrinkles.
- In the dermis – hypodermis, the steatosis was substituted by a mature collagen substance.
- The regeneration of mature collagen s was not only produced in this layer, but also in others, in different structures (epithelium of the vessels, etc.).
- The RC316 ointment penetrates all the layers of the skin since the excipient acts as a trans³dermal carrier.
- The muscular layer is reorganised, recovering its tonicity, with suppression of flaccidity and, therefore, the wrinkled appearance of the skin.
- The dermoepidermal union or juncture with Radiocare recovered, establishing the normal physiological mechanism of nutrition of the epidermis.
- This shows that its mechanism of action is due to the growth induction of the mature collagen, maintaining the skin's normal keratinisation, that is, not altering its structure, thereby resulting in an exceptional product able to regenerate skin structures and furthermore, being unique as at this time there are no other inducers of mature collagen formation.

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VI. RADIOCARE IN THE CLINICAL PRACTICE

Following excellent results obtained in the experimental and preclinical evaluation of Radiocare, it became necessary to apply it to humans and to learn about its performance in the clinical practice; therefore a very complete clinical research plan was followed that undertook practically all therapeutic possibilities of Radiocare:

- a) The prevention of radiodermatitis.
- b) Its use in the treatment of acute radiodermatitis in patients subjected to radiotherapy.
- c) The treatment of chronic, late-forming and recurring radiodermatitis.
- d) Thermal burns.
- e) Other radiodermatitis: Post-chemotherapy, of Professionals.

PREVENTION OF RADIODERMATITIS

The preventive treatment of radiodermatitis is a crucial aspect in treating this pathology since it entails not only the purely physiopathological aspect but also the psychosocial component which adds another aspect for considering in the evolution of the patient. The related aspects that must be considered are:

1. The appearance of radiodermatitis, which is an adverse personal reaction that appears as an undesirable consequence produced in the treatment, is accompanied by an increase in the symptoms and signs of the disease and reduces the quality of life and the appearance of disorders in three aspects:
 - a. Organic: pain, itching, erythema, scaling, oedema, vesiculation, surface ulceration and residual pigmentation, with possible infection.
 - b. Mental: asthenia, irritability, insomnia, anxiety, depression.
 - c. Immunological, and even more so if one adds a prior or concomitant treatment with antitumour cytostatic agents.
2. Being a disease with impact on the family, in which the aesthetic appearance as well as the psychological damages affect the quality of family life.
3. The new therapies currently used in oncological treatments are increasingly more aggressive, attempting to a higher survival and disease-free. In fact the new medicines and the use of beams with higher energy, specific, with a higher dosage of total irradiation, and with a mixture of photons and electrons, produce an increase of radiodermatitis.

4. Preventive treatment is the ideal solution, especially if you take into account that Radiocare has no toxicity either taken topically or internally.

The protective effect of Radiocare has been evaluated for radiodermatitis in 27 patients, dividing the irradiation field in two parts and administering Radiocare to one of them, extending a thin layer, with a dosage of 0.1g. per cm² once a day, either from the first day of radiotherapy or from the first 1000cGy (Rads), although we would prefer the use of Radiocare beginning at least 10 to 15 days prior to the treatment³ comparing the results on both sides, if on the side without Radiocare the appearance of erythema or radiodermatitis is observed from 50360Gy in the place of the application of the ointment up to 70Gy have been administered without the appearance of erythema.

When trying to prevent the appearance of radiodermatitis in the cases of irradiation of the complete breast, the areas of highest sensitivity, which are those of the nipple and the juncture with the mammary areola, must be protected in a special way.

TREATMENT OF ACUTE RADIODERMATITIS IN PATIENTS SUBJECTED TO RADIOTHERAPY

In an open controlled clinical study, in which 100 patients diagnosed with acute radiodermatitis were evaluated, Radiocare (n=50) or its excipient (n=50) was administered during three months, evaluating after a week, a month, two, three and six months from the start of the treatment, using a 53point scale

- 0: absent
- 1: mild
- 2: moderate
- 3: severe and
- 4: very severe

In order to measure the intensity of the following clinical parameters: erythema, scaling, pigmentation, itching and burning. Similarly, 5 groups of patients were established according to the amount of radiation received:

- from 1000 to 2000
- from 2000 to 3000
- from 3000 to 4000
- from 4000 to 5000
- from 5000 to 6000

also an additional evaluation factor was added: application of chemotherapy in these patients, and its relation to the signs and symptoms in each of the groups, such as the performance of Radiocare in the symptoms of these groups of patients.

DIAGNOSIS	%
Breast cancer	61.0
Carcinoma of cervical region	24.6
Other tumours	22.4

The average age of the patients was from 59.09 \pm 12.81 years, with 63% women and 37% men, who had received an average dose of 5219.23 \pm 57.85 cGy (Rads), with average treatment duration of 6 weeks, with the diagnoses of these patients being:

Observance of a statistically significant clinical improvement in the group of 50 patients treated with Radiocare compared to the group that only received the excipient, according to the following values:

% Improvement/Time	ERYTHEMA	ITCHING	BURNING
WEEK	22.16 (p=0.009)	42.88 (p=0.004)	48.48 (p=0.001)
1 MONTH	54.78 (p=0.016)	66.4 (p=0.013)	87.87 (p=0.001)
2 MONTHS	77.12 (p=0.016)	not known	not known

The graphs show how the improvement of these patients was significant both clinically and statistically at one week and one month from the start of the treatment, with the results obtained in the third month remaining until the sixth month, with the pigmentation improving progressively in all cases.

It was also observed that the percentage of improvement of the erythema was higher with basal doses of radiotherapy over 5000 cGy, but neither the itching nor the burning that improved at one week and one month did so independently of the basal dose of radiotherapy according to the statistical analysis.

No significant effect of the chemotherapy was observed on the clinical signs and symptoms of radiodermatitis, or differences in the response to the treatment with Radiocare.

No adverse reactions were observed during the Radiocare treatment protocol, as well as the use of the excipient.

Therefore, it can be concluded that Radiocare is a therapeutic alternative for a large group of patients diagnosed with malignant tumours that need radiotherapy, providing extremely good results in breast and neck radiodermatitis.

In an open study (Abad), patients were included from different groups basically classified by areas in which radiotherapy was applied:

1. Supradiaphragmatic radiodermatitis (Thorax)
 - a. Acute R. in mammary crease
 - b. Acute R. of the postmastectomy scar
 - c. Acute R. of the axilla
 - d. Acute R. in other locations
2. Infradiaphragmatic radiodermatitis
 - a. Acute R. of the abdomen
 - b. Acute radiocellulitis of gluteus

In all of them Radiocare was applied topically every 24 hours, in a thin layer of 0.2 g/cm², observing the patients for a period of 4 weeks (28 days), analysing the values in intervals of 3 days.

Acute Radiodermatitis of the Trunk

In these cases, as in all of them, it is essential to use a specific treatment that does not interrupt the radiotherapy treatment, since the delay or discontinuity in the treatment causes the loss of local control of the tumour and possibly the decrease of the disease-free time.

Seventy-nine patients were included, to which a dose of 0.2 g per cm² of Radiocare was administered once a day. Using the Gehan statistical evaluation method, the following was observed: (Table 1)

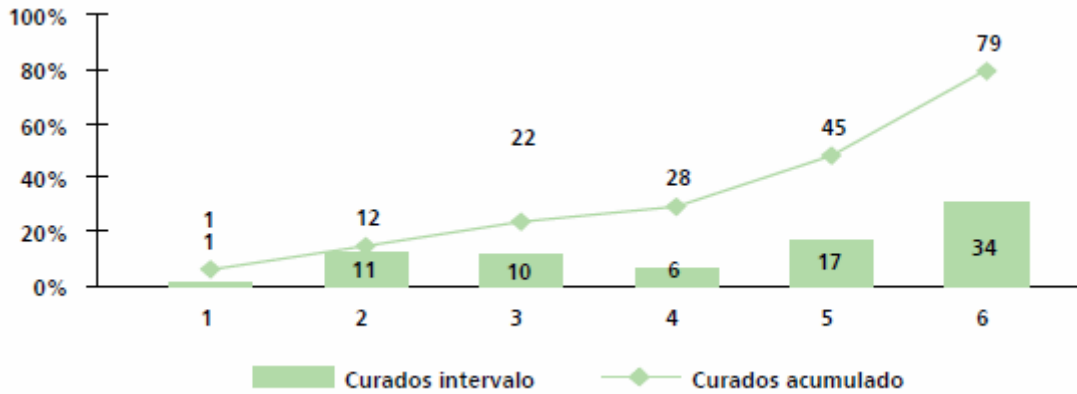
Table 1. ACUTE RADIODERMATITIS OF THE TRUNK

DESCRIPTIVE STATISTICS							
Interval number	1	2	3	4	5	6	7
Interval limits (days)	10 13	13 16	16 19	19 22	22 25	25 28	
Number of patients in each interval	79	78	67	57	51	34	
Number of patients cured of the process in the interval	1	11	10	6	17	34	
Healing in the interval (%)	4.3%	14.1%	12.6%	7.6%	21.5%	42%	
Accumulated Frequencies	1	12	22	28	45	79	
% of Accumulated Frequencies	1.3%	15%	28%	35%	57%	100%	

An interesting fact is obtained from the observation of these patients, the healing of the radiodermatitis is not presented with a “continued healing behaviour”.

The number of patients that are healed throughout the different intervals is not regular, existing two marked periods: the one at three weeks (22 days, intervals 1 to 4) with 35% (28 cases) and that of the last week (28 days) with 34 cases, in which 100% healing is achieved. (Figure 1, adapted from Abad).

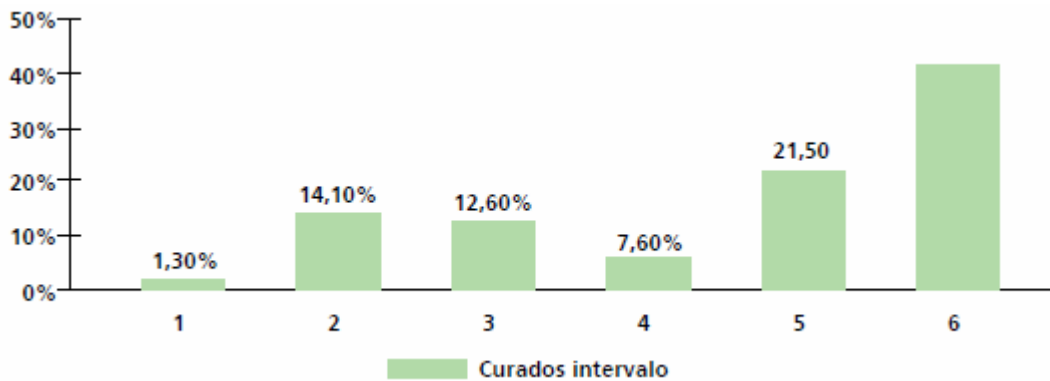
Figure 1. Evolution of healed patients per interval and accumulated



Healed per interval Healed accumulated

In the following figure (Figure 2) the same fact can be demonstrated.

Figure 2. Evolution of Percentage of healed patients per interval



Healed per interval

It is seen that in the interval between days 22 and 28, there were 51 healed cases while in the interval between days 10 and 22 there were only 28 cases, which signifies nearly twice the number of healings (1.8 times) in the intervals 5 and 6 compared to the intervals 1 to 4.

The interval of days 19-22 (clinical period of “healing latency”) is where there is the least number of healed cases. Afterwards comes a “critical time of healing”, from which the number of healed patients increased.

There are two concepts that help understand what has been observed here:

1. The Rate of Decrease at the beginning of each interval, and
2. The Role of Healing expectation.

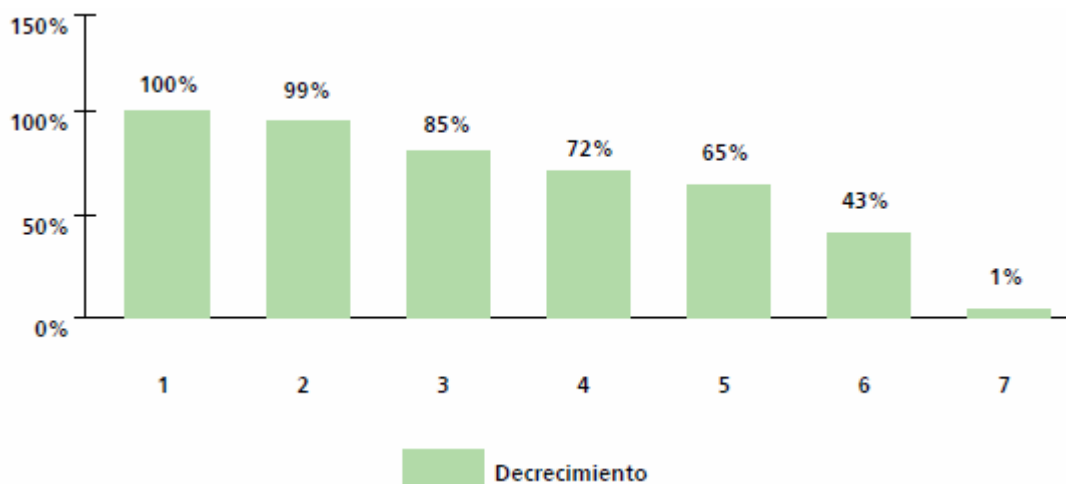
The Rate of Decrease at the beginning of each interval reflected 65% of the cases at 22 days. Twentythree days of treatment had to be passed in order to obtain 99% of healing, as can be seen in table 3.

Table 3. Rate of Decrease at the start of each interval and its standard error

Interval number	1	2	3	4	5	6	7
Interval limits (days)	10313	13316	16319	19322	22325	25328	
Rate of decrease of the process at the start of the interval, expressed in percentage (%)	100%	99%	85%	72%	65%	43%	1%
Standard error of the rate, expressed in percentage	0%	3%	8%	10%	11%	11%	3%

Graphically, it can be represented as follows, adding the trend line in order to make it more graphic (Figure 2, adapted from Abad).

Figure 2. Rate of decrease of the process at the start of the interval and the trend line



Decrease

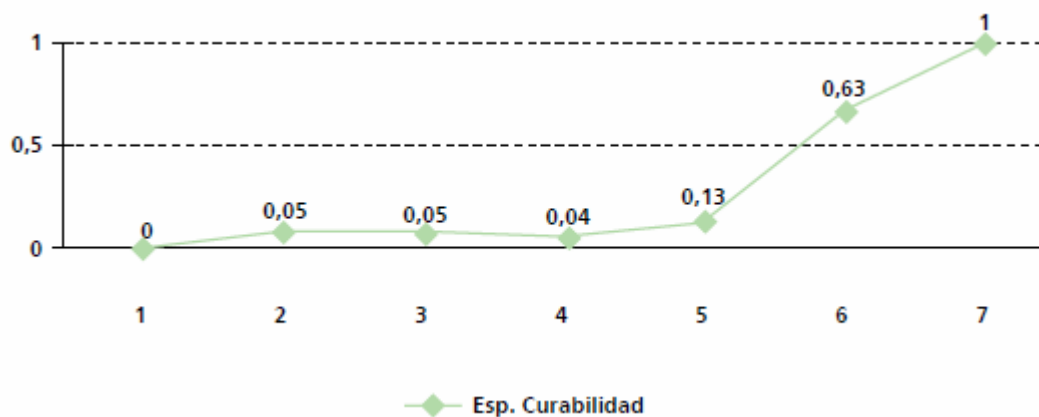
The role of healing expectation can be observed in the following table, in which one can observe that in the first 25 days it does not pass 20%, and 100% is reached at 28 days.

Table 4. Role of healing expectation and its standard error

Interval number	1	2	3	4	5	6	7
Interval limits (days)	10313	13316	16319	19322	22325	25328	28331
Role of healing expectation in the disease	0	0.05	0.05	0.04	0.13	0.63	1
Standard error of the role of healing expectation in the disease	0.01	0.03	0.03	0.05	0.05	0.05	0.28

Therefore, if one wants to achieve the maximum number of healings, the treatment must be administered for at least 29 days, which can also be observed in Figure 3, in which the maximum number of healings appears in interval 7, that is, in the interval of the days 28 to 31.

Figure 3. Role of healing expectation



Healing expectation

It is also interesting evaluate the radiodermatitis in specific locations on the trunk:

1. Radiodermatitis in the submammary crease

In the following table (Table 5) the healing time according to this location can be observed. It statistically shows that there is a latency period of 10 days until the first cases of healing are presented.

Fifty percent of the cases reach healing at 14 days and 100% at 16 days.

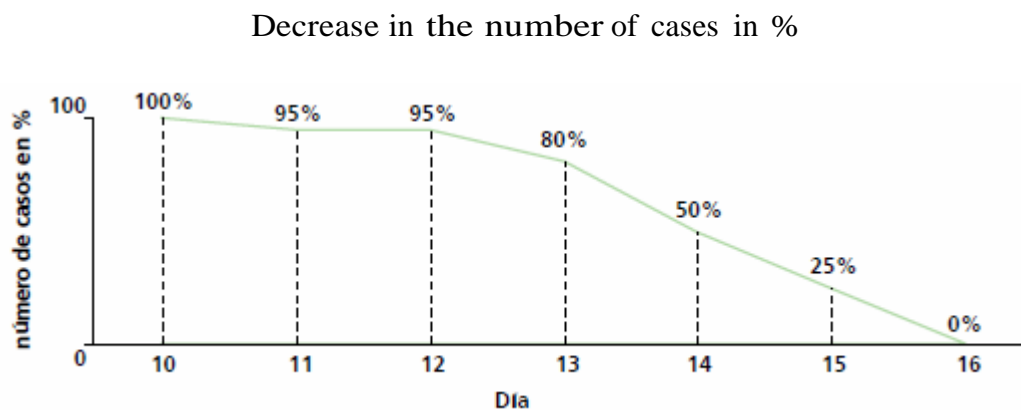
Taking a confidence interval of 5% of the average healing time, it is situated between 15 and 17 days. These radiodermatitis are the ones that seem to heal the earliest.

Table 5. Healing time of radiodermatitis in the submammary crease

Time in days	10	11	12	13	14	15	16
Decrease in number of cases in %	100	95	95	80	50	25	0

Its graphic representation appears in the following figure (Figure 4).

Figure 4. Healing of radiodermatitis of the submammary crease in % and by day



Although it is known that this radiodermatitis can heal without treatment, in cases of small lesions, there are specific cases which healing is longer, even over 30 days (Dertrase and Bepanthen), and it is unethical to prolong the healing in these patients because of the personal and family consequences it may generate.

2. Radiodermatitis produced on the postmastectomy thoracic scar

Clinically it has been observed that radiodermatitis on a prior surgical scar, as a result of a mastectomy, takes longer to heal.

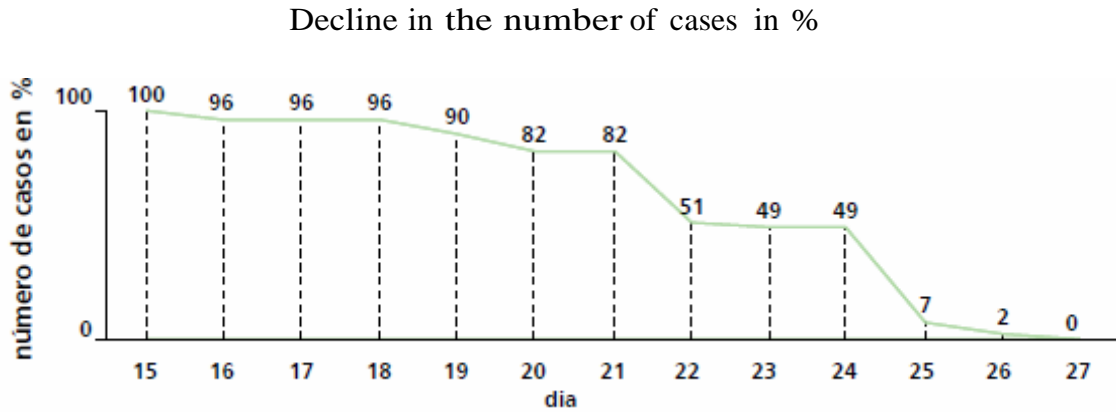
Table 6 shows that the decline in the number of patients begins between day 22 and 24, which is when 50% of the cases are healed and reaches 100% on day 27; that is, with nearly a month of treatment.

Table 6. Radiodermatitis produced on the postmastectomy thoracic scar

Time in days	15	16	17	18	19	20	21	22	23	24	25	26	27
Decrease in the number of cases in %	100	96	96	96	90	82	82	51	49	49	7	2	0

Figure 5 graphically represents this decline in the existing number of patients for each day of observation.

Figure 5. Healing of radiodermatitis on postmastectomy scar in % and by day



Looking at the treatment of this type of radiodermatitis, when compared with the time that it took to heal the patients suffering Dertrase and Bepthantene, it can be deduced that the treatment with Radiocare diminishes almost half of the time of healing (51 days compared to 26327 days).

3. Radiodermatitis of the axilla

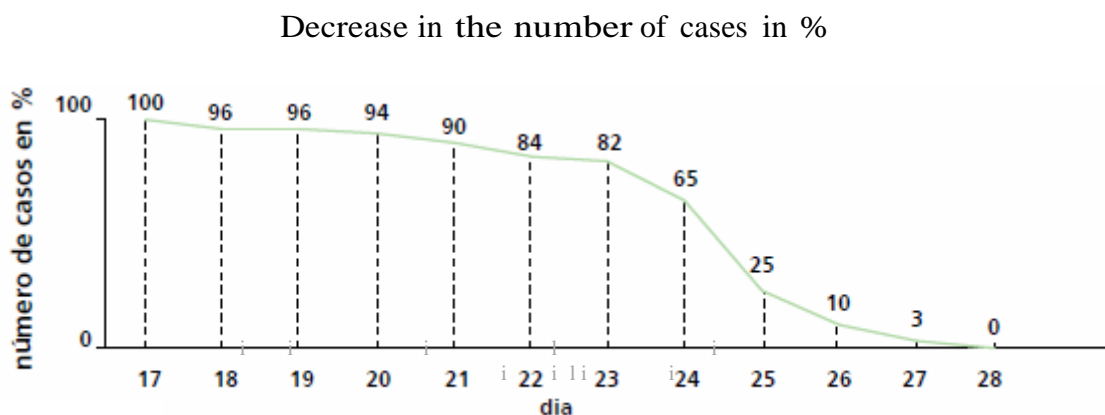
In the next table we can observe that in our evaluation a higher decrease of radiodermatitis in the axilla is produced from the day 24 with a maximum on the day 28 of the monitoring.

Table 2. Radiodermatitis of the axilla

Time in days	17	18	19	20	21	22	23	24	25	26	27	28
Decrease in the number of cases in %	100	96	96	94	90	84	82	65	25	10	3	0

This can also be seen in figure 6.

Figure 6. At least 27 days are required to heal the radiodermatitis process of the axilla



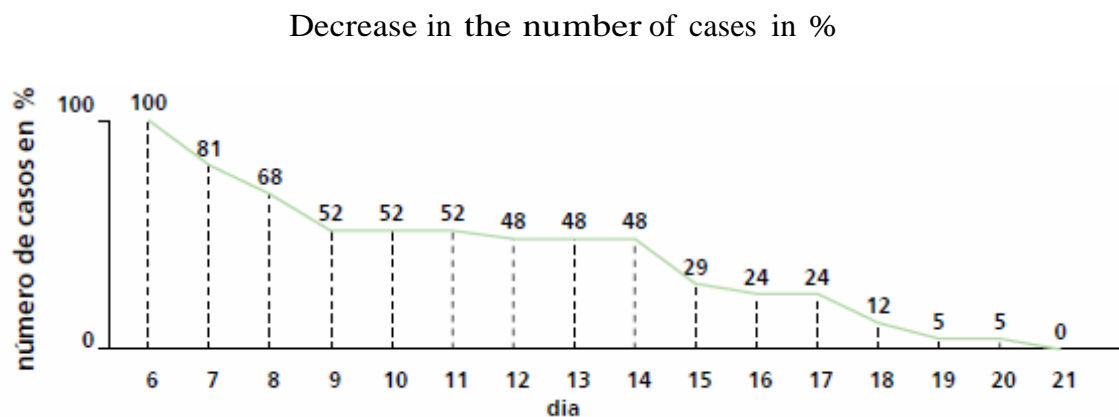
4. Acute radiodermatitis of the anterior and posterior part of the abdominal regions

In the 21 cases treated for acute radiodermatitis of the anterior and posterior part of the abdomen, the healing began from the first week: at 12 days, 50% were healed and at 21 days, statistically all were healed, as can be seen in Table 8 and Figure 7.

Table 8. Acute radiodermatitis of the anterior and posterior part of the abdominal region

Time in days	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Decrease in the number of cases in %	100	81	68	52	52	52	48	48	48	29	24	24	12	5	5	0

Figure 7. Decrease in the number of cases in % of each period



TREATMENT OF CHRONIC RADIODERMATITIS IN PATIENTS SUBJECTED TO RADIOTHERAPY

Chronic Radiodermatitis

Fortunately at this time the appearance of chronic radiodermatitis is exceptional, but when it does appear, and depending on the intensity of the lesions and the time of evolution until it is diagnosed, it is clear that it can benefit from treatment with Radiocare.

In these cases the lesion includes the skin, the subcutaneous cellular tissue, the muscles, the bone and even the adjacent organs such as the pleura and/or the lung.

At this moment taking into account the patients evaluated and treated for chronic or late-appearing radiodermatitis by Dr. Abad, the average time of appearance of lesions from the end of the primary treatment to the diagnosis and starting of the treatment with Radiocare was 118.9 +/3 38.6 months, with an average treatment

period until healing of 4.7 +/3 5.7 months. Although it must be mentioned that the number of cases is small (5 could be evaluated) and an evaluation with a larger number of patients will be necessary. However, because of the fortunate rarity of this type of radiodermatitis, it is a study that will take monitoring over many years in order to demonstrate statistical significance. For this reason at this time it cannot be considered, especially having the clinical experience of the few treated cases, of which some details are interesting to mention:

- The complete restoration of the tissues will be much more difficult than in the case of a lesion exclusively of the skin.
- The loss of substance or structures (nasal pyramid, rib wall, etc.) are irreparable, only being able to “compensate” the suppression of the symptoms of the radiodermatitis with an increase in the quality of life.
- In some cases it is necessary to use repairing plastic surgery with skin grafting.

Recurring Radiodermatitis

Only about 10% of cases of radiodermatitis are recurring, which requires reinitiating the treatment with Radiocare in previously healed radiodermatitis and with the added benefit that during the treatment we find that the lesions are usually healed much easier and earlier than the original lesions.

Thermal Burns

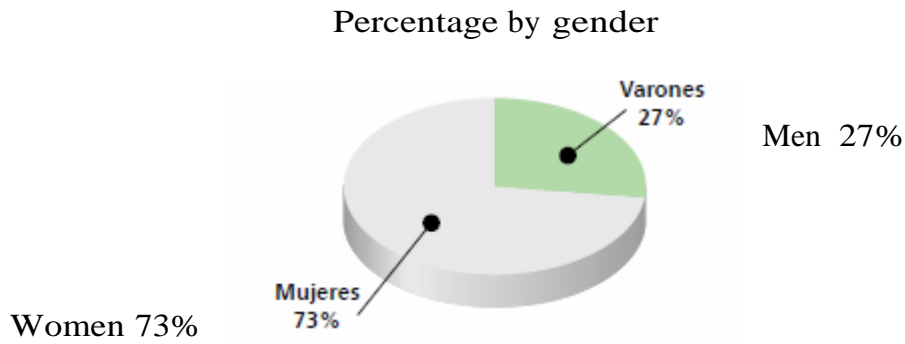
Thermal burns are understood as those that are produced by a heat source that applied to the skin usually accidentally (occupational or domestic accidents) and others voluntarily (prolonged exposure to the sun in leisure areas) cause a lesion on the skin (burn).

In the study that serves as a basis for the report from which the data discussed below were taken, 131 patients were included, examined and treated in the Hospital San Juan de Dios. From the data collected, the sociodemographic and clincotherapeutic characteristics related basically with this type of pathology were established, without forgetting to reflect the atmosphere of the hospital care in a specialised centre, with which the proximity to reality is absolute.

From the sociodemographic point of view, the following stand out as the most important data:

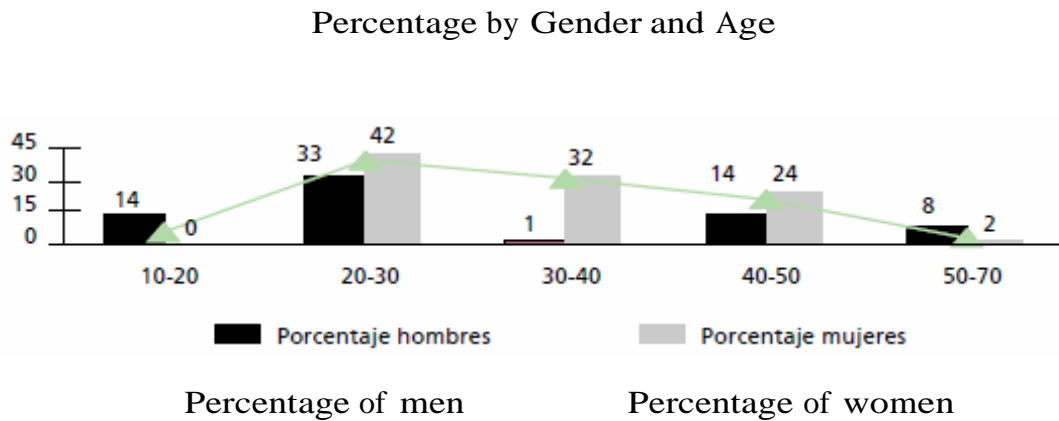
The appearance of lesions are more frequently produced in women (73% vs. 36% in men), with an average age of 32.9 vs. 32.5.

Figure 1. Distribution by gender



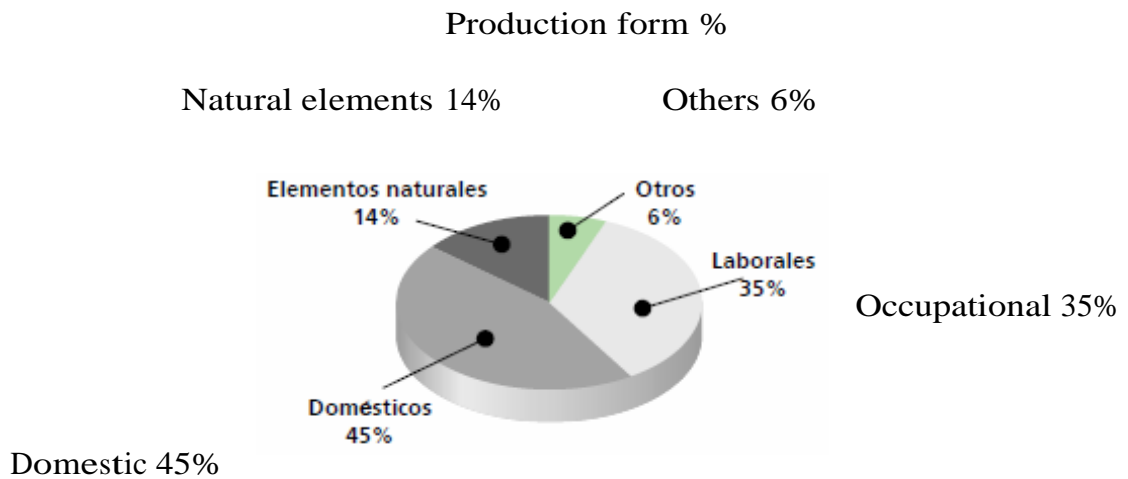
Seventy3five percent of the cases occur in people under 40 years of age, with predominance of occupational burns for males and domestic burns for females.

Figure 2. Percentage distribution by Gender and Age



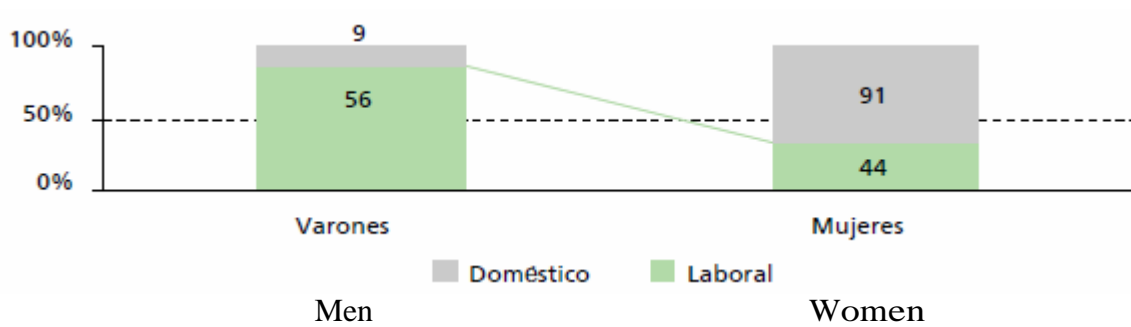
The distribution by forms producing the lesions can be classified in percentage as follows:

Figure 3. Origin of the Burns



When evaluating the place of occurrence of said thermal burns, results reflect the traditional logic of our country.

Figure 4. Place of Occurrence by Gender



We also obtained as a datum that the domestic arena seems to be the most dangerous with an age average higher than in the occupational arena. In the occupational arena predominate burns by live flames (31%) and by chemical products (33%), while in the domestic arena burns from a hot solid (16%) and hot liquid (59%) predominate, with the forearms and the hands being affected most frequently in both areas. The 54% and 50% of thermal burns occurring in occupational and domestic settings, respectively. The anatomical distribution of the lesions, in percentage and distributed by gender are as follows:

Table 1. Anatomical location by Gender

Anatomical Location	Percentage of Males	Percentage of Females
HEAD	3%	19%
Neck	0%	7%
Anterior trunk	5%	10%
Posterior trunk	6%	4%
Upper limbs	5%	1%
Arm	2%	3%
FOREARM	18%	13%
HAND	30%	16%
Lower limbs	11%	3%
Lower limbs (anterior face)	0%	1%
Anterior thigh	3%	5%
Anterior leg	10%	10%

Anterior foot	3%	6%
Posterior thigh	0%	1%
Posterior leg	3%	0%
Genitals	2%	1%

Another interesting point is the degree of depth of the lesions. In the following table the shown distribution is obtained from the data of the patients of this study:

Table 2. Anatomical depth

Depth of the lesions	Percentage of Males	Percentage of Females
Epidermal	0%	8.4%
Superficial dermal	50%	48.4%
Deep dermal	47.2%	42.1%
Subdermal	2.8%	1%

Once Radiocare is applied to the burns of these patients, the following was evaluated:

- time for pain to disappear
- average healing time depending on the producing agent

Time for pain to disappear:

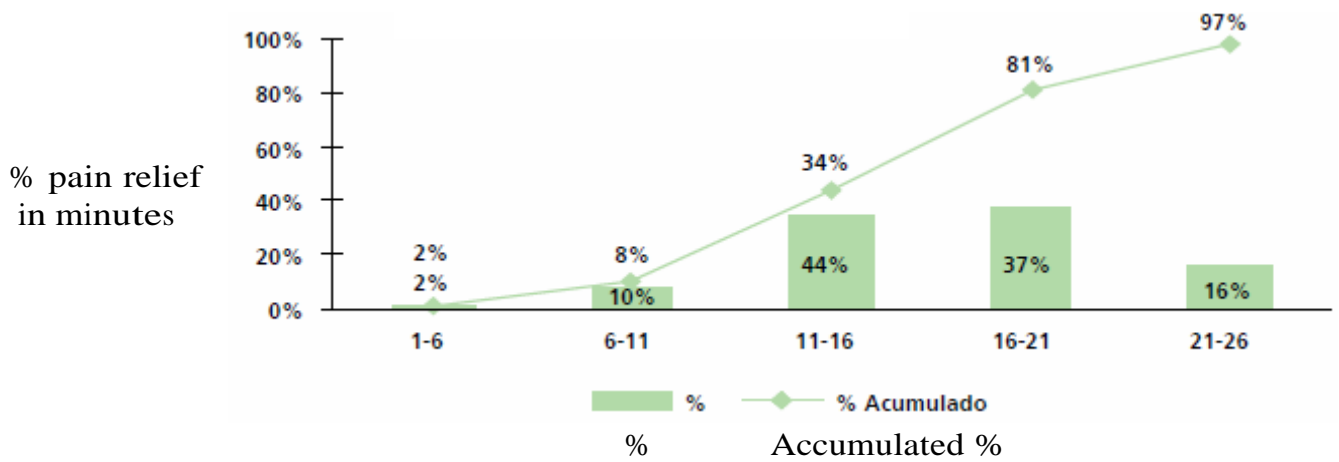
The average time for the disappearance of pain was 18 minutes with a median of 20 minutes, as can be observed in the following table.

Table 4. Time for symptom to disappear

TIME in minutes	Percentage
136	1.5%
6311	8.4%
11316	34.4%
16321	37%
21326	16%

It is seen that 44% of the patients feel relief from their pain in the first 16 minutes after the application of Radiocare, and 81% of the total in the course of the first 21 minutes.

Figure 5. Evolution of the pain relief in minutes

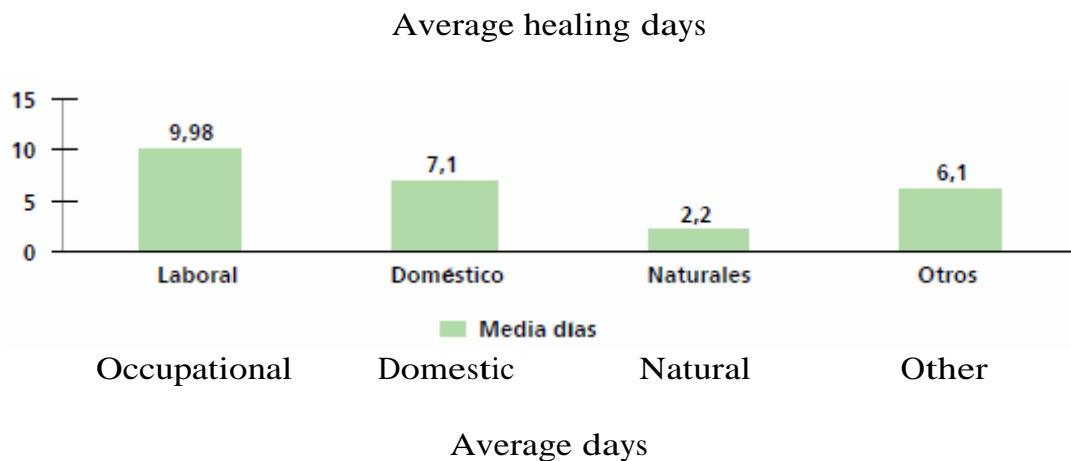


It is also observed that males take longer to manifest pain relief (average of 20 minutes) than women (17.65 minutes), with the difference being statistically significant, also verifying that the time that it takes for the pain to disappear is directly proportional to the age of the patients, with the disappearance of pain taking longer.

Average time of healing according to the cause

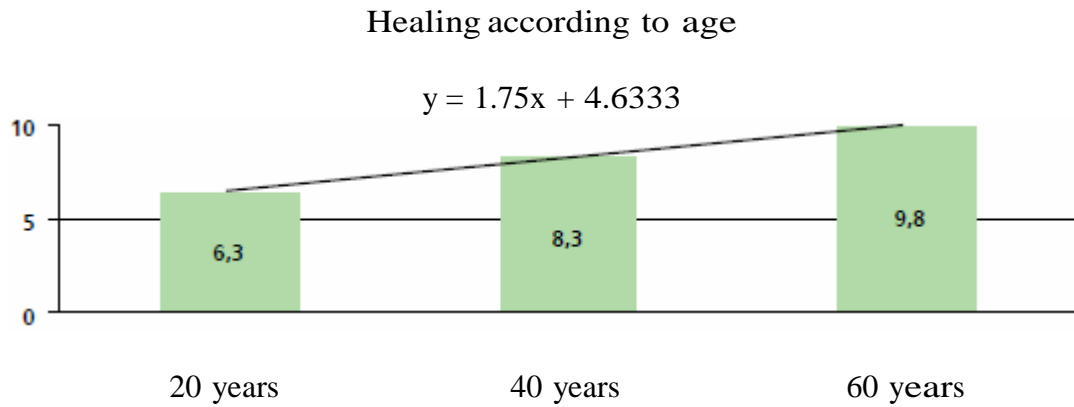
The healing time in days depends on the cause of the thermal lesion, as can be seen in the following graph:

Figure 6. Average of healing time in days



The healing time varies from 2.2 days for those produced by natural elements to 9.98 days for those caused in work-related environments; the healing time is also higher as the age increases, as can be seen in the following graph adapted from Abad, in which its trend line is presented:

Figure 7. Healing, according to age

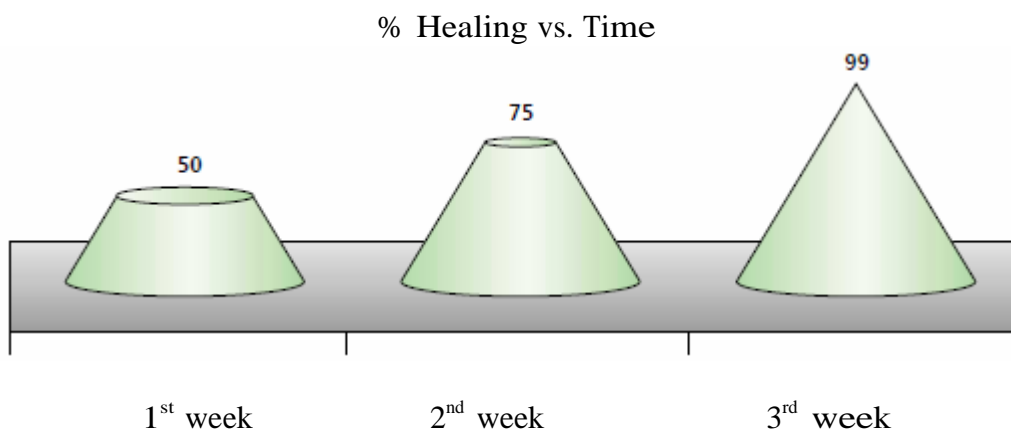


In summary, it is interesting to highlight, in accordance with the following graph, that the healing took place as following:

- At the end of the first week, 50% of the patients were healed
- At the end of the second week, 75% of the patients were healed
- At the end of the third week, 99% of the patients were healed

Without finding statistically significant differences in the healing time according to gender, it is seen that the healing expectation is optimal in the two first weeks.

Figure 8. Healing over time



OTHER RADIODERMATITIS

New forms of radiodermatitis are appearing nowadays because of the diagnosis and therapeutic advances, in the way they are applied: in the combined chemoradiotherapy treatments and in interventionist radiology.

1. The antineoplastic chemotherapy agents are very selective chemical substances with great activity towards the patient from which its antitumour effectiveness is derived, but also its toxicity. The application of combined chemoradiotherapy treatments in oncological patients produce collateral effects that result in an increase in radiodermatitis. Because of the development of good results demonstrated in radiodermatitis, it is logical to think that Radiocare is appropriate for the treatment of radiodermatitis that appears in combined chemo3radiotherapy treatments.
2. The scientific literature shows clearly that radiodermatitis is at present occurring as a consequence of vascular and interventionist radiology. And this does not leave any doubt that there are some professionals exposed to radiation with possible affection, not only of the skin, but also of other tissues and organs (crystalline, gonads, spinal cord, etc.). It is necessary to remember that in industrialized countries between 300 to 900 X3rays per 1,000 inhabitants are given, mainly of the thorax.

The substantial aspect of this new situation lies in the fact that the accidents that occur are by chance, while in the current radiotherapy they are fully foreseeable by means of calculating the dosage prior to the treatment.

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