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ENZYMATIC DEBRIDEMENT WITH PROTEOLYTIC ENZYMES ENRICHED IN BROMELAIN VS. SURGICAL DEBRIDEMENT FOR BURN WOUND MANAGEMENT.

A RANDOMIZED OPEN-LABEL CLINICAL TRIAL

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LIST OF ABBREVIATIONS

VHUHB	Vall d'Hebron University Hospital Barcelona
SOC	Standard of Care
TBSA	Total Body Surface Area
CPE-B	Concentrate of Proteolytic Enzymes enriched in Bromelain
ED	Enzymatic Debridement
ICU	Intensive Care Unit
CG	Control Group
EG	Experimental Group
IC	Informed Consent
MVSS	Modified Vancouver Scar Scale
QoL	Quality of Life

ABSTRACT

BACKGROUND. Early surgical debridement followed by autografting is currently the gold standard treatment for deep burns. However, tangential debridement is considered to be a complicated technique with several associated morbidities, including blood loss, surgical aggression and poor selectivity in the case of intermediate and extensive burns. Oftentimes the removal of the eschar is associated with a loss of healthy dermal tissue and a decrease in the skin's ability to regenerate, requiring coverage with autografts. The use of a new enzymatic debrider has recently been proposed, a bromelain-enriched proteolytic enzyme concentrate, which appears to exhibit selectivity towards necrotic tissue, completely debriding the eschar and allowing spontaneous re-epithelialization from healthy dermal remnants. This product has proven to be effective and selective, having an impact on reducing the number of surgical interventions to which a large burn patient is exposed, reducing hospitalization time, as well as reducing the rate of escharotomies, improving post-burn cicatrization, and improving the patient's degree of satisfaction.

OBJECTIVES. The aim of this study is to evaluate if the use of enzymatic debridement with CPE-B in the treatment of deep thermal burns affecting over 15%TBSA is more effective than the actual SOC, being its action more specific towards the necrotic tissue, achieving a complete debridement of the eschar and so reducing the need for surgical intervention and its associated morbidities.

STUDY DESIGN AND POPULATION. A randomized, open-label and controlled clinical trial was designed with 562 patients (TBSA over 15%) admitted in the Vall d'Hebron Burn Unit between March 2021 and September 2023 who will meet inclusion criteria.

METHODS. The sample will be randomly assigned to one group of intervention: 271 patients will be included in the control group and will be treated with tangential excision, and 291 will be treated using CPE-B, 20 of them will be used as a pilot test. The main outcome will be total mortality rate. Other covariates will be considered such as: need for surgery and autografting, hospitalization time, escharotomies rate, hypertrophic scarring rate...

KEY WORDS. *Burns, Enzymatic debridement, Bromelain, Eschar, Tangential excision, Escharotomy, Transfusion, Scarring, Mortality.*

INTRODUCTION

I. Background.

Burns are part of the most serious group of traumas, with greater morbidity and aesthetic impact and with greater social impact, constituting a global public health problem, which according to the WHO causes almost 180,000 deaths a year (1). Although there are no exact data on the incidence of burn injuries, it is estimated that in our environment there are approximately 300 burn patients per 100,000 inhabitants per year (2). In Catalonia, about 100-150 burns/100,000 inhabitants/year are treated, of which about 2,000 are treated in the Burn Unit of the Vall d'Hebron University Hospital in Barcelona; 550-600 of these patients require admission (3).

Throughout the last years, thanks to the evolution of the available treatments, the mortality has been reduced, causing an increase in the functional, aesthetic, and quality of life sequels, which also entails a high indirect economic expense due to work disabilities, which reach up to 5% (4), the prolonged attention of the patients and the emotional traumas derived from the aesthetic changes, present in up to 43% of the patients (2). There are also psychological sequelae in burned patients, some of them very important, like post-traumatic stress disorder and depression (5).

Burn injuries are produced by contact of the body with a heat source, which initially causes local tissue necrosis, however if the affected total body surface area (TBSA) is extensive (TBSA>15%), there may be repercussions on the body's functioning. In this case, a series of alterations are produced at a systemic level of the fluids and electrolytes, metabolic changes, bacterial contamination of the tissues and complications of the vital organs. The most frequent complication is post-burn shock, a process of cardiovascular dysfunction due to the inflammatory and hypermetabolic response. The burn causes an extravasation of plasma due to increased permeability of the cell membrane, which will lead to a series of hemodynamic changes such as decreased cardiac output, plasma volume, diuresis, peripheral flow and oxygen release, increasing systemic vascular resistances. This clinical picture, known as general disease of large burns, is a serious situation that requires complex and multidisciplinary action (3,6). Mortality associated with burn patients is related to sepsis, poor wound healing, hormonal imbalance, and pulmonary, hepatic or renal failure (7).

We find three areas of histopathological damage in one burn (*see Figure 1*). The coagulation zone (eschar, necrosis) is the area that was closest to the heat source. The tissue in this zone is either

necrotic or in the process of necrosis due to denaturation of the proteins. This zone is considered irreversible damage. Next to the necrotic zone is the zone of stasis and edema, in which a moderate denaturation of the proteins has been originated, with an associated edema and a low blood flow, due to capillary leakage and membrane rupture. Below the stasis zone is the hyperemic zone, where blood flow gradually increases (8).

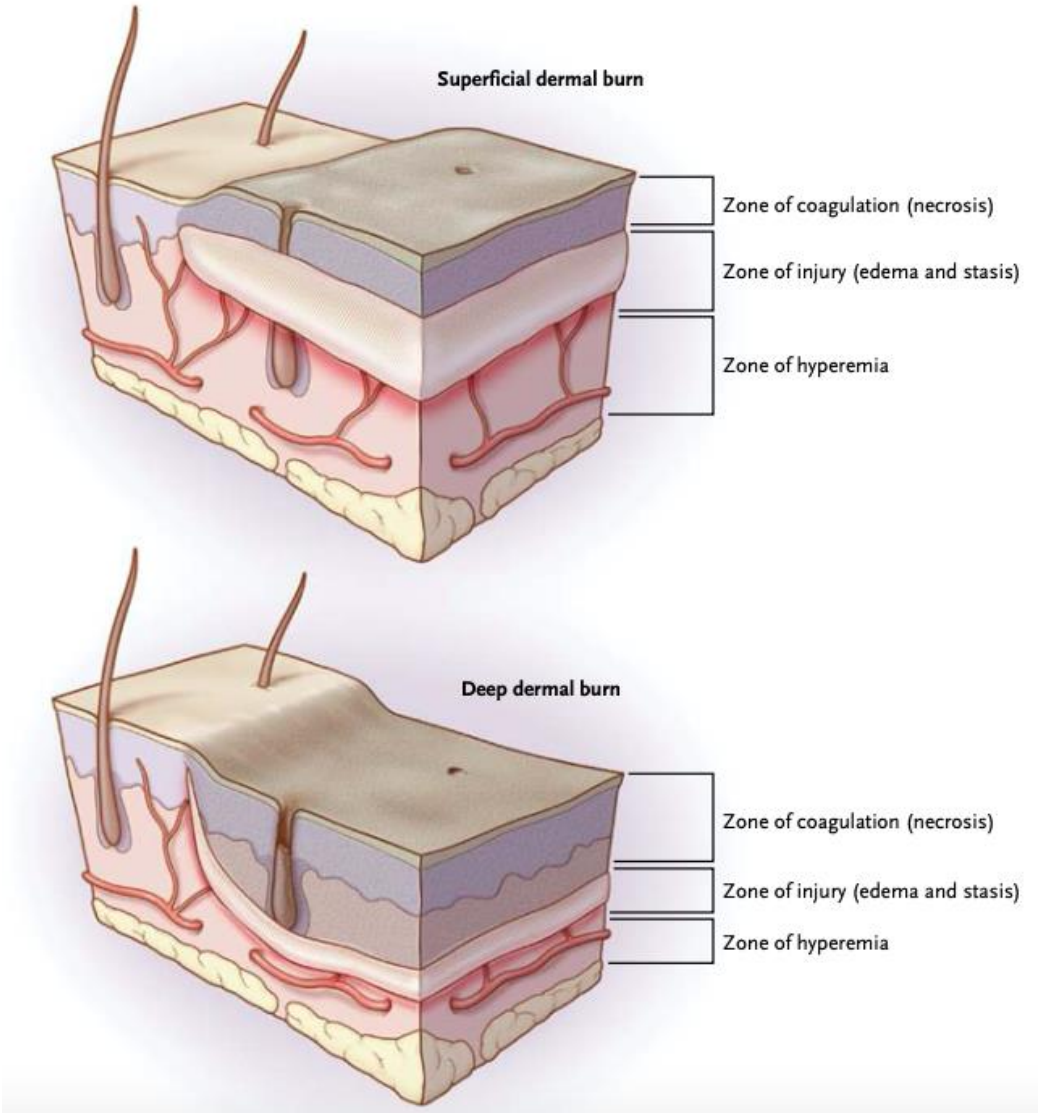

Figure 1:Zones of Injury in Superficial and Deep Dermal Burns

Source: Dennis P, Excision and Skin Grafting of Thermal Burns (9)

In the case of deep burns there is an edema between the eschar and the fascia of the underlying muscle, two inextensible textures. This increase in pressure, especially relevant in circular burns of the limbs, can lead to a compartment syndrome, which, due to the hypoperfusion produced by the ischemia of the vessels present in the compartment, with the consequent necrosis of the unburned epithelial cells, leads to the deepening of the lesion (10).

Burns are classified according to two fundamental elements:

1. Their depth (*see Figure 2*), being classified as:

-**Erythema** (grade I), typical injury by solar exposure, no loss of skin integrity, spontaneous healing, should not be calculated in the extension of the total burned surface;

-**Dermal-superficial** (grade IIa), the lesion reaches the papillary dermis, we'll see presence of blisters, a hyperemic and exudative bed, can achieve spontaneous epithelialization before twelve or fourteen days;

-**Intermediate dermis**, one of the most complex lesions to manage since according to the evolution of the wound it can epithelialize spontaneously or require surgical intervention later, a fact that entails a potentially defective healing;

-**Deep dermal** (grade IIb), the lesion reaches the reticular dermis, no blisters normally appear, the surface is pale and dry, indicating poor vascular perfusion. Incapacity of spontaneous re-epithelialization, indication of surgical treatment;

-**Total thickness** (grade III), the whole dermis is affected and sometimes also the subcutaneous tissue and the muscular planes. There is no capacity for re-epithelialization, the wound is seen as a dry bed, white-yellowish, with a leathery appearance and sometimes with the presence of thrombosed vessels.

Facing a burn wound, the initial evaluation by the surgeon will determine its depth and therefore the therapeutic action, although in 30-60% of cases this evaluation is incorrect (11). We can also use the Doppler laser technique, which between the second and fifth day after the burn will measure the existing vascular flow in the lesion and will guide the diagnosis in a more objective way, 95% success rate (12).

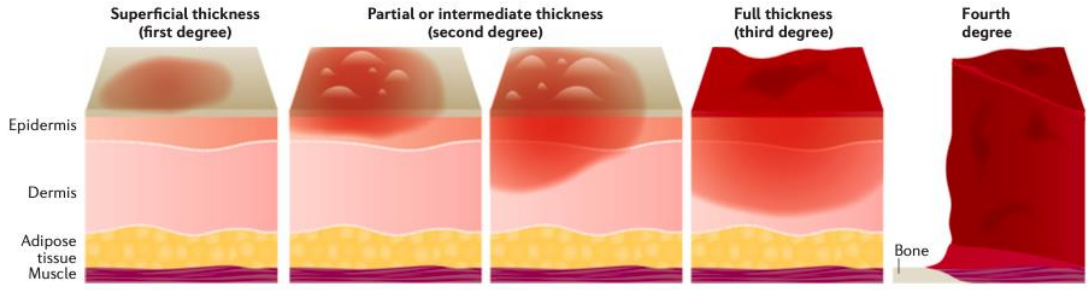

Figure 2: Burn Depth Classification

Source: Nature Reviews Disease Primers, Burn Injuries (13)

2. Their extension, finding in clinical practice different ways to calculate it, being the main ones:

-**Wallace's Rule of 9**: the head, neck and upper limbs represent 9% of the total body surface; the thorax, the back and each of the lower limbs 18%; and the genitals 1%. These proportions differ for children. (*see Figure 4*)

-**Rule of 1**: The palm of the patient's hand is equivalent to 1% of the TBSA.

-**Specific tables** (Lund and Browder) used in burn units and children. (*Figure 3)*

RULE OF 9s	Total	Subdivision
Head	9%	Anterior Head = 4,5%
		Posterior Head = 4,5%
Torso	18%	Chest = 9%
		Abdomen = 9%
Back	18%	
Each Arm	9%	Anterior Arm = 4,5%
		Posterior Arm = 4,5%
Each Leg	18%	Anterior Leg = 9%
		Posterior Leg = 9%
Perineum	1%	

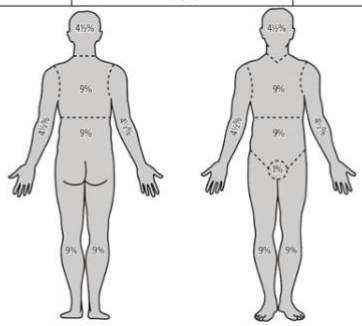

Figure 4: Rule of 9s

AGE (years)		0	1	5	10	15	Adult
Front or back half		(%)	(%)	(%)	(%)	(%)	(%)
A	(Head)	$9\frac{1}{2}$	$8\frac{1}{2}$	$6\frac{1}{2}$	$5\frac{1}{2}$	$4\frac{1}{2}$	$3\frac{1}{2}$
B	(Thigh)	$2\frac{3}{4}$	$3\frac{1}{4}$	4	$4\frac{1}{4}$	$4\frac{1}{2}$	$4\frac{3}{4}$
C	(Leg)	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{3}{4}$	3	$3\frac{1}{4}$	$3\frac{1}{2}$

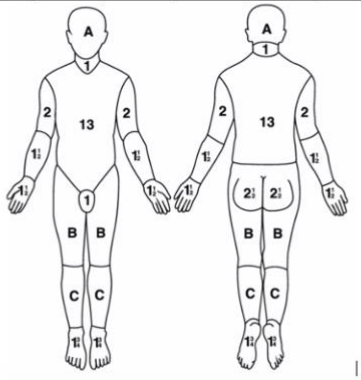

Figure 3: Lund and Browder's chart

We will consider a patient to be badly burned if their injuries exceed 20-25% TBSA, (14) if they have deep burns exceeding 10% TBSA, burns affecting the face/neck, inhalation burns, associated trauma, or burns in patients with severe underlying diseases (ASA II or greater) (15)

Another way of classifying burn injuries is by their harmful mechanism: thermal injuries (flame, scald, contact), radiation burns, chemical burns and electrical burns, with thermal burns being the most common (16).
Another important factor to take into account is the severity of the injury, which is usually calculated using the following two scales:

1. **ABSI index**, which is made up of the percentage of TBSA (1 point for every 10%), age (1 point for every 20 years), smoke inhalation injuries (1 point if present), sex (1 point if female, 0 if male), presence of full thickness burns (1 point if present)

This index is also useful as a prognosis in mortality and hospital stay, with an ABSI score of 2-3 being related to <1% mortality, and an ABSI score >11 to >80% mortality (17).

2. **Revised BAUX index**, which is based on the following formula: $Revised\ BAUX\ index\ =\ Age\ (years)\ +\ TBSA\ (\%)\ +\ 17 \times inhalation\ (1/0\ if\ yes/no)$

From this formula the probability of death will also be calculated, following the formulas:

Logit mortality = $\frac{e^{-8,8163+(0,0075*Revised\ Baux\ Index)}}{1+e^{-8,8163+(0,0075*Revised\ Baux\ Index)}}$ Probability of death = $\frac{Logit}{1+Logit}$

Analyzing these scores, we conclude that mortality in the burn patient is clearly increased in cases of greater extension of the injury. The data available today is insufficient to establish an approximate mortality of large burned patients, placing it in a study conducted in 2006, evaluating patients with criteria of "large burn", on 42.3% intra-ICU and 44.1% until discharge from hospital (15). The main complications that caused the death of the patients were respiratory distress and renal failure.

It is complicated though to decide if these data are applicable to the current clinical situation because of the great variability that exists within the term "great burn" and the evolution of therapeutic options today.

II. Therapeutic options.

II.I. Surgical Tangential Debridement

In the last decades, since Janzekovic (18) reintroduced the concept of early tangential surgical debridement, the mortality of large burn patients has decreased significantly. Previously, the gold standard was the conservative technique, waiting for the necrotic eschar to detach from the wound and for the wound to heal on its own. All of this led to a very high risk of infection and failure to recover from the wound, sometimes with increased injured tissue (19).

The main objective of surgical debridement is to preserve healthy tissue through surgical excision of the necrotic eschar. It has been shown that the earlier this intervention is performed, the better the results obtained, decreasing inflammation, the risks of infection, wound sepsis, and multiorgan failure (20).

It is important to bear in mind that this operation cannot be carried out until the patient is in an adequate general state. In case of presenting other more serious pathologies, these will have to be attended to at first. We must have the patient with constant electrocardiographic monitoring,

pulsiometry and frequent monitoring of vital signs, oral intake and diuresis (9). The use of Ringer Lactate is recommended to maintain a diuresis of 0.3 ml per kg/body weight and a systolic blood pressure above 80mmHg.

It will be recommended that the operating room be at a temperature of 30ºC to avoid a drop in body temperature (21), and that intravenous fluids be warmed before administration to keep the patient's temperature stable.

The most frequent complication of this technique is intraoperative blood loss. It has been calculated that between 100 and 200 ml of blood is lost for every 1% of skin surface that is debrided (22). For this reason, we must monitor the patient's needs, guaranteeing access to blood transfusions if necessary.

Excisions will be performed with different instruments according to the area to be debrided. A Goulian knife can be used for small surfaces or with many contours, and for longer and flatter surfaces the use of Watson (*see Figure 5*) or Humby knifes is recommended (23). To these tools you can add a guard that will control the thickness of the cut that we are going to exercise. Excisions will be done in layers until we find a tissue that seems viable, seeing a dotted bleeding pattern. Cuts larger than 10 x 10 cm should not be made to avoid blood loss (24). It is also useful to use gauze with topical epinephrine or thrombin, but the hemostasis effect may sometimes make it impossible to see viable tissue and extract more tissue than necessary. If the burn is on an extremity, a tourniquet is recommended to reduce the amount of bleeding (9).

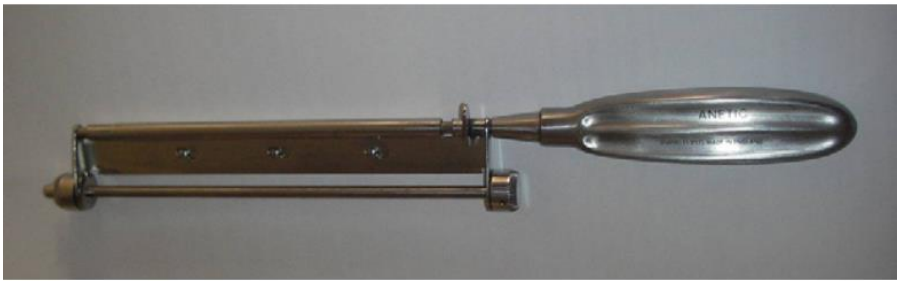

Figure 5: Watson Knife

Source: S.L.A. Jeffery, Device related tangential excision in burns. (23)

Currently it is very common to performe a dermatome debridement with a rotating burr (*see Figure 6*), demonstrating a lower loss of viable tissue due to its characteristics, which by rotating the tool achieves more precision when removing the necrotic tissue, but it involves a significant loss of blood.

Figure 6: Rotating Burr

Source: S.L.A. Jeffery, Device related tangential excision in burns. (23)

Once the debridement has been completed and hemostasis has been achieved, if the operation allows it, the grafting process will be performed. Donor graft (allograft) or skin substitutes can be used, even if they have a high rate of infection and rejection by the patient. Most commonly, skin autograft is used to cover the wound. Fine pieces of skin, consisting of epidermis and papillary dermis, will be collected from the patient himself.

These pieces will be collected from unaffected areas, often the anterior thigh or abdomen (9). A dermatome with a thickness of 0.20 or 0.51 mm is used, and once the piece has been collected it can be applied directly to the wound if it manages to cover it, or passed through a meshing machine, which will extend it and may cover more surface area. The skin will be sutured or stapled to the edges of the wound, covered with non-adherent dressings (often impregnated with silver or topical antibiotic) and then with a medium compressive bandage to help the wound heal.

The patient will then return to the intensive care unit until respiratory and renal function is within the limits of normal and pain can be controlled with analgesia. The graft areas will be checked frequently for signs of hematoma, seroma, or infection. In the event of graft failure, surgical debridement should be performed, and a decision made as to whether to allow the graft to heal by second intention or to re-graft.

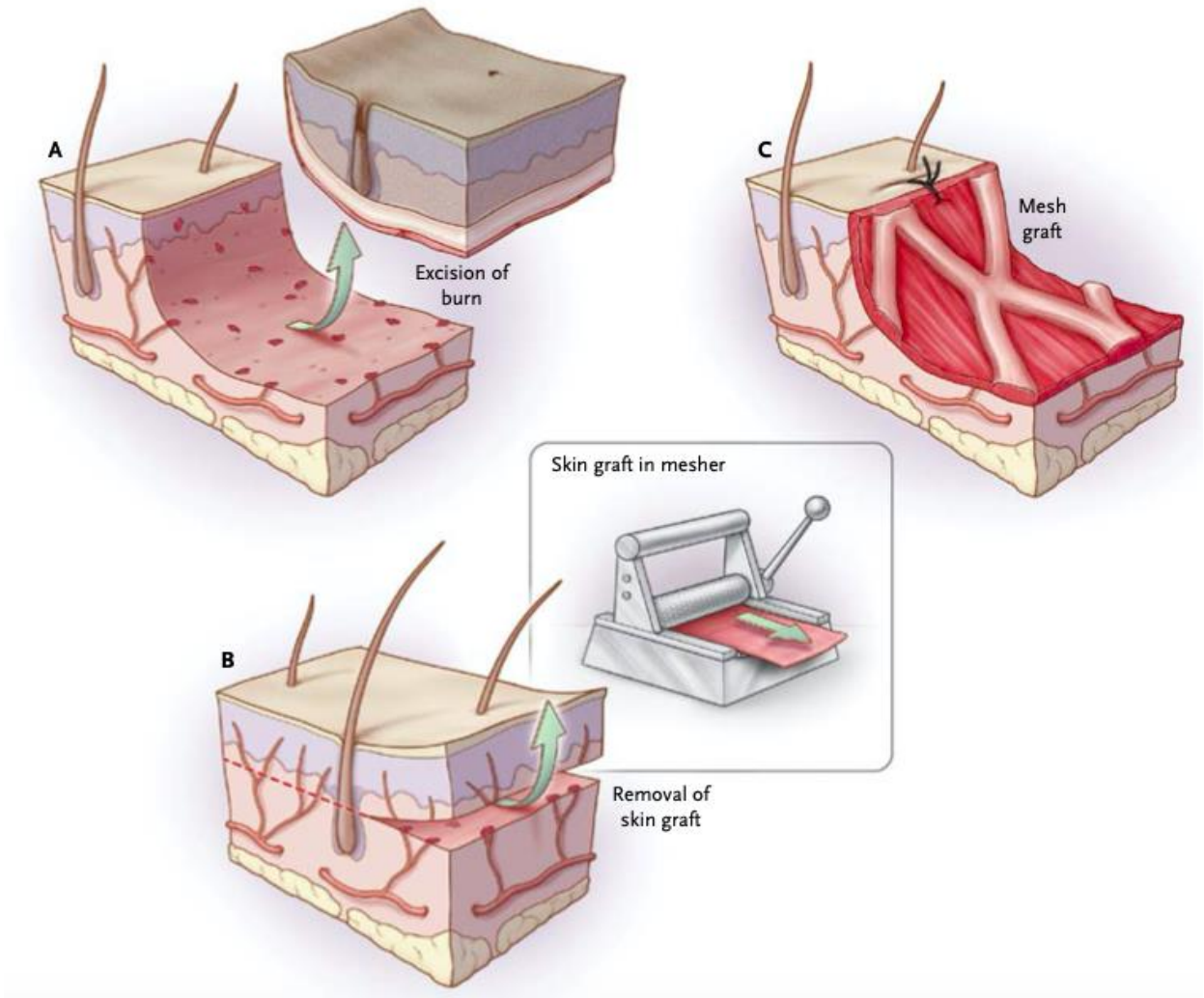

Figure 7: Excision and Grafting

Source: Dennis P, Excision and Skin Grafting of Thermal Burns (9)

II.II. Enzymatic Debridement with CPE-B

The therapeutic strategy to be studied in this clinical trial is enzymatic debridement with proteolytic concentrate of enzymes enriched in bromelain. It is a product that presents selective properties towards the necrotic tissue, which with the topical application manages to debride the eschar of the wound, preserving in totality the healthy tissue, increasing its capacity of spontaneous epithelization. The presentation of the drug and its use will be detailed below.

All data is extracted from the drug's technical sheet updated in November 2017 (25). *More detailed information about the product can be found on the European Medicines Agency website (http://www.ema.europa.eu/).*

I. Administration, dose, frequency and duration of treatment.

Topical use. The powder must be mixed with the gel to generate a uniform gel and apply it within a maximum of 15 minutes after the preparation of the mixture. It should be applied in a clean, humid lesion area, after the removal of the blisters. If the lesion area was covered by topical products, these should be removed, and the wound cleaned before applying the gel.

Apply the mixture with a thickness of 1.5 to 3 millimeters. It should then be covered with a sterile occlusive film dressing, and with a dressing fixed with a bandage. It will remain in the wound for 4 hours, and then the product will be removed using aseptic techniques. The eschar will be removed with a sterile blunt-edged instrument. Finally, the appropriate dressings are applied (*see Study Circuit*).

According to the European consensus in current use (26), a sequential treatment guideline should be applied in which the lesion is debrided in different sessions, treating 15% TBSA in each session until complete debridement of the eschar is achieved.

II. Form of presentation, composition and conservation.

The drug is presented under the comercial name of NexoBrid® (MediWound Germany GmbH). The vial is composed of 2g of bromelain-enriched proteolytic enzyme concentrate, corresponding to 0.09g/g of bromelain-enriched proteolytic enzyme concentrate after mixing (or 2g/22g of gel).

Proteolytic enzymes are a mixture of enzymes from the stem of *Ananas comosus* (pineapple plant).

It contains the following excipients: ammonium sulfate, acetic acid, carbomer 980, anhydrous disodium phosphate, sodium hydroxide, water for injectable preparations.

The product must be used after mixing, within a maximum of 15 minutes. It has a validity period of 3 years. It must be kept and transported refrigerated (between 2ºC and 8ºC). It should be kept in an upright position to keep the gel at the bottom of the bottle and in the original packaging to protect it from light. Do not freeze.

III. Pharmacological properties.

III.I. Pharmacodynamic properties.

The concentrate is a topically applied enzymatic debriding agent for eschar removal in deep and full thickness partial thickness burn lesions. The mixture of components dissolves the necrotic tissue in a selective way. The exact mechanism of action or the components involved in this effect were not identified yet, knowing only that the main active component is bromelain.

III.II. Pharmacokinetic properties.

Absorption According to bibliography, Cmax is close to 40mcg/ml in humans, Tmax is around 2h. Systemic absorption may depend on both the applied drug dose and other patient-specific factors. *Distribution* In plasma, approximately 50% of bromelain binds to human plasma antiproteinases, alpha2 macroglobulin and alpha1 anti-chemotrypsin. *Elimination* The terminal half-life has an average according to the literature of 11.7h +-3.5h.

IV. Guide to use

Treatment with CPE-B is associated with pain. Therefore, the operator must administer the appropriate analgesic treatment by administering prophylactic analgesics/sedatives before use. A 0.5% chlorhexidine-soaked dressing should be applied for at least 2 hours to moisten the wound and minimize the possibility of infection. To prevent irritation of the surrounding skin, a layer of sterile ointment should be administered to protect these areas. To prevent possible irritation from lacerations or escharotomies, these should be protected with a sterile ointment or paraffin-soaked dressing. The wound should be sprayed with 0.9% saline solution before application. Then the gel and powder should be mixed to obtain the final product (*see Figure 8*). The gel should be applied on the eschar with a thickness of 1.5 to 3 mm. Afterwards, the area should be covered with a sterile occlusive dressing attached to the barrier of the ointment material that we use for the edges of the wound. The wound should be covered with a thick bandage. It should be left for a total of 4 hours and then removed with the help of a sterile instrument (for example a tongue depressor). The wound should be cleaned well. First it will be done with a dry sterile gauze or cloth, and then with a gauze soaked in sterile sodium chloride isotonic solution 0.9%. The area should be cleaned until a pink surface, bloody spots or whitish tissue appears. A dressing soaked in 0.5% chlorhexidine should be applied for at least 2 hours.

Figure 8: Homogeneous Mixture of the Product

Source: Nexobrid ® Educational Material (27)

V. Special warnings and precautions for use.

The concentrate is systematically absorbed in the burned areas. Its use it is not recommended for deep wounds where foreign materials and/or vital structures are or may be exposed, nor should it be used on contaminated wounds with radioactive substances or dangerous substances that may cause unexpected reactions with the drug. It should be used with caution in patients with cardiovascular or pulmonary disease. For facial burns, eyes should be protected by using a vaseline balm as an adhesive barrier. In case of eye exposure, the eyes should be irrigated with plenty of water for at least 15 minutes. Caution should be exercised in patients with coagulation disorders and increased risk of bleeding from various factors such as peptic ulcers and sepsis. Patients should be monitored for signs of coagulation abnormalities. All topical antibacterial medications should be removed before application of the debrider.

Monitoring We will monitor the patient's vital signs, water and electrolyte status, complete blood count, serum albumin and liver enzyme concentrations. We should also monitor patient's body temperature, any signs of inflammatory and infectious processes, signs of worsening as a result of administered analgesia (nausea, risk of sudden vomiting...) as well as antibiotic prophylaxis, signs of allergic reactions, and possible effects on hemostasis. It is not known whether this

concentrate is excreted in breast milk in case of breastfeeding patients. In any case, breast-feeding should be stopped for at least 4 days from the beginning of drug application.

VI. Rules for the use of concomitant treatment.

No interaction studies have been conducted with this drug. It is known to be an inhibitor of cytochrome P450 2C8 (CYP2C8) and P450 2C9 (CYP2C9), a fact that should be taken into account if used in patients treated with CYP2C8 and CYP2C9 substrates, drugs such as amiodarone, chloroquine, paclitaxel, repaglinide, thorasemide, ibuprofen, losartan, warfarin, among others.

Topical antibacterials (argentic sulfadiazine or povidone-iodine) reduce the effectiveness of the drug and can sometimes cause the formation of a pseudo-eschar that prevents debridement.

Bromelain may potentiate the actions of fluorouracil and vincristine, and increased toxicity should be monitored. It may also potentiate the hypotensive effect of ACEi, so patients receiving these drugs should be monitored for blood pressure. It may also increase somnolence caused by some medications (benzodiazepines, barbiturates, narcotics, and antidepressants).

VII. Causes of treatment interruption.

In case of an anaphylactic reaction by bromelain or other components of this drug, it should be removed, the skin surface should be rinsed with water and the patient's vital signs should be stabilized. The drug will not be reapplied, and the patient will become part of the control group, notifying the case through the national notification system.

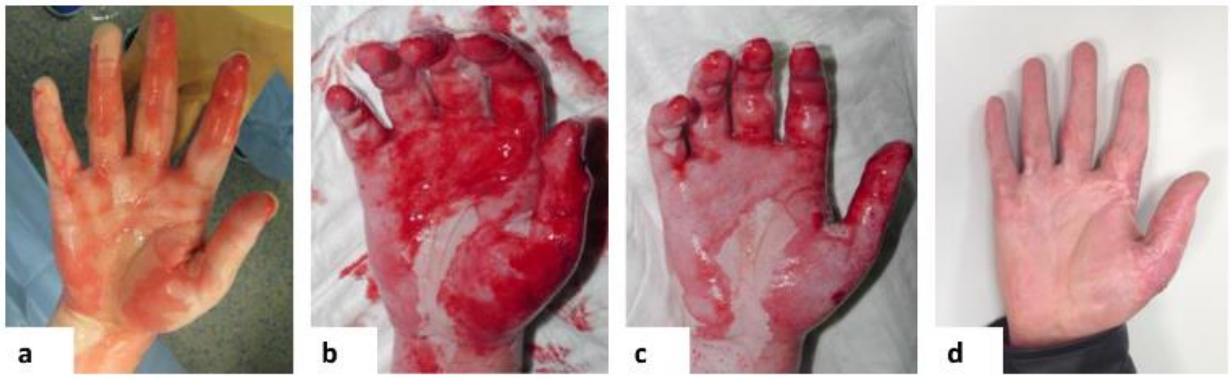

Figure 9: ED application to a mixed partial thickness hand burn

A) Burn on arrival, B) Wound after ED application, C) Wound bed with punctate bleeding of white dermis, D) Aesthetic and functional outcome 3 months after injury. *Source*: A. Schulz, et al Burns (2016) (28)

JUSTIFICATION

The main factor that has increased the survival of large burns in recent years has been the performance of early surgical tangential debridement, consisting of the removal of successive layers of necrotic tissue, and subsequent coverage of the burned surface in one or more surgical times (29).

That is why the current standard of care (SOC) treatment in front of a patient with intermediate, deep and third degree (subdermal) burns is the early surgical debridement by means of an eschar dermatome, achieving a decrease in the rate of infection, sepsis and hospital stay of the patients (30). However, this same technique is also an important source of morbidity associated with two main factors: on one hand, the great loss of blood, both related to the operation itself and the post-surgical period, losing up to 1ml for each cm^2 debrided (31,32); and on the other hand the low selectivity of the technique, which sometimes results in a loss of viable dermis or a remnant of necrotic tissue (33). Due to the excision of healthy tissue, part of the potential for spontaneous epithelialization is lost, associating sometimes difficult healing and poor aesthetic results.

Over the years there have been several studies using different enzymatic debridements, trying to solve the complications that traditional surgical debridement entails, however the results have not been adequate, either because of slow action, lack of specificity on healthy tissues or formation of a granulation tissue that makes reepithelialization impossible, so until today the use of any of them has not been standardized (34).

In recent years there have been several promising studies mentioning the use of a new enzymatic debrider, a proteolytic enzyme concentrate enriched in bromelain, a protein extracted from the stem of *Ananas Comosus*, presenting itself commercially under the name Nexobrid® (MediWound) (28). This product presents a high specificity towards the necrotic tissues, achieving a practically total debridement of the lesion, leaving a viable dermis bed for re-epithelialization. It has been shown in numerous studies that it allows to reduce the hematic loss and the loss of healthy tissue, reducing also the need of the use of grafts, among others.

Its main indication is in thermal burns, since the eschar produced by this type of lesions allows the action of the enzyme. In other types of burns (electrical, chemical) its effectiveness has been much lower, probably due to the characteristics of the eschar, which is usually harder and does not allow the penetration of the product (35).

Rosenberg's study (36), the first multicenter clinical trial evaluating long-term outcomes in patients with deep and full thickness partial thickness burns with 5-30% TBSA, shows that the use of the concentrate of proteolytic enzymes enriched in bromelain (CPE-B) reduces the percentage of wounds that require surgery (24.5% vs. 70%, $p<0.0001$) and the percentage of final grafted area (13.1% vs. 56.7%, $p<0.0001$), also reducing the time from injury to complete debridement (2.2 days vs. 8.7 days, $p<0.0001$).

In a retrospective study that analyzes the economic impact of the treatment of thermal burns there is evidence that the main determinant of the cost of treatment of a large burn is the stay in the Critical Burn Unit (48.7% of the total cost) and the conventional hospitalization (19.4% of the total cost), being the use of CPE-B only 13.9% of the total cost (37). This study is complemented by another more recent one, which shows that the use of the enzymatic debrider decreases the patient's Critical Burn Unit stay (31.4+38.6 days to 20.2+-19.2 days, $p<0.05$) (38). We therefore interpret that the use of CPE-B also theoretically decreases the economic expense involved in the treatment of large burns.

The same study, a retrospective cohort study evaluating large burns of 20-50% TBSA, also showed a reduction in bleeding, decreasing the need for transfusions of red blood cell concentrates (4.7+- 4.4 vs. 0.2+-0.7, $p<0.05$), and a reduction in the need for escharotomies in circular burns (29.1% vs. 9.4%, $p<0.05$) (38). These form part of the factors of morbimortality presented by the current SOC of the severely burned patient, therefore the need arises to know if diminishing these factors will also diminish the mortality rate, a question that the same study raises but, in spite of seeing a tendency to the reduction of the mortality rate, it does not achieve a statistical difference (24.8% in the control group against 15.6% in the enzymatic debridement group, $p=0.19$).

Despite being considered a safe drug in most studies, it is not exempt from adverse events. The most frequently reported adverse reactions are *local pain* and transitional *pyrexia/hyperthermia*. In studies where the treatment regimen includes recommended preventive analgesia, pain was reported in 3.6% of patients treated with the debrider. It was classified as mild, moderate, or severe in 0.9%, 0.9%, and 1.8% of cases, respectively.

Also, pyrexia or hyperthermia was reported in these studies in 19.1% of the patients. In certain clinical studies, wound complications such as deepening or drying out (2.4%) and partial graft failure (2.9%) were reported. Finally, general infections (not related to the wound, such as urinary tract infections, viral infections) and infections of the same wound were also registered (25).

Despite these promising results, the number of studies conducted is insufficient, and most of them are retrospective studies, limited to a very low sample, which does not ensure that the differences are statistically significant and/or free of bias. Furthermore, to date, the Nexobrid® data sheet does not indicate the use of this drug in burns with an extension greater than 15% TBSA, an indication possibly related to an alteration of platelet aggregation and a decrease in various coagulation factors that has been seen in the medical literature after oral bromelain intake (25). Although no such alteration has been demonstrated during the clinical development of the product, the indication continues to limit use to 15% surface area burned per session, recommending at all times coagulation monitorization during the treatment. However, today the TBSA limit has been exceeded with effectiveness and safety rates equivalent to those of smaller surfaces, dividing treatment into different sessions (35,39).

It is for all this that the need arises to perfect the protocols for applying enzymatic debridement with CPE-B and to expand the sample of patients in order to achieve a study with sufficient power to provide more conclusive results and thus achieve the implementation of the use of enzymatic debridement with bromelain in the routine management of large thermally burn patients.

OBJECTIVES

I. Clinical endpoint.

To check if the use of enzymatic debridement with the concentrate of proteolytic enzymes enriched in bromelain in the treatment of large thermal burns is more effective than the traditional technique of tangential surgical debridement, being its action specific towards the necrotic tissue, achieving a complete debridement of the eschar and allowing a spontaneous re-epithelialization from the epithelial reserve present in the debridement bed, reducing the need for surgical intervention and the associated morbidities.

Primary endpoint: Analyze if there is a reduction in the mortality rate of the large burn patient associated with the use of enzymatic debridement with CPE-B compared to the current standard of care, tangential surgical debridement.

II. Secondary endpoints.

- To analyze if there is a reduction in the duration of hospital and Intensive Care Unit (ICU) stay of the patient treated with enzymatic debridement, directly associated with a decrease in the total economic expenditure.

- To analyze whether the number of surgical interventions, the need for grafting and the total grafted surface area are reduced if treated with ED.

- To analyze whether enzymatic debridement has a preventive effect on compartment syndrome and therefore reduces the number of escharotomies performed, especially in the case of circular burns on the limbs.

- To analyze if with the use of CPE-B a spontaneous re-epithelialization is carried out that is not associated with hypertrophic scarring and assess the number of days that such a process entails.

- To analyse whether the need for transfusions and the number of red blood cells decreases in the patient treated with enzymatic debridement.

- To assess the functional and aesthetic outcome of the scars resulting from enzymatic debridement therapy and to analyse whether there is any difference between the outcome of the two techniques.

- To identify the presence of adverse events that the drug may present that have not yet been registered and assess the impact of those side effects that are currently reported. To check if there is a relation between the use of CPE-B and an increase of coagulopathies.

III. Study Hypothesis.

The enzymatic debridement with the concentrate of proteolytic enzymes enriched in bromelain is more effective than the traditional technique of tangential surgical debridement, being sufficiently selective to produce a complete debridement of the necrotic eschar and allowing a spontaneous re-epithelialization, decreasing the sources of morbidity that surgical debridement presents (blood loss, compartment syndrome...), reducing the mortality rate of the large thermal burned patient.

MATERIAL AND METHODS

I. Study Design.

This study is an interventional, prospective, randomized, open-label, controlled, confirmatory clinical trial. An approximate duration of 3 years and 6 months is foreseen, being 2 year and 6 months the necessary one to prepare and coordinate the study, recruit the sample, apply the treatment and assess the immediate result, and 1 year based on the follow-up to assess the functional and aesthetic result (at 3, 6 and 12 months after home discharge).

II. Study Population.

Patients admitted to the Burn Unit of the Vall d'Hebron Hospital with a burned skin surface affectation of more than 15% TBSA or with a surgical indication for debridement.

III. Inclusion Criteria.

The study will include patients a) of any age and sex, b) who present burns by thermal mechanism (scalding, flame or contact), c) whose depth is greater than dermal-intermediate (degree IIb), d) who have signed the informed consent, either the patient himself or the most direct family member in the event that the patient is under sedation or intubation.

IV. Exclusion Criteria.

Will include a) lack of consent by the patient to receive the treatment or to be part of the subsequent follow-up, b) pregnancy or lactation, c) history of allergy or hypersensitivity to pineapple, papaya, bromelain or papain, d) patients with electrical or chemical burns.

The investigator may terminate participation in the study if a patient who at first met the inclusion criteria it developed a new exclusion criteria or it presents one of these conditions which was not previously recognized.

V. Participant Withdrawal.

Participants are free to withdraw from participation in the study at any time. He/she should tell the research team that he/she intends to withdraw.

VI. Sample Selection.

After determining the lesion traits, any patient who meets the inclusion criteria will be enrolled in the study. The depth of the lesion will be determined prior to randomization to minimize bias and will be performed by expert professionals based on standard clinical characteristics (color, capillary filling, skin flexibility, sensitivity, presence of blisters, and presence of thrombosed veins) adding if necessary, the doppler laser technique for a more objective diagnosis. The extension will be determined by the specific table of Lund and Browder. Subsequently, a randomization scheme will be used following a 1:1 treatment allocation ratio between the standard procedure (surgical debridement) and the enzymatic debridement with CPE-B technique.

VII. Randomization.

After recruiting and getting the patient's signed informed consent, a statician expert will create a database with as many ordered codes as patients estimated on the sample size. These codes will be assigned consecutively to the patients, and they will be randomly distributed with a 1:1 proportion into two groups. This will reduce biases of selection, generating randomization with the Statistical Package for the Social Sciences (SPSS).

Afterwards, the investigator will decide which treatment, the standard procedure (surgical debridement) or the enzymatic debridement with CPE-B, corresponds to each group. The patient will be aware of which group he fits.

VIII. Masking techniques.

As this will be an open-label study, the investigators will be aware of which treatment is receiving each patient. In this trial it's difficult to mask the intervention because of obvious reasons, EG will receive a completely different treatment than CG. This is commented on below as a further limitation of the study.

The statistician who whill analyse the results and the physician who will do the follow-up of the patient will not be aware of the group origin of the data.

IX. Sample Size.

The most recent study has been taken into account by assessing the mortality rate in patients with major burns, which approximates a mortality of 24.8% in patients treated with surgical debridement (38).

Thus, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 271 subjects are necessary in the control group and 271 in the experimental group (542 in total) will be required to detect as statistically significant a proportion difference, expected to be of 0.248 in the control group and 0.15 in the experimental group. It has been anticipated a drop-out rate of 5%. The ARCSINUS approach has been used. For the experimental group we will need to add a pilot test, a total of 20 patiens who will serve as staff preparation in the application of the enzymatic debrider, whose results will not be recorded for the statistical analysis of the study.

Therefore, the total sample will amount to a minimum of 562 patients. It will take approximately one year and a half to recruit the sample in its totality, since the epidemiological data mention a total of 550-600 patients admitted in the Vall d'Hebron Burn Unit per year (3).

X. Study Variables.

All measurements will take place at the Vall d'Hebron Hospital. In the *Table 1* we will present a summary of all the included variables in this study.

X.I. Independent variables.

We will consider the following two independent variables: Treatment with DE (experimental group) and treatment with SOC (control group).

X.II. Dependent variables.

In order to answer the marked objectives of the study we will have the following dependent variables:

X. II. I. Variables related to the clinical course.

- Number of surgeries performed on the patient with the objective of debriding the necrotic eschar and covering the injured area. We consider this variable a discrete quantitative variable.

- Time from signing the consent form until the first debridement (either surgical or enzymatic) begins. This continuous quantitative variable will be measured in days, using the necessary decimals to express it more accurately in case it is not a fixed number (for example, if 1 day and 12 hours have passed, the result will be noted as "1.5"). We will be able to obtain this

information from the patient's medical history, calculating the time that has elapsed from admission to the start of treatment.

- Percentage of TBSA surgically debrided. We will approximate the number of this continuous quantitative variable using Lund and Browder's table. In the GC patients it will be the total surface that has had to be debrided, in the EG patients it will only be notified in case the enzymatic debridement fails and surgery is required.

- Percentage of grafted skin surface. We will approximate the number of this continuous quantitative variable using Lund and Browder's table. It will be collected once the patient's healing process has been assured and no further intervention is needed to cover areas of injury. If we consider that the skin graft has failed and the surgical intervention must be repeated, the surface used in both operations will be counted.

- Proportion of completely debrided lesions. We will consider the number of injuries that each patient presents, and we will count from the total how many of them have been completely debrided. This continuous quantitative variable will be subject to the decision of the medical professional who will diagnose the lesion according to whether it is completely debrided or not and will leave a detailed note in the patient's clinical course.

- Time until complete debridement is achieved from the signature of consent. Once the physician has confirmed that the lesion is completely debrided, the days between the patient signing the legal consent and the final diagnosis will be calculated. This continuous quantitative variable will be measured in days, and the absolute number of patients who have achieved complete debridement in all their lesions will also be collected next to it.

- Time to complete re-epithelialization, considering that the re-epithelialization diagnosis must be made by the medical professional. The continuous quantitative variable will be measured in the same way as the previously mentioned variables regarding time. We should also collect the absolute number of lesions that have been re-epithelialized (regardless of whether they have been spontaneous re-epithelialization or by surgical coverage).

- Total time of stay in hospital, collected from the information in the patient's medical history, counting the days from the patient's admission to his or her discharge. We will consider this to be a continuous quantitative variable.

- Time of stay in ICU, continuous quantitative variable that will be counted and expressed in the same way as the previously mentioned.

- Loss of Hb and decrease in hematocrit. To obtain this continuous quantitative variable, a hemogram will be taken of each patient before starting treatment and 24 hours after its

completion. A count of the decrease in Hb and hematocrit will be made, and will be expressed in mmol/L.

- Number of patients who received transfusions. The clinical course of each patient should reflect whether or not he or she has required a blood transfusion. We will count these data to obtain this discrete quantitative variable.

- Number of red blood cell concentrates during debridement and during patient's hospital stay. Based on the above variable, we will make an objective count of how many transfusions each patient has required. We consider that the standard is 260cc/concentrate, and in case of using more or less the number will be adjusted as required (for example, if 390cc have been used, we will note that the number of concentrates has been "1.5"). This is a continuous quantitative variable.

- Number of surgical escharotomies performed. We will make a count according to the information of the clinical course of each patient, and in case of having required a surgical escharotomy it will be noted. This is a discrete quantitative variable.

- Finally, the variable that justifies the main objective of the study is the total mortality rate. We will count the exitus rate from the clinical course of each patient, obtaining a discrete quantitative variable.

X.II.II. Variables related to the scar, which a blinded medical professional will collect 3, 6 and 12 months after hospital discharge.

- MVSS, a scale that can get a score from 0 to 13, which the doctor will assign to each scar the patient has as a result of the burn injury (not those from the autograft, *see below*). It will be considered a discrete quantitative variable. The detailed scale is available in the *Annexe 2*.

- Number of hypertrophic scars, which will be diagnosed by the medical professional based on standard clinical criteria. It is a discrete quantitative variable.

- Number of reconstructive surgeries that the scar has required, which will be counted once the 12 months post hospital discharge have passed, based on the information in the patient's medical history. It is a discrete quantitative variable.

- Physical and mental QoL, a questionnaire that will be given by the medical professional to the patient and will be filled in at the medical consultation. The result will be collected and introduced into the study as a discrete quantitative variable. The full questionnaires are available in the *Annexe 3*.

X.II.III. Variables related to the graft donor scar, which will be collected by a blind medical professional 3, 6 and 12 months after discharge.

- Number of scars produced to cover the burn injury area, which will be counted by the medical professional in his office and collected as a discrete quantitative variable.

- Percentage of scarred TBSA, which will be calculated using Lund and Browder's table and expressed as a continuous quantitative variable.

- MVSS of each scar, the resulting score will be collected as a discrete quantitative variable.

X.III. Covariables.

To reduce the risk of confusion and to ensure equality between both study groups that the randomization process allows, we will collect the following data.

X.III.I. Patient demographic variables.

- Age of each patient. Discrete quantitative variable collected from the patient's medical history. In order to avoid confusing age biases, we will divide the resulting variables into the next subgroups: pediatric population (0-15 years), young-adults (15 years -35 years), adults (35 years-65 years) and elders (>65 years).

- Sex of each patient. Dichotomous qualitative variable to be collected from the patient's medical history.

- Charlson comorbidity index, collected from the personal history contained in the medical record and from the questions that may be asked by the health professional. We will calculate the patient's life expectancy at ten years from his pathological history. This is a discrete quantitative variable. The index can be calculated on-line at the following website: http://www.samiuc.es/indice-de-comorbilidad-de-charlson-cci/

- The patient's smoking habits, which will be asked directly to the patient or his closest relative in case he is sedated or intubated. Smoking habit is suposed to be related to a bad scarring because of a bad blood peripheric flow. We will obtain a dichotomous qualitative variable (tobacco habit yes/no) and a discrete quantitative variable (packages/year).

- Presence of coagulopathies. Since in some studies the possibility of an interaction between bromelain and the presentation of coagulopathies is mentioned, we will collect this quantitative dichotomous variable among the data of the study, to identify, in case the patient

presents some pathology of coagulation, if it is a *de novo* pathology or a pathology that he already presented.

X.III.II. Variables related to burns.

- % TBSA, which will be determined by the specific table of Lund and Browder (*see Annexe 1*) at the time of admission of the patient and will be detailed as a continuous quantitative variable.

- Mechanism of injury, which will be determined by asking the patient or the emergency health care services. The mechanism will be by flame, scald or contact. It is a qualitative polytomical variable.

- Presence of inhalation injury, which will be diagnosed during the transfer to our center or during admission. It will be a dichotomous qualitative variable (whether or not there is an inhalation injury). We will consider this covariate since the presence of inhalation injury is a factor that significantly increases the mortality of the large burn patient.

- Depth of the lesion, determined by an expert professional from the standard clinical characteristics mentioned above (*see chapter Introduction*). This result will be collected at the time of diagnosis prior to randomization. It will be considered a qualitative polytomical variable. We will divide the lesions into:

  - Dermal-surface burn (2A grade)
  - Dermal-intermediate burn
  - Deep Dermal Burn (2B grade)
  - Full thickness burn (3 grade)

- Number of patients with circular burns in limbs, relating this discrete quantitative variable to the increased risk of suffering a compartment syndrome and, therefore, of requiring an escharotomy.

- Number of patients with circular burn in trunk or neck, relating this discrete quantitative variable with the increased risk of suffering a compartment syndrome and/or respiratory failure, thus also increasing the probability of exitus.

- ABSI index, which will serve to ensure similar life expectancy among both groups. This discrete quantitative variable will be calculated by the medical professional by assessing the percentage of SCQ (1 point for every 10%), age (1 point for every 20 years), hot smoke inhalation injuries (1 point if present), sex (1 point if female, 0 if male) and the presence of full thickness burns (1 point if present).

- Revised BAUX index, which has the same objective as the previous covariate, and will be collected in the same way. The continuous quantitative variable is calculated as follows:
*Revised BAUX index: Revised Baux score = Age (years) + STQ (%) + 17*Inhalation(1/0)*

	VARIABLE	MEASURE INSTRUMENT	CATEGORIES OR VALUES
INDEPENDENT VARIABLES	Intervention Therapy	-	Surgical Procedure (SOC)
			Enzymatic Debridement
DEPENDENT VARIABLES	1. Total Mortality Rate	Medical Record	Number of exitus
	2. Nº of total surgeries	Medical Record	Number of surgeries
	3. Time to first debridement	Medical Record	Time expressed in days
	4. % TBSA surgically debrided	Lund/Browder table	% TBSA
	5. % TBSA surgically autografted	Lund/Browder table	% TBSA
	6. Proportion of completely debrided wounds	$\frac{nº\ total\ wounds}{nº\ completely\ debrided\ wounds}$	Proportion
	7. Time to complete debridement	Medical Record	Time expressed in days
	8. Time to re-epithelialization	Medical Record	Time expressed in days
	9. Time of hospital stay	Medical Record	Time expressed in days
	10. Time of ICU stay	Medical Record	Time expressed in days
	11. Loss of Hb/hematocrit	Blood test pre-treatment and 24h post	mmol/L
	12. Nº patients that required transfusions	Medical Record	Nº patients
	13. Blood cell concentrates needed / patient	Medical Record	Nº concentrates (1 concentrate = 260cc)
	14. Nº surgical escharotomies	Medical Record	Nº Escharotomies
	15. MVSS of wound	Assessed by physician	Score (0-13)

	16. Nº of hypertrophic scars	Medical Diagnosis	Nº scars
	17. Nº reconstructive scar surgeries	Medical Record	Nº surgeries
	18. QoL	Ask patient to fill	Physical score
			Mental score
	19. Nº scars resulting from autografting	Medical Diagnosis	Nº scars
	20. %TBSA scarred from autografting	Lund/Browder table	%TBSA
	21. MVSS of donor site wounds	Assessed by physician	Score (0-13)
COVARIABLES	1. Age	Patient's documentation	Age divided if: Pediatric (0-15y), Young Adults (15-35y), Adults (35-65y) and Elders (>65y)
	2. Sex	Patient's documentation	Man
			Woman
	3. Charlson comorbidity index	Medical Record, calculate index on-line	Score
	4. Smoking habits	Asked to patient	Yes / No
			Pack / Year
	5. Coagulopathies	Medical Record	Yes / No
	6. %TBSA	Lund/Browder table	%TBSA
	7. Mechanism of injury	Asked to patient	Flame
			Scald
			Contact
	8. Inhalation injury	Medical Diagnosis	Yes / No
	9. Depth of the burn	Medical Diagnosis	Dermal-Surface (2A grade)
			Dermal-Intermediate
			Deep Dermal (2B grade)

			Full Thickness Burn (3)
	10. Nº patients with circular burn	Medical Diagnosis	Limbs
			Neck / Trunk
	11. ABSI index	Formula	Score
	12. Revised BAUX index	Formula	Score

Table 1: Variables of the study

XI. Statistical Analysis of Data.

All data collected in this trial will be introduced to REDCap (Research Electronic Data Capture available in https://www.project-redcap.org/), a secure wep application available at no cost for not-for-profit institutions. The statistical Analysis will be executed with Statistical Package for the Social Sciences (SPSS Statistics 21.0, IBM®) for Windows®. A confidence interval of 95% will be assumed and the differences will be statistically significant with an error probability of less than 5% ($p<0.05$).

XI.I. Descriptive analysis

Qualitative variables will be measured by means of absolute and relative frequencies in the form of a percentage. For the quantitative variables of normal distribution, the mean and standard deviation will be estimated, and for those of non-normal distribution the median and the first and third quartiles will be estimated.

XI.II. Bivariate inference

For the comparison analysis between the independent variable and the qualitative dependent variables, if $n<60$ we will use Fisher's exact test, for the rest of the variables we will use the x^2 test (chi square).

For the "time to event" variables, the log-rank test will be used to make comparisons between treatments. In addition, the mean and distribution will be estimated by the Kaplan-Meier method. For other continuous and normal variables, we will use the analysis of one factor variance (ANOVA method), while for non-normal continuous variables we will use the Kruskal-Wallis test.

The difference between survival curves of both treatment groups will be analysed with the log-rank test.

All analyses will be stratified by the covariables. When covariates are quantitative, they will be categorized into quartiles.

XI.III. Multivariate analysis

The effectivity of the enzymatic debridement over the total mortality rate will be assessed in a Cox regression, where the dependent variable is the mortality rate and the independent variable is the intervention group, controlling for all the covariables.

The rest of the dependent variables forming part of the secondary objectives will be assessed in logistic regression, where the independent variable will be the intervention group, controlling for all the covariables.

XII. Collection of Data.

All the clinical data related to the burn wound and to the clinical course will be recorded by the professional who is in charge of the patient. The demographic variables will be collected from patient's clinical history archive. There will be an investigator in charge of checking the information collected during the admission, and of validating the data collection, assuring that all the information is correctly recorded.

XIII. Intervention.

Both of the treatments are detailed in section II of the Introduction, Therapeutic Options. *See II.I. Surgical Tangential Debridement and II.II. Enzymatic Debridement with CPE-B.*

STUDY CIRCUIT

I. Initial Care and Diagnosis.

After identifying and rescuing victims, a primary medical assessment should apply the ABCs of resuscitation to ensure a permeable airway and adequate ventilatory and cardiocirculatory function. Subsequently, the patient will undergo a second medical evaluation in which, once the vital signs are considered to be assured, an anamnesis and a rapid physical examination will be carried out in which the depth and extension of the injury will be diagnosed, thus verifying if the patient meets the criteria for transfer to the Vall d'Hebron Burns Unit (*see Annexe 6*). Once any object in contact with the injury has been removed, we can make use of hydrogels that provide cooling to the wound, relieve pain and reduce heat loss during transport, avoiding possible hypothermia. If necessary, we will also administer water resuscitation to the adult following the different existing formulas to calculate the water requirement of the patient. The crystalloid chosen is Ringer-Lactate (2,3,6).

Once the patient has arrived at our Unit, he or she will be monitored, and the wound will be cooled with sterile compresses moistened with physiological serum or with the application of hydrogels. Subsequently, the debridement of the blisters must be done in a sterile environment to correctly visualize the wound bed and make an accurate diagnosis of the depth of the wound.

It is at this point that the practitioner should make use of standard criteria and experience to make an accurate diagnosis. Later, if the criteria for inclusion in the study are met, the patient will be randomly assigned to the control group (CG) or the experimental group (EG) and we will begin the additional cures according to the group in which he or she is.

II. Control Group.

The patient will benefit from the current SOC, based on early surgical debridement and autograft coverage. Cures need to be individualized for each case. Therapeutic decisions related to injury healing will be made by the practitioner depending on the state of the injury and the conditions in which it has occurred. We currently have the following therapeutic options:

Lotions The most commonly used are argentic sulfadiacin (Silvederma®) and nitrofurazone (Furacin®), both lotions with bacteriostatic activity that do not penetrate the eschar. Nitrofurazone, in addition, being hydrosoluble, can be used in very exudative lesions or in contact with blood. The use of these lotions is combined with non-adhesive silicone dressings such as Mepitel® that will prevent the cream from adhering to the wound bed. If the patient presents deep

burns with escar, it will be indicated the use of argentic sulfadiacin + cerium nitrate (Flammazine Cerium®) or povidone iodine (Betadine Gel®), which are creams with the ability to penetrate the eschar and locally control possible infection of the wound. They can also be combined with non-adherent dressings or steroid creams for a better response.

Dressings Apart from Mepitel®, which is a passive dressing that is limited to complement the use of creams, there are also the interactive dressings. These provide a bactericidal activity, through the silver they incorporate, manage exudate, modulate the process of epithelialization and reduce pain. Each dressing will provide different characteristics to the wound healing. The most used are:

-Aquacel Ag®. A hydrofiber dressing containing ionic silver. After its application it will be irrigated with physiological serum. It maintains its activity for 7 days.

-Mepilex Ag®. It consists of an absorbent foam impregnated with ionic silver. It doesn't adhere too much to the wound bed, which allows its extraction for the revision of the wound without causing pain to the patient. It maintains its activity for 7 days.

-Acticoat®. It's a dressing which contains silver in nanocrystalline form. Causes less injury to healthy tissues and presents a slight induction of skin regeneration. If available, it is the first choice for covering infected burns.

In the first 24 hours, in case of circumferential burns, progressive edema can cause vascular constriction and circulatory involvement in the extremities, neck or trunk. If the patient develops, or has a high risk of developing, a compartment syndrome, the indication is to perform an escharotomy. Incisions will be made in the necrotic eschar that should reach the deeper area of the burned wound. The injured extremities must be kept elevated to decrease the edema.

In case the patient presents pain, analgesics will be prescribed on demand. Prophylactic antibiotic therapy is not recommended, it will only be used if the injury is very dirty or affects very deep structures.

The timing of the surgery must be adjusted to the clinical situation of each patient. The surgery must be done in adequate clinical conditions. In the surgical plan, blood losses should be estimated to adjust the blood product reserve. For the use of blood products, the guidelines of recommendations published for polytraumatized and critically burned patients should be followed, which recommend avoiding transfusion in situations of clinical stability and hemoglobin above 8gr/dl, unless active bleeding is expected intraoperatively and in the case of patients with coronary pathology (38).

Necessary monitoring, vascular access, and measures to avoid hypothermia should be programmed. The anesthetic method of choice is usually analgosedation, although we can make use of regional or epidural anesthesia. The technique of tangential surgical debridement will be performed to eliminate the necrotic tissue. A decision will be made as to whether skin autografting can be performed simultaneously with debridement or whether it should be deferred until the patient's situation improves. In the event of loss of substance, reconstruction using a free flap will be considered. The debrided tissue can also be covered with temporary skin substitutes, such as Biobrane®, Supratel® or the use of skin homografts (of a cadaver donor usually).

The gold standard in the large burns grafting is the Mcmillan and Alexander technique (also known as the sandwich technique). Mesh autografts will be placed over the patient's healthy dermis in a very wide location (1:6 or 1:9), which will not cause immune rejection, and 1:3 mesh homografts will be placed over them to facilitate wound closure (29).

In the post-surgery period, it is very important the continuity of care. The most frequent complications are bleeding, hypothermia and hemodynamic alterations derived from the new aggression (2).

The subsequent cures will be based on the combination of the lotions and dressings previously mentioned, until the patient is considered stable and a good healing of the treated wounds is demonstrated, at which time we will be able to discharge him/her from the hospital.

III. Experimental Group.

Once it has been decided that the patient will receive the enzymatic debridement treatment, the first thing to do will be a previous cure. All antibacterial drugs should be removed before the application of the drug, since they can interfere with the activity of the enzyme, reducing its effectiveness. The goal of the cure will be to maintain the moisture of the eschar to allow the enzyme to access the lesion. We will use chlorhexidine 0.5% as a local liquid antiseptic applied in gauze, covering the whole lesion, prolonging the cure for a minimum of 2 hours to achieve the desired effect.

If we foresee that the treatment will have to be deferred for more than 24 hours, we will choose the Mepilex® or Prontosan® dressing as an alternative pre-treatment cure. If deferred >72 hours, we should adequately prepare the wound, removing the superficial layers of eschar mechanically by scalpel and treating the wound with chlorhexidine 0.5% for a minimum of 12 hours.

In case the patient presents a high risk of developing a compartment syndrome, pre-treatment is not necessary, and we will proceed directly to the application of the drug. If the patient presents respiratory failure due to circumferential burn on the trunk, an emergency surgery for escharotomy will be performed, without applying the enzymatic debrider.

Enzymatic debridement causes significant pain during application and removal. The currently recommended technique is sedoanalgesia and locoregional control (in the axilla or neuroaxis) carried out in a critical or intermediate care area. The patient's analgesia should be an interdisciplinary factor and should be maintained during the 4 hours of product application, with one hour under heavy sedation, then residual sedation during product removal. The patient should be monitored. We should assess the patient's pain at all times according to the EVA scale and keep a track of the score in the study notes.

Since it is considered a drug subject to additional monitoring, any suspected adverse reaction registered during the clinical trial because of the use of this product should be reported to AEMPs through the national reporting system. The registration of the event will be done through the electronic form to which the professional will have access at the following link: https://www.notificaRAM.es

The powder and gel should be mixed for 1-2 minutes until a uniform mixture is obtained. The previous cure should be removed, and the area should be irrigated with a sterile isotonic solution of 9mg/ml (0.9%) of sodium chloride. The area around the eschar should be surrounded with an adhesive barrier of sterile paraffin ointment, which will isolate the necrotic area and prevent the drug from spilling and irritating the healthy skin area. The mixture should be applied topically to the burn within 15 minutes, with a thickness of 1.5 to 3 millimeters, applying the drug in the proportion of 5g per 3% TBSA. It will then be covered with a sterile occlusive film dressing that will adhere to the sterile adhesive barrier material. The wound will be covered with a thick, loose and soft dressing fixed with a bandage and left to act for 4h.

After this time the product and the dissolved eschar will be removed with a sterile instrument. The wound will be cleaned with a dry sterile gauze and then with a sterile gauze impregnated in sterile isotonic solution of 9mg/ml (0.9%) of sodium chloride. The area should be rubbed until the appearance of a pink surface with bleeding points or a whitish tissue.

If it is considered that the debridement has not been effective, it is not recommended to apply the drug again unless the reason for the failure has been identified, such as a bad mixture of the product, bad adherence to the necrotic tissue, a leakage of the gel...

Post-debridement treatment will be based on the application of compresses with 0.5% chlorhexidine and an occlusive bandage that should be left on for up to 12 hours to eliminate the enzymes, the gel and the dissolved eschar.

After this time interval, the bandage will be removed and the definitive diagnosis will be made, which will be guided by the color and bleeding patterns of the lesion. If the lesion is uniformly red or pink it will indicate a high probability of spontaneous re-epithelialization. If it is white with red spots, the wound will have a good chance of re-epithelialization. If we see a lesion with a red elongated circle or oval patterns, we will associate it with a further delay in the scarring and skin grafts will be recommended. If we find exposed adipose tissue it will be an indication of skin grafting (*see Table 2, Figure 10*).

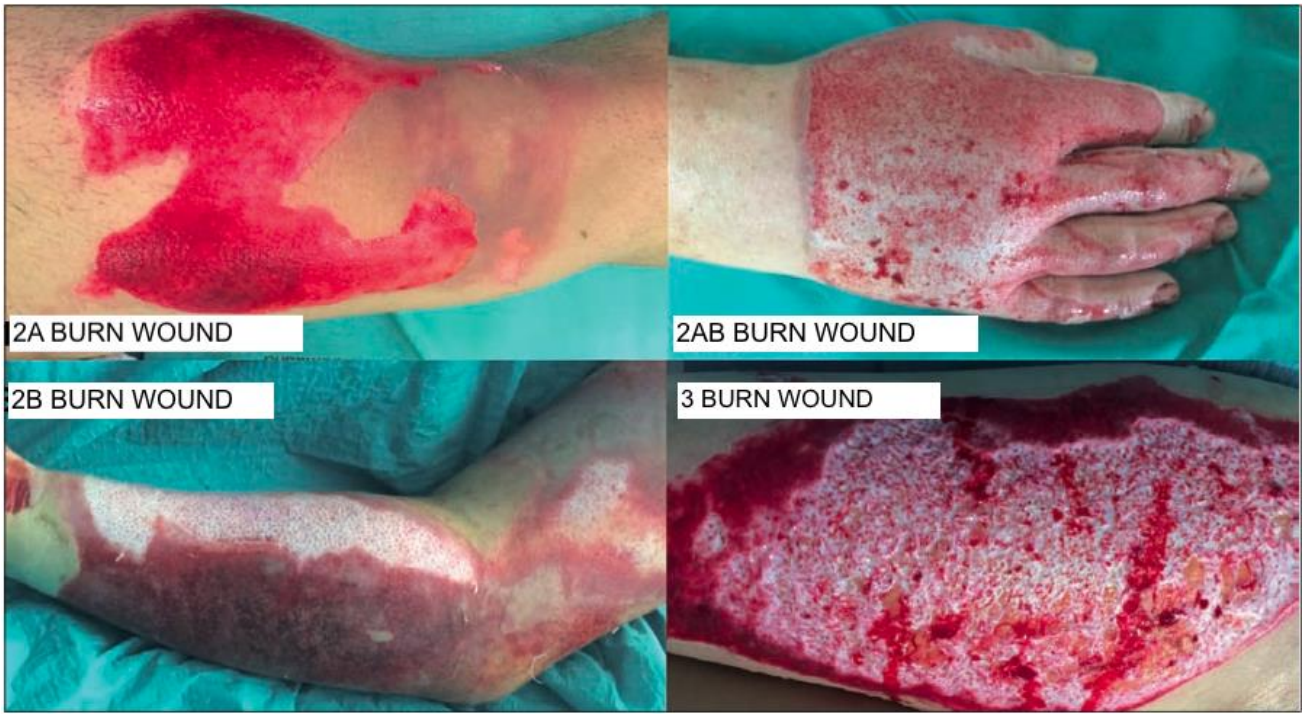

Figure 10: Burns According to the Classification proposed on Table 2

Source: Cirugía Plástica Ibero-Latinoamericana - Vol. 43 - No 2 de 2017 (39)

VISUAL DIAGNOSIS	PROGNOSIS
Intradermal Purple Red 2A Uniformly Red	Probable Epithelialization
2AB White with red spots 2B Intermediate dermal white	Intermediate Probability of Epithelialization
2C Red elongated circle 3 Adipose tissue	Indication of skin grafting

Table 2: Visual Diagnosis and Prognosis post CPE-B application.

Adapted from Cirugía Plástica Ibero-Latinoamericana - Vol.43 - No2 de 2017 (26)

The professional should draw schematically and photograph the color of the bed and the bleeding pattern, an essential step to document the result of the treatment. Subsequently, an individual treatment plan will be drawn up according to the patient's situation.

The use of biosynthetic polylactic dressing (Suprathel®) is recommended in patients where spontaneous re-epithelialization is expected. A silver hydrofiber dressing (Aquacel®) can also be used, which is less expensive. In patients who have a skin grafting indication, hydrocolloids will be applied until the time of surgery. If the burn is exudative, it is also recommended the use of Mepitel® with Nitrofurazone. In the case of facial injuries the use of manuca-honey has proven to be very useful (39).

The drug sometimes produces the appearance of a pseudo-eschar, totally normal, which usually remains attached to the surface for about 14 days and does not hinder spontaneous healing. We can also observe granulation tissue between 14-21 days after enzymatic debridement, which can be avoided by the use of corticoid creams in the post-treatment cure.

If after 21 days there are no signs of re-epithelialization, the skin graft will be considered. In case the surgical intervention is carried out, the patient will be prepared for it. For the choice of the technique, the general recommendations mentioned above in the control group will be followed.

Once the patient is stable, he/she can proceed with the hospital discharge and the referral to the External Care Unit where the dressing change and the lesion evaluation will be performed.

IV. Follow-Up.

Lesion healing can be improved by pressure therapy, silicone, moisturizers, physical therapy or additional surgery. The patient must be well informed of the precautions to be followed to achieve a good aesthetic and functional result. We must also offer the possibility of reconsulting in case of having any doubt or urgency regarding their recovery.

We will make control visits at 3, 6 and 12 months, or sooner in case the patient does not present a good evolution. In each visit a brief analysis should be made regarding the evolution and the state of the patient and a physical exploration of the lesions, both those of the burn and those resulting from the donor area in the autograft. The professional will use the MVSS scale (*see Annexe 2*) to define the result in an objective manner and will photograph the scars.

We expose the study's circuit summary in *Figure 11*.

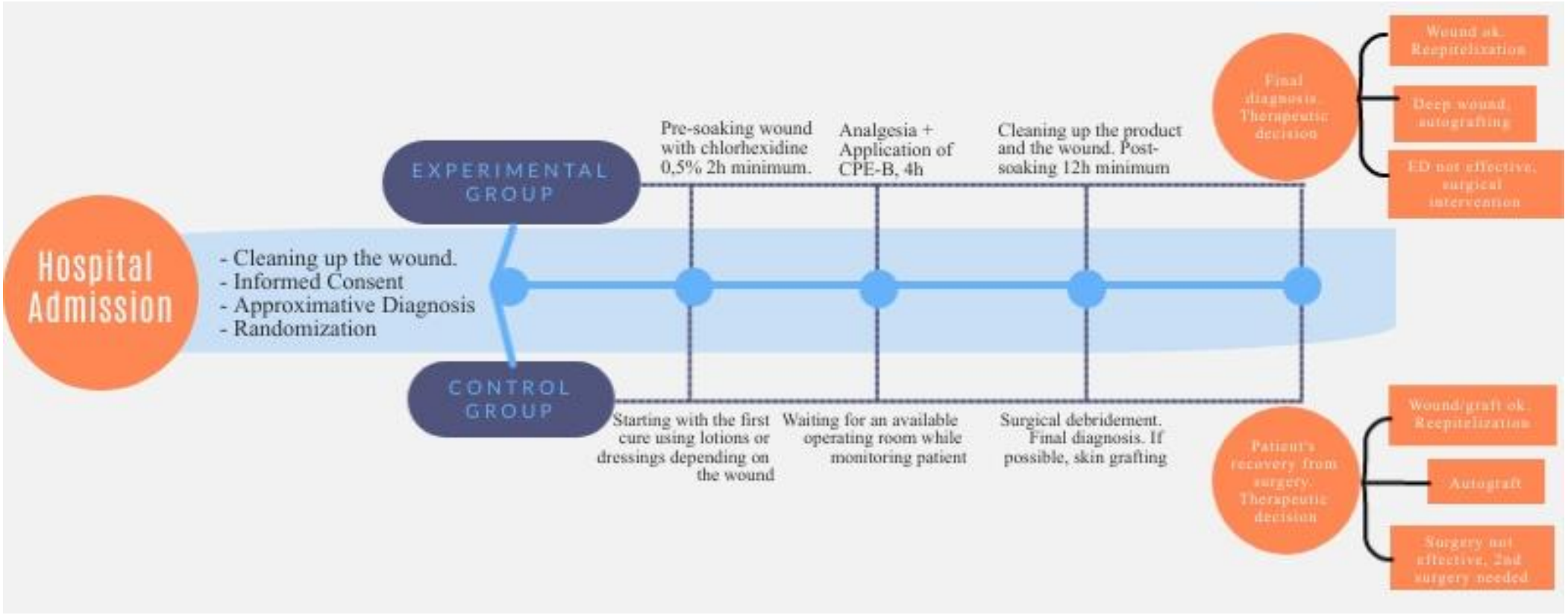

Figure 11: Summary of study's circuit

WORK PLAN AND CHRONOGRAM

I. Work Plan.

The whole study will take approximately 3 years and 6 months. It will be divided in the following phases.

I.I. Phase 0: Study Design and Protocol Validation (4 months)

The main investigator will first do a bibliographic research in databases, then design a detailed study protocol with the definition of the objectives and variables. The project will be evaluated by the Clinical Research Ethics Committee of the Vall d'Hebron University Hospital Research Institute, all suggested changes will be taken into account. Then, the project will applicate for a registry number to the EudraCT (European Union Drug Regulating Authorities Clinical Trials), and we will get the participation acceptance of Vall d'Hebron hospital directive committees. Finally, the study protocol will be presented to AEMPS (Agencia Española del Medicamento y Productos Sanitarios) for the posterior authorizations needed.

I.II. Phase 1: Preparation and Coordination (2 months)

A detailed chronogram will be elabored with all the steps to follow. A meeting involving all the collaborators participating in the study will be made, discusing the design, aims and methods of the clinical trial. This meeting will include Plastic Surgery specialists, Anesthesia specialists, nursing staff, nursing assistants, administrative staff, statistics and every other person collaborating in the study. The Marketing Authorisation Holder (MAH) of the commercial product will ensure that all healthcare professionals involved in this study will receive a specific training and they will be provided with an educational pack, which will contain a summary of product characteristics and patient information leaflet, and a healthcare professional information pack, which is a step-by-step treatment guide.

I.II. Phase 2: Patients Recruitment and Data Collection (2 years and 6 months)

Sample recruitment will take 1 year and 6 months. All information will be explained to the patient and they will be invited to voluntarily participate in the study. If they agree, and if they meet inclusion criteria and do not present any exclusion criteria, they will be enrolled in the study by consecutive sampling and they will be randomly assigned to one of the two therapeutic groups. Along with the patient's medical history and with information we will ask at admission, we will collect all demographic variables.

Afterwards one group of patients will receive the standard procedure (control group) and the other one will receive CPE-B treatment (experimental group). All data necessary for the study, such as wound characteristics and clinical course related variables, will be collected during patient's hospitalization.

It is important to have several committee meetings among study participants to jointly assess therapeutic decisions on an individual basis.

All patients will be followed up for 12 months, and a blinded physician will assess the functional and aesthetic outcome of the scars, and also the mental and physical state of the patient.

I.III. Phase 3: Data Analysis and Interpretation (4 months)

A blinded statician will analyse the whole data collected once the field work is ended and will present the results to the research team. Lastly, a final meeting will be held to discuss the results obtained and make a joint conclusion of the study.

I.IV. Phase 4: Results Publication (2 months)

The main investigator will incorporate the results obtained into a final article that will summarize the study conducted. The article will be presented in national and international congresses of scientific popularization.

II. Chronogram.

YEAR	2020	2021						2022		2023		
MONTH	NOV - DEC	JAN - FEB	MAR	APR	MAY - DEC	JAN - NOV	DEC	JAN - NOV	DEC	JAN - MAR	APR	MAY
PHASE 0: STUDY DESIGN AND PROTOCOL VALIDATION												
Protocol elaboration												
Validation												
PHASE 1: PREPARATION AND COORDINATION												
Organization meetings												
Specific Training												
PHASE 2: PATIENTS RECRUITMENT AND DATA COLLECTION												
Patient recruitment												
Intervention												
Data collection												
Follow-up												
PHASE 3: DATA ANALYSIS AND INTERPRETATION												
Data analysis												
Interpretation												
PHASE 4: RESULTS PUBLICATION												
Final document elaboration												
Dissemination												

Table 3: Chronogram

ETHICAL AND LEGAL CONSIDERATIONS

I. General Ethical Considerations of Research.

The project will be evaluated by the Clinical Research Ethics Committee of the Vall d'Hebron University Hospital Research Institute and will not be applied unless it has its approval. The clinical trial has been proposed according the *Principles of Biomedical Ethics of Beauchamp and Childress* (incorporated in the Spanish law Ley 41/2002), and will be conducted in accordance with the principles of human experimentation of the *World Medical Association Declaration of Helsinki* of 1964 (last revision October 2013).

The balance of the individual benefits and risks to which the subjects are exposed is considered to be justified with the expected impact at the level of the scientific society. The current data on efficacy and safety of enzymatic debridement suggest that it is a safe drug and will not pose a greater risk than the current standard treatment of major burns. Both treatments showed effectiveness compared with expectant management, and though CPE-B treatment seemed to present more advantages than the standard technique, it can't be treated like an ethical problem because nowadays the first treatment line is still surgical procedure.

Since this is a trial with drug interventions, EudraCT database and AEMPS must give its authorization too.

It is not a risk-free therapeutic alternative, but we consider that the need to carry out a scientifically and methodologically rigorous experiment justifies the events to which the subjects will be exposed. It will follow the Spanish law "Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con Medicamentos y el Registro Español de Estudios Clínicos." and the "Ley 14/2007, de 3 de Julio, de Investigación Biomédica" where the basic requirements of studies in which a human being undergoes an invasive procedure are being specified. In order to mantain the patient's safety, as this study includes invasive techniques, an insurance policy will be contracted.

The exclusion criteria follow the principles of justice and beneficence, since those established ensure patient safety, avoiding for example a possible anaphylactic reaction. The healthcare personnel that will participate in the study will be correctly accredited and trained for their corresponding responsibilities, so the principle of non-maleficence is assured.

All data will be managed anonymously, using an identification number instead of the patient's name, in order to respect the confidentiality of the database and of the patient, according to the

Spanish Law "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales".

The research team is committed to publish the results with transparency and clarity, and regardless of the results of the study, all data will be published, without excluding unfavorable data in the field of the study. Researchers should not declare any conflict of interest.

II. Information to subjects.

Participants will be given an informative document on the procedure to be performed (*see Annexe 4*), were all risks, benefits and alternatives to the procedure will be detailed using the best updated data, to ensure they understand the study before they sign the informed consent (*see Annexe 5*). In case the patient is under sedation or intubation, the informative documents and the IC will be given to the most direct family member.

The subjects will be informed about the confidentiality of the information and data of their identity and this information can only be reviewed by authorized personnel during the check-up and quality control visits or in case of an unexpected serious adverse reaction. This study will follow the principle of autonomy and the "Ley Orgánica 41/2002, de 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica" will be respected.

FEASIBILITY

The study will take place exclusively at Vall d'Hebron Burn Unit, which is the reference unit for the treatment of critical burn patients in Catalonia, Andorra and the Balearic Islands. It has recently obtained the EBA accreditation (European Burn Association), a recognition of the high quality of care of burn patients. The hospital offers a multidisciplinary team formed by specialists in psychiatry, nursing, intensive care medicine, anesthesiology, pediatrics, plastic surgery, among others. In addition, it has innovative technologies and facilities suitable for carrying out this clinical trial.

The hospital will provide the study with the necessary tools, such as staff recruitment, availability of surgical rooms and material needed for the operations, availability of beds in the Intensive Care Unit and in the hospital, and availability of a treatment area for those patients who have been discharged from the hospital and continue with the follow-up. The electronic devices for the counting of the data and the elaboration of the statistical analysis will also be provided by the same hospital.

The unit performs about 500 operations per year, so one and a half years will be enough to recruit the entire sample.

STUDY LIMITATIONS AND STRENGTHS

One of the problems presented by this study is the great variety of factors involved in the dependent variable "mortality". It is difficult to reach a clear association between a single independent variable and an increase or reduction in the mortality rate. To reduce the risk of confusion, we introduced among the covariables the Charlson comorbidity index, the ABSI index and the revised BAUX index, values that represent the risk of mortality presented by the patient. If the mean of these values is similar between both groups, we can make a more accurate association thanks to the process of randomization. In case of having very different results between both groups we can make a stratification process of the individuals in subgroups with similar mortality risk in order to reduce the factors of confusion.

On the other hand, another conflict that arises is the fact that we do not have an objective diagnostic tool to measure the depth of the lesions, the need for graft coverage and whether the debridement is complete or not. These factors are purely subjective and will be carried out by the expert professional according to his/her own criteria and the standard clinical characteristics mentioned above. This process can lead to procedural bias, so to reduce it as much as possible we implemented the following standards in the study design:

I. That the diagnosis of the depth of the lesion will be carried out before the process of randomization of the patients.

II. That the therapeutic decision regarding surgical reintervention, the need for graft coverage and the diagnosis of complete eschar debridement will be discussed individually for each patient among the group of medical professionals participating in the study and a mutual agreement will be reached based on standard clinical criteria.

III. That the follow-up of the patients and the evaluation of the scars will be carried out by an assessor masked to the original treatment assignment.

To avoid possible membership bias, we will stratificate the results into the next subgroups: pediatric population (0-15 years), young-adults (15 years -35 years), adults (35 years-65 years) and elders (>65 years), since the physiological characteristics of this patient are very different between them, and the mortality risk is different because of associated pathologies.

We must also take into account a possible bias due to the effect of the volunteer, since there have been several studies that have proven that the professional in charge of performing the surgical debridement technique, knowing that he or she is part of this study, usually dedicates more time and attention to correctly debride the eschar, being less aggressive surgically and obtaining better results than under normal conditions (36).

Finally, we must mention the great limitation that is the required budget of this study. Acquiring a medicament that has recently been marketed is highly expensive and requires a very high final price. We also need to treat a large number of patients to achieve a statistically significant result.

In addition, the health care costs involved in treating a critical burn are very expensive nowadays. The articles place an average value of 88,218 € per patient in the most economically developed countries. The main component that increases the cost of this procedure has turned out to be the hospitalization in an ICU and hospitalization, reaching 82% of the total cost in a systematic review of Hop et al. (40).

That is why, thanks to the results obtained in previous studies, we know that the use of CPE-B reduces the stay in ICU and the general hospitalization of the patient, therefore it also reduces the total cost of the treatment of the critical burn. Mendez et al. places the average cost per patient at 20,843 € in cases of treatment with enzymatic debridement (41).

This is why we assume that, despite requiring a very high initial investment, this investment is justified with the possible results that we will obtain, which will potentially reduce in the future the average total cost of handling the burned patient.

BUDGET

I. Staff.

The hospital will provide the expert staff already hired in the burn unit to carry out the admission, the cures, the therapeutic strategies and the follow-up of the patient, without any additional cost.

A statistical professional should be sub-contracted to analyze the results of the study. A total of 40 hours is foreseen, which will be paid 25 €/hour. It will cost a total of 1.000 €.

It will also be necessary to hire a clinical researcher to monitor and control the data collection and to coordinate the medical team and patients in the participation in the study. It will be necessary 1 hour per week, a total of 157 hours, paid 25 € per hour, with a final cost of 3.925 €.

II. Material.

We will consider the additional costs of enzymatic debridement, and not the costs involved in the treatment and routine follow-up of burn treatment (surgical interventions, grafts, cures, creams and dressings used), nor will we consider stays in the ICU or total hospitalization, as these are services offered in the standard treatment of a burn patient.

The necessary materials will be:

- Nexobrid (2g), the enzymatic debriding gel that we will use to debride the necrotic eschar. The average cost according to the latest published articles is 3,000 € per patient (41,42).

- Locoregional or plexus anesthesia for the performance of the debridement, which amounts to approximately 212 € per patient.

We will treat 291 patients with the CPE-B treatment, needing 3.212€ per patient, it will cost 935.000 €.

III. Insurance.

Since the study is based on the performance of invasive procedures, it will be necessary to hire an insurance, with an approximate cost of 40,000 €.

IV. Publication and dissemination.

Once the study has been completed and the article with the final results has been written, the cost of publishing an Open Access article is 1,800 €.

For the principal investigator to present the study at a national congress, 500 € will be required for registration and 200 € for travel, accommodation and meals.

To present it to an international congress, 800 € will be needed for registration and approximately 500 € for travel, accommodation and meals.

A total of 3,800 € will be invested in the publication and dissemination of this study.

A budget summary is presented in *Table 4*, see below.

	Concept	Amount	Cost	Subtotal
Staff	Statistical Professional	40 hours	25 € / hour	1.000 €
	Clinical Researcher	157 hours	25 € / hour	3.925 €
Material	Nexobrid®	291 patients	3.000 €	873.000 €
	Anesthesia	291 patients	212 €	61.692 €
Insurance	Lability Insurance	1	40.000 €	40.000 €
Publication and Dissemination	Publishing Cost	1	1.800 €	1.800 €
	National Congress	1	700 €	700 €
	International Congress	1	1.300 €	1.300 €
			TOTAL	**983.417 €**

Table 4: Budget Summary

CLINICAL AND HEALTH CARE IMPACT

Currently, the use of tangential debridement of necrotic eschar is an effective method, but one that carries many associated morbidities. The use of enzymatic debridement is a technique that has been practiced for a few years in clinical practice without any specific guidelines, with limitations on its use due to the small number of studies existing on the subject, without forming part of any protocol or clinical practice guidelines in the management of the burn patient.
The studies that exist today on the use of CPE-B are limited, among them many are retrospective, with an insufficient sample to establish any statistical relationship, or they set out objectives that are dispersed among them, without ever unifying all the questions that have been raised so far in a single interventional study. It is for these reasons that this study promises to have a great impact on health care, above all in the field of reconstructive surgery.

If the hypothesis mentioned at the beginning of the study is proven, we would be in front of a minimally invasive procedure that would reduce the mortality rate of a patient as complex as the critical burned patient. Furthermore, it would also mean a decrease in the number of surgical interventions, reduced hospitalization, faster and more effective treatment and greater patient satisfaction. All this would mean a radical change in the way we approach the treatment of large burns, implementing the use of CPE-B as first-line treatment in these cases.
Likewise, by managing to reduce all the previously mentioned factors, the total cost of treatment of these patients would also be significantly reduced, which would have a very positive impact on the national health system.

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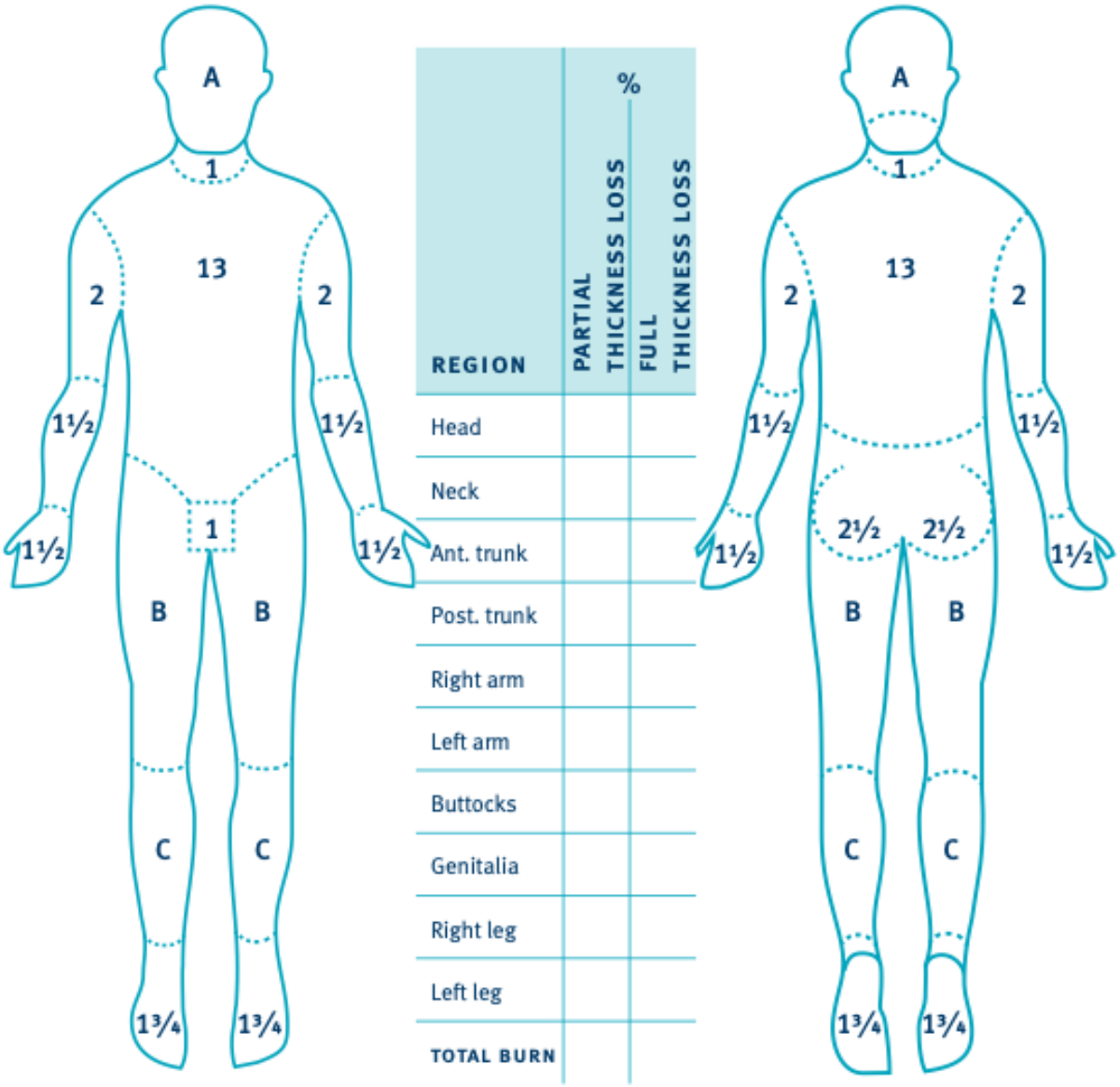
ANNEXE I. LUND AND BROWDER CHART



REGION	% PARTIAL THICKNESS LOSS	% FULL THICKNESS LOSS
Head		
Neck		
Ant. trunk		
Post. trunk		
Right arm		
Left arm		
Buttocks		
Genitalia		
Right leg		
Left leg		
TOTAL BURN		

AREA	AGE 0	1	5	10	15	ADULT
A = ½ of head	9 ½	8 ½	6 ½	5 ½	4 ½	3 ½
B = ½ of one thigh	2 ¾	3 ¼	4	4 ½	4 ½	4 ¾
C = ½ of one lower leg	2 ½	2 ½	2 ¾	3	3 ¼	3 ½

Figure 12: Lund and Browder chart

Source: "*Hettiaratchy S, Papini R. Initial management of a major burn: II – assessment and resuscitation.*" (43)

ANNEXE II. MODIFIED VANCOUVER SCAR SCALE

This scale was extracted and adapted from the "V. Finlay, et al., Modified Vancouver Scar Scale score is linked with quality of life after burn, Burns (2016)" (44)

Scar Characteristic		Score
Pliability	NORMAL	0
	SUPPLE	1
	YIELDING	2
	FIRM	3
	BANDING	4
	CONTRACTURE	5
Pigmentation	NORMAL	0
	HYPO-PIGMENTATION	1
	MIXED PIGMENTATION	2
	HYPERPIGMENTATION	3
Vascularity	NORMAL	0
	PINK	1
	RED	2
	PURPLE	3
Height	Normal / Flat	0
	>0 to 1mm	1
	>1 to 2 mm	2
	>2 to 4 mm	3
	>4 mm	4

Table 5: Modified Vancouver Scar Scale

TOTAL SCORE : 13

ANNEXE III. QUALITY OF LIFE QUESTIONNAIRE

This survey will be handed to the patient in order to be filled. It's the Spanish Standard SF-36 Health Study, adapted from "Versión española de SF-36v2TM Health Survey © 1996, 2000 adaptada por J. Alonso y cols 2003." (45) *This document will also be available in Catalan.*

CUESTIONARIO "SF-36" SOBRE EL ESTADO DE SALUD

INSTRUCCIONES: Las preguntas que siguen se refieren a lo que usted piensa sobre su salud. Sus respuestas permitirán saber cómo se encuentra usted y hasta qué punto es capaz de hacer sus actividades habituales.
Conteste cada pregunta tal como se indica. Si no está seguro/a de cómo responder a una pregunta, por favor conteste lo que le parezca más cierto.

1. En general, usted diría que su salud es: (marque un solo número)

Excelente	1
Muy buena	2
Buena	3
Regular	4
Mala	5

2. ¿Cómo diría usted que es su salud actual, comparada con la de hace un año? (marque un solo número)

Mucho mejor ahora que hace un año	1
Algo mejor ahora que hace un año	2
Más o menos igual que hace un año	3
Algo peor ahora que hace un año	4
Mucho peor ahora que hace un año	5

3. Las siguientes preguntas se refieren a actividades o cosas que usted podría hacer en un día normal. Su salud actual, ¿le limita para hacer esas actividades o cosas? Si es así, ¿cuánto?

ACTIVIDADES	**Sí, me limita mucho**	**Sí, me limita un poco**	**No, no me limita nada**
a. **Esfuerzos intensos**, tales como correr, levantar objetos pesados, o participar en deportes agotadores	1	2	3
b. **Esfuerzos moderados**, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de l hora	1	2	3
c. Coger o llevar la bolsa de la compra	1	2	3
d. Subir **varios** pisos por la escalera	1	2	3
e. Subir **un solo** piso por la escalera	1	2	3
f. Agacharse, arrodillarse o ponerse en cuclillas	1	2	3
g. Caminar **un kilómetro o más**	1	2	3
h. Caminar **varias manzanas** (varios centenares de metros)	1	2	3
i. Caminar **una sola manzana** (unos 100 metros)	1	2	3
j. Bañarse o vestirse por sí mismo	1	2	3

4. Durante las 4 últimas semanas, ¿ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa su salud física?

	SÍ	**NO**
a. ¿Tuvo que **reducir el tiempo** dedicado al trabajo o a sus actividades cotidianas?	1	2
b. ¿**Hizo menos** de lo que hubiera querido hacer?	1	2
c. ¿Tuvo que **dejar de hacer algunas tareas** en su trabajo o en sus actividades	1	2

cotidianas?		
d. ¿Tuvo **dificultad** para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal)?	1	2

5. Durante las 4 últimas semanas, ¿ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de algún problema emocional (como estar triste, deprimido, o nervioso)? (marque un solo número por cada pregunta)

	SÍ	**NO**
a. ¿Tuvo que **reducir el tiempo** dedicado al trabajo o a sus actividades cotidianas, **por algún problema emocional**?	1	2
b. ¿**Hizo menos** de lo que hubiera querido hacer, **por algún problema emocional**?	1	2
c. ¿No hizo su trabajo o sus actividades cotidianas tan **cuidadosamente** como de costumbre, **por algún problema emocional**?	1	2

6. Durante las 4 últimas semanas, ¿hasta qué punto su salud física o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, los amigos, los vecinos u otras personas? (marque un solo número)

Nada 1
Un poco 2
Regular 3
Bastante 4
Mucho 5

7. ¿Tuvo dolor en alguna parte del cuerpo durante las 4 últimas semanas? (marque un solo número)

No, ninguno 1
Sí, muy poco 2
Sí, un poco 3
Sí, moderado 4
Sí, mucho 5
Sí, muchísimo 6

8. Durante las 4 últimas semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)? (marque un solo número)

Nada 1
Un poco 2
Regular 3
Bastante 4
Mucho 5

9. Las preguntas que siguen se refieren a cómo se ha sentido y cómo le han ido las cosas durante las 4 últimas semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted. Durante las últimas 4 semanas ¿cuánto tiempo... (marque un solo número por cada pregunta)

	Siempre	**Casi siempre**	**Muchas veces**	**Algunas veces**	**Sólo alguna vez**	**Nunca**
a. se sintió lleno de vitalidad?	1	2	3	4	5	6
b. estuvo muy nervioso?	1	2	3	4	5	6
c. se sintió tan baja de moral que nada podía animarle?	1	2	3	4	5	6
d. se sintió calmado y tranquilo?	1	2	3	4	5	6
e. tuvo mucha energía?	1	2	3	4	5	6
f. se sintió desanimado y triste?	1	2	3	4	5	6
g. se sintió agotado?	1	2	3	4	5	6
h. se sintió feliz?	1	2	3	4	5	6
i. se sintió cansado?	1	2	3	4	5	6

10. Durante las 4 últimas semanas, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos o familiares)? (marque un solo número)

Siempre 1
Casi siempre 2
Algunas veces 3
Sólo alguna vez 4
Nunca 5

11. Por favor, diga si le parece CIERTA o FALSA cada una de las siguientes frases: (marque un solo número por cada pregunta)

	Totalmente cierta	**Bastante cierta**	**No lo sé**	**Bastante falsa**	**Totalmente falsa**
a. Creo que me pongo enfermo más fácilmente que otras	1	2	3	4	5
b. Estoy tan sano como cualquiera	1	2	3	4	5
c. Creo que mi salud va a empeorar	1	2	3	4	5
d. Mi salud es excelente	1	2	3	4	5

Gracias por contestar a estas preguntas

ANNEXE IV. INFORMATIVE DOCUMENT FOR PATIENTS

This document will also be available in Catalan.

HOJA DE INFORMACIÓN AL PACIENTE

Título del estudio: Enzymatic debridement with proteolytic enzymes enriched in bromelain vs. surgical debridement for burn wound management.

Nombre del investigador: _____

Centro hospitalario: Hospital Universitario Vall d'Hebron

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación que lleva a cabo la Unidad de Quemados del Hospital Vall d'Hebron de Barcelona, al que se le invita a participar. El estudio ha recibido la aprobación del Comité Ético de Investigación Clínica del Institut de Recerca Hospital Universitari Vall d'Hebron.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea detenidamente esta hoja informativa que contiene la información detallada sobre los procesos de este estudio.

Podrá consultar cualquier duda que tenga con el personal que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Su participación en este estudio es totalmente voluntaria, y puede decidir no participar o cambiar su decisión en cualquier momento del transcurso de este estudio, retirando su consentimiento y notificándolo al personal médico adiente. Esta acción no tendrá ninguna repercusión en su relación con el personal sanitario ni supondrá un perjuicio en su atención sanitaria.

DESCRIPCIÓN DEL ESTUDIO

Este estudio se centra en el tratamiento de las quemaduras extensas.

En el proceso de la quemadura se encuentra una capa superficial de la piel que se ve afectada y supone una barrera para el tejido que se encuentra debajo. En esta capa de tejido se suelen acumular bacterias, colonizando la piel, pudiendo provocar una infección sistémica en el peor de

los casos. Además, no permite que el tejido sano pueda cicatrizar, entre otros factores perjudiciales. Es por esto por lo que la capa de piel que se haya afectado debe retirarse cuanto antes. La técnica estándar para retirar este tejido, llamado escara necrótica, es mediante el **desbridamiento quirúrgico**.

Es una técnica que ha aumentado en los últimos años notablemente la supervivencia de los pacientes que presentan quemaduras extensas. Se basa en la retirada con bisturí de la escara necrótica, en el quirófano y bajo anestesia general. En caso de que el estado general del paciente lo permita, en la misma intervención quirúrgica se realiza una cobertura de las lesiones por quemadura, ya sea con tejido de donante o con su propia piel extraída de otras zonas sanas.

En los últimos años se ha desarrollado una técnica menos invasiva, llamada **desbridamiento enzimático**, que se basa en la aplicación de un gel encima de la herida que ahora presenta, cubrirla durante 4 horas, y después retirar el producto. Durante este tiempo el gel desbridará la escara necrótica sin necesidad de intervenir quirúrgicamente.

Este estudio pretende comparar ambas técnicas de desbridamiento de la escara necrótica. Tiene como objetivo comprobar si con la nueva técnica los resultados son más eficientes, si presenta menos complicaciones, si reduce los días de hospitalización, entre otros. Así, esperamos que con la realización de este estudio se pueda incorporar el uso del desbridamiento enzimático como primera línea en el tratamiento de quemaduras extensas.

Incorporará un total de 562 pacientes con el diagnóstico de grandes quemados que sean trasladados a la Unidad de Quemados del Hospital Vall d'Hebron. Serán aleatoriamente separados en dos grupos, de los cuales el primer grupo se someterá a la técnica tradicional quirúrgica, y el segundo grupo recibirá el nuevo fármaco en investigación. Ambos grupos serán estrechamente vigilados y monitorizados, y la mejor atención sanitaria se les será ofrecida.

PROCEDIMIENTOS DEL ESTUDIO

En este estudio dividiremos a los pacientes en dos grupos de forma aleatoria. Si usted accede, deberá firmar una hoja de consentimiento que el profesional médico le ofrecerá. En ese momento entrará en el estudio y se le asignará de manera aleatoria uno de los dos grupos terapéuticos. Usted sabrá en todo momento en qué grupo se encuentra y qué tratamiento recibirá. Si forma parte del *Primer Grupo*, un equipo de enfermería se dedicará a hacer las curas que su herida necesite. Se aplicarán cremas y apósitos para proteger y preparar la herida para la siguiente intervención. Cuando las instalaciones del servicio lo permitan será usted trasladado/a a quirófano. Ahí, un equipo de anestesia le aplicarán los medicamentos necesarios para anestesiarle/a. Durante

la intervención quirúrgica, que suele demorarse unas 2 horas dependiendo de la complejidad de la lesión, los cirujanos plásticos retirarán la escara necrótica con un bisturí hasta llegar al tejido sano. Si usted se encuentra en un buen estado general, se llevará a cabo una técnica llamada injerto cutáneo. Los cirujanos usaran piel de donante, o piel suya propia para cubrir las zonas de lesión que la quemadura ha dejado. En caso de usar piel suya, una herramienta llamada dermatomo se hará servir, que cortará una fina lámina de piel sana y se aplicará sobre la herida inicial. El lugar del que se haya retirado la lámina de piel, al ser una cicatriz superficial, suele tener buenos resultados estéticos.
Si su estado general no es el adecuado para esta intervención, después de retirar la escara necrótica usted volverá a la unidad en la que se encuentre para cubrir las heridas con diferentes apósitos, hasta que se pueda realizar la cobertura quirúrgica.

Si forma parte del Segundo Grupo, un equipo de enfermería le tapará con una solución de Clorhexidina 0,5% y unas compresas las heridas que presente. Después de aproximadamente 2 horas un especialista anestesiólogo le administrará un tipo de anestesia u otro según la localización y la extensión de su quemadura. Todo esto será realizado en la misma cama donde se encuentre. Una vez empiece a hacer efecto la anestesia, se le aplicará el gel en estudio por toda la superficie de la herida y posteriormente se tapará con un vendaje. Despues de 4 horas se retirará y se limpiará el gel y los restos de escara necrótica de la herida con instrumentos estériles y gasas. Este proceso puede ser doloroso, pero si la anestesia está bien administrada usted no debería sentir más que molestias. Posteriormente se le tapará la herida con compresas remojadas en clorhexidina y se le dejará descansar. Una vez haya transcurrido todo, un profesional médico acudirá a observar la herida. En ese momento, según el aspecto de la lesión, el médico decidirá si el tejido cicatrizará solo, si hay que intervenir quirúrgicamente para ejercer una cobertura, o si debemos dejar pasar unos días con actitud expectante. En caso de que haya probabilidades de que el tejido cicatrice solo, se le pondrán apósitos en las heridas que faciliten la cicatrización. En caso de necesitar intervención quirúrgica para cobertura, se le preparará para la intervención y seguirá los mismos pasos que los participantes del Primer Grupo. Cuando usted se encuentre estable podrá solicitar el alta hospitalaria y hacer el seguimiento de sus heridas en nuestra Unidad de Curas.

En todo momento estará monitorizado/a y habrá personal sanitario a su acceso. Se le realizarán analíticas de sangre y se le administrará analgesia en caso de que usted lo vea necesario.

Una vez haya obtenido el alta hospitalaria, se le solicitará acudir a las visitas programadas con su médico. Se le hará un seguimiento a los 3, 6 y 12 meses, en el que un doctor valorará sus cicatrices y se le entregará un cuestionario sobre calidad de vida que deberá rellenar.

BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Los datos que se recogerán de este estudio pretenden confirmar nuestras hipótesis y proporcionar suficiente información para validar el uso del nuevo fármaco e incorporarlo en el protocolo de tratamiento como tratamiento de primera línea. Si esto sucede, estaremos delante de un tratamiento menos invasivo que ofrecerá muchos beneficios a los pacientes gran quemados que serán trasladados a nuestra unidad de aquí en adelante.

Aún y así, ambas técnicas utilizadas presentan sus riesgos. Esta intervención quirúrgica, como cualquier operación, presenta ciertos riesgos como pueden ser la hemorragia, sepsis, resultados incompletos, necesidad de reintervención quirúrgica, fallo de la cobertura, resultados poco estéticos, entre otros. El uso del gel desbridante puede también presentar ciertos eventos adversos. Los estudios describen presencia de dolor, aumento de la temperatura corporal, infecciones no asociadas a la herida, empeoramiento de la lesión inicial, alteración de la coagulación, como también resultados finales poco estéticos o fallada del tratamiento, entre otros. Al ser un fármaco en seguimiento adicional, cualquier evento adverso no mencionado en este documento será notificado a la Agencia Española de Medicamentos. Usted estará en todo momento vigilado/a para identificar la aparición de cualquier posible evento secundario que no se haya descrito y poder actuar rápidamente en caso de urgencia.
El fármaco está compuesto de bromelaína, una proteína extraída del tallo de la piña. Si usted presenta alergia a la bromelaína, a la piña, papaya o papaína, debe notificarlo a su médico. Si durante el curso terapéutico demuestra una reacción alergica a cualquiera de estos componentes, el tratamiento será detenido y su salud será priorizada.

Si desea conocer los resultados de la investigación, adquiridos gracias a su colaboración, podrá ponerse en contacto con el equipo investigador o con los responsables del proyecto y la información se le será proporcionada.

CONFIDENCIALIDAD

Todos los datos recogidos serán estrictamente confidenciales. El investigador se compromete al cumplimiento de la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales, en todos los datos referentes al tratamiento, la comunicación y la cesión de información. Los datos que se recogerán serán almacenados mediante un código de identificación, sin existir en ningún momento forma de identificarle personalmente, y sólo el equipo médico y el personal de enfermería que le atienda podrá relacionar sus datos con su historia clínica. Su identidad no será revelada salvo excepciones en caso de urgencia médica o requerimiento legal.

En ningún caso su nombre aparecerá en la publicación de los resultados. En caso de retirar el consentimiento y requerir el abandono del estudio, la información personal será destruída y usted no formará parte de los resultados finales.

SEGURO

Al tratarse de un estudio con riesgos asociados, el grupo de investigación dispone de una póliza de seguros que se ajusta a la legislación vigente (Real Decreto 1090/2015), que le otorgará una indemnización en caso de que cualquier lesión o perjuicio sea provocado a raíz de la realización del estudio, siempre que no sea consecuencia de la propia enfermedad que usted presenta.
Si desea más información póngase en contacto con el investigador principal del estudio.

CONTACTO CON EL INVESTIGADOR

En caso de presentar una duda respecto a lo redactado en este documento informativo, o precisar de información adicional debe ponerse en contacto con el investigador principal y será atendido/a lo antes posible. Los datos del investigador se los proporcionará el profesional médico que le esté atendiendo en este momento.

Muchas gracias por su atención.
Equipo médico Hospital Universitario Vall d'Hebron

ANNEXE V. INFORMED CONSENT

This document will also be available in Catalan.

CONSENTIMIENTO INFORMADO

Título del Proyecto: Enzymatic debridement with proteolytic enzymes enriched in bromelain vs. surgical debridement for burn wound management.
Investigador principal: _____
Servicio: Unidad de Quemados del Hospital Universitario Vall d'Hebron

Yo, _____, con DNI / NIE _____ he sido informado por el Dr. / Dra. _____, colaborador/a del citado proyecto de investigación, y declaro que:

- He leído la Hoja de Información que se me ha entregado
- He podido hacer preguntas sobre el estudio
- He recibido respuestas satisfactorias a mis preguntas
- He recibido suficiente información sobre el estudio
- Comprendo que mi participación es voluntaria
- Comprendo que todos mis datos serán tratados confidencialmente
- Comprendo que puedo retirarme del estudio:
    - Cuando quiera
    - Sin tener que dar explicaciones
    - Sin que esto repercuta en mis cuidados médicos

Con esto doy mi conformidad para participar en este estudio,
A día _____ de _____ de _____, Barcelona
Firma del paciente: Firma del investigador:

Firma del representante legal,
familiar o persona vinculada de hecho:

APARTADO PARA LA REVOCACIÓN DEL CONSENTIMIENTO

Yo, _____ revoco el consentimiento de participación en el estudio, arriba firmado, con fecha _____

Firma _____

ANNEXE VI. ADMISSION CRITERIA TO THE VALL D'HEBRON BURN UNIT

1. Extensive burns	Burns with ≥ 15%TBSA in patients of 10-50 years old
	Burns with ≥ 10%TBSA in patients <10 years old, >50 years old and pregnant women
2. Full thickness burns with ≥ 5%TBSA	
3. All freezer burns	
4. All electrical burns when caused by high voltage (≥1.000 volts)	
5. Chemical burns when caused by hydrofluoric acid	
6. Ionizing radiation burns	
7. Deep, full thickness, dermal burns when they affect anatomical areas (compromised by function or aesthetics)	
8. All circular dermal and full thickness burns	
9. Patiens with compatible clinic of smoke inhalation and / or cabron monoxide poisoning	
10. Patients who present	Associated acute trauma
	Basic pathology susceptible to aggravation (cardiopathy, hepatopathy, etc...)

Table 6: Admimssion Criteria

Adapted from "*Protocol de consens entre: Unitat de Cremats de l'Hospital Universitari Vall d'Hebron, Sistema d'Emergències Mèdiques (SEM)"* (6)