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Safety and efficacy of a proteolytic enzyme for enzymatic burn débridement: a preliminary report

Lior Rosenberg[a,*], Oren Lapid[a], Alex Bogdanov-Berezovsky[a], Ronen Glesinger[a], Yuval Krieger[a], Eldad Silberstein[a], Amiram Sagi[a], Keith Judkins[b], Adam J. Singer[c]

[a]*Department of Plastic and Reconstructive Surgery, and the Burn Unit, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, POB 151, Beer-Sheva 84101, Israel*

[b]*Pinderfields Burn Center, Mid Yorkshire Hospitals NHS Trust, Wakefield, England, UK*

[c]*Department of Emergency Medicine, Stony Brook University, Stony Brook, NY, USA*

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Abstract

A prospective, non-comparative study design was used to describe our experience with a bromelain-derived debriding agent, Debridase, in 130 patients with 332 deep second degree and third degree burns treated between 1984 and 1999. Debridase was applied after saturating the burns with a moist dressing for 2–24 h. Debridase was applied for a period of 4 h under an occlusive dressing. Mean patient age was 18.6 ± 19.3. 42 (32.3%) were female, and 63 (48.5%) were children under age 18. Most burns were small. Debridase was applied once in 241 (72.6%) of the 332 wounds, twice in 67 (20.18%) cases, three times in 12 (3.61%) cases, and four times in 2 (0.6%) cases. The percentage débridement by number of applications was 89 ± 21% for a single application, 77 ± 27% for two, and 62 ± 27% for three Debridase applications, respectively. There were no significant adverse events. The availability of a fast acting, reliable and complication-free enzymatic debriding agent may open new horizons and provide a new treatment modality for burns.

Keywords: Burns; Enzymatic débridement; Debridase

1. Introduction

One of the major characteristics of burns is the formation of an eschar, which is made up of burned and traumatized tissue. The presence of the eschar that covers the entire injured area prevents accurate diagnosis of the burn's depth and may lead to the extension of injury to neighboring, originally undamaged tissues. The eschar also serves as a medium for bacterial growth, and is therefore a source of infection, contamination and sepsis. As a result, prompt removal of the eschar is imperative to the healing of burns [1–5].

The current method of choice for burn débridement is surgical tangential excision as advocated by Janzekovic in 1970 [6]. While effective, surgical débridement has several major disadvantages. Tangential excision is non-selective and may sacrifice healthy surrounding tissues, often converting a partial thickness burn into a full thickness defect [1,6–8]. Furthermore, surgical excision is painful and exposes patients to the risks of repeated anesthesia and significant bleeding. Enzymatic débridement has been suggested in the past, however the agents used have had several drawbacks. In particular, most enzymatic agents require prolonged and repeated exposures in order to achieve sufficient débridement often necessitating further surgical or chemical débridement. Furthermore, repeated applications, especially when using moist occlusive dressings for extensive periods of time, may result in local infection and promote systemic spread of the infectious process [9–13].

The ideal débridement agent or method should have the following attributes:

* Corresponding author. Tel.: +972 55 20 11 96; fax: +972 86 40 30 33.
E-mail address: prollior@netvision.net.il (L. Rosenberg).

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1. Safety: i.e., without any systemic adverse effects and minimal if any bleeding.
2. Selectivity: resulting in removal of the necrotic eschar without affecting the surrounding viable tissue, thus permitting accurate diagnosis of the extent of the original damage.
3. Effective: removing the entire eschar, preferably in a single application.
4. Rapid: resulting in rapid reduction of the infection risk and permitting sequential débridement of large areas over a short time span.
5. Simple to use and cost effective.

Bromelain is a well-known group of enzymes extracted from pineapple fruits or stems. It contains more than 50 different components and is widely used as an over-the-counter food additive and is also used in the cosmetic industry. The late Drs. Klein and Houck, [14,15] attempted to debride burn eschars with bromelain. They initially used commercially available lyophilized preparations achieving good but inconsistent results [16–18]. Further work led to the development of a proprietary extraction method that purified active ingredients from the crude bromelain to obtain a highly effective debriding mixture that they called "Debridase" [19]. The developers claimed that the effective action of Debridase was due to the synergistic activity of its various components.

We have been using and evaluating Debridase for more than 15 years for the débridement of deep second and third degree burns in our burn unit. The current study summarizes our results.

2. Materials and methods

A prospective non-comparative study design was used to evaluate our experience with Debridase in over 250 consecutive burn patients between 1984 and 1999. All study patients gave written informed consent and the study was approved by the national and local hospital ethics committees.

2.1. Study setting and patients

The study was conducted at the regional burn unit of the Department of Plastic and Reconstructive Surgery, Soroka University Medical Center. Patients were eligible for inclusion if they were between the ages of 1 and 80 years and had deep second or third degree burns potentially requiring surgical débridement. Patients were excluded in the presence of severe smoke inhalation, a recent history (<4 weeks) of myocardial infarction, concurrent acute injury or disease that might compromise the patient's life or welfare; significant hematological, cardiovascular, hepatic, or neoplastic diseases; or other immediate life threatening conditions. Patients were also excluded if they had poorly controlled diabetes mellitus (HbA_{1c} > 9%); a history of allergy, atopic disease or a known sensitivity to pineapples; or were pregnant or nursing.

2.2. Enzymatic débridement with Debridase

Each burn wound was cleaned with saline soaked gauze and covered with a hydrating dressing (e.g., an antimicrobial impregnated gauze or saline soaked absorbent dressing) for 2–24 h. After removing the dressing, reassessment of the burn's depth was made. Deep dermal or full thickness wounds were covered with a mixture of Debridase powder and carrier hydrating gel at a concentration of 2 g enzyme in 20–40 g hydrating carrier gel for every 10 cm × 10 cm of eschar. The burns were then covered with an occlusive dressing for a period of up to 4 h. During this period, the patient was closely observed for the presence of pain or itching and pain-relieving medications were given as necessary. Four hours (2 h in the cases of imminent burn induced compartment syndrome) after application the occlusive dressing was removed aseptically and the entire area wiped clean using a wooden tongue depressor, dry gauze and later with saline soaked gauze until the appearance of a clean, bleeding surface or until no further eschar could be removed. After wiping the treated area the wounds were reassessed and covered with a saline soaked absorbent dressings for another 2–24 h. If at this point débridement was deemed still unsatisfactory, Debridase was reapplied as discussed above.

2.3. Treatment following Debridase application

Following débridement full thickness burns were grafted with autografts or keratinocyte cultures as is customary in our burn unit. Deep burns with dermal remnants or superficial burns were treated conservatively with topical antimicrobial agents (such as silver sulfadiazine) or a biologic dressing (such as an allograft) combined sometimes with allo or auto keratinocyte cultures. In most cases, combinations of the above mentioned treatments were used.

2.4. Outcomes

The primary endpoints of this study were the extent of the achieved débridement and the number of Debridase applications required. Another endpoint was the presence of adverse events such as pain, itching, fever, local and systemic infection.

Visual assessment of débridement efficacy was determined by an experienced plastic and burn surgeon by estimating the amount of original eschar that was removed according to the following classification: excellent (85–100%) (Fig. 1), good (70–84%) (Fig. 2b), fair (60–69%) (Fig. 2c), or poor (50–59 (Figs. 2c and 3b arrows). Débridement of less than the original 49% of the eschar was considered a treatment failure. In cases where additional Debridase was applied, the débridement efficacy was

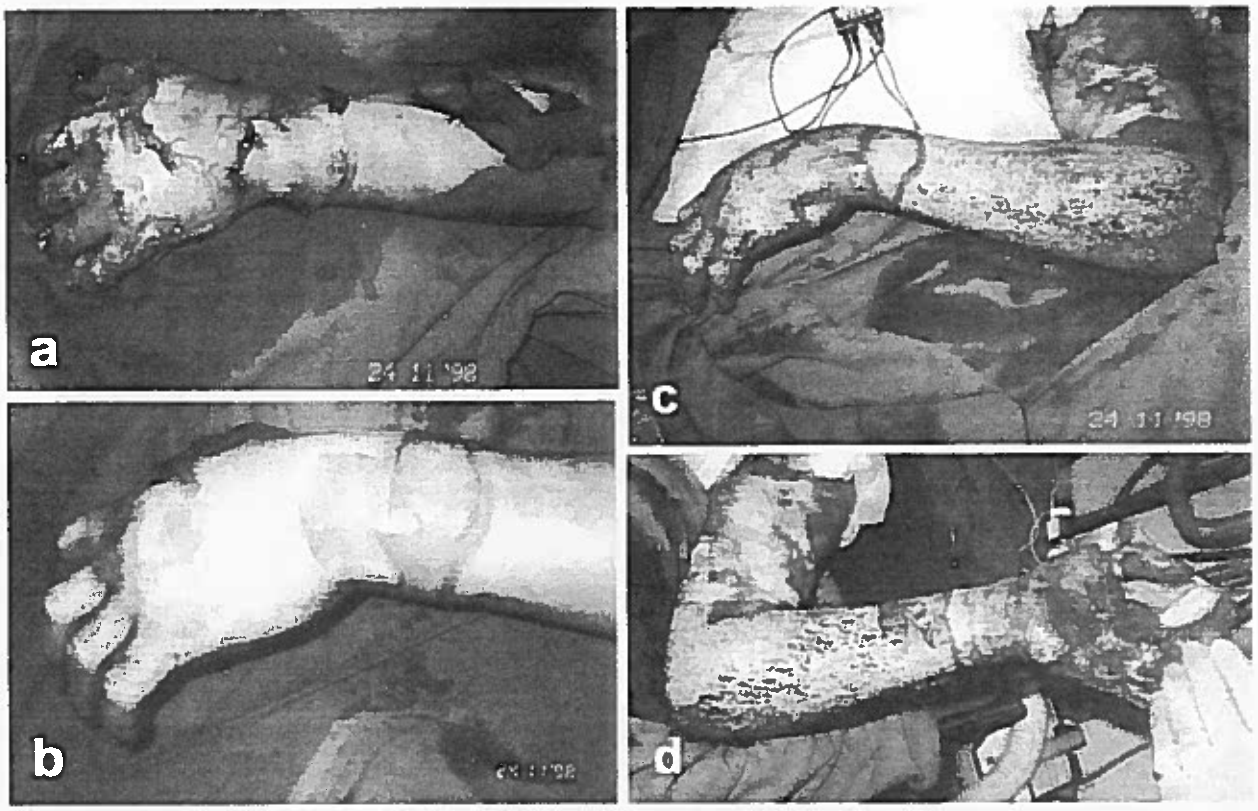

Fig. 1. Deep hand burns (a) before and (b) after blister removal. (c and d) Debridase application on the entire upper limb (hand, forearm and arm) for 4 h resulted in an excellent débridement with preservation of all uninjured areas. The clean dermis (interface layer) can be seen clearly with typical punctuated bleeders (much fewer than in surgical débridement). The undamaged tissues (those protected by the wrist watch) and the more superficial areas along the burn edges were spared.

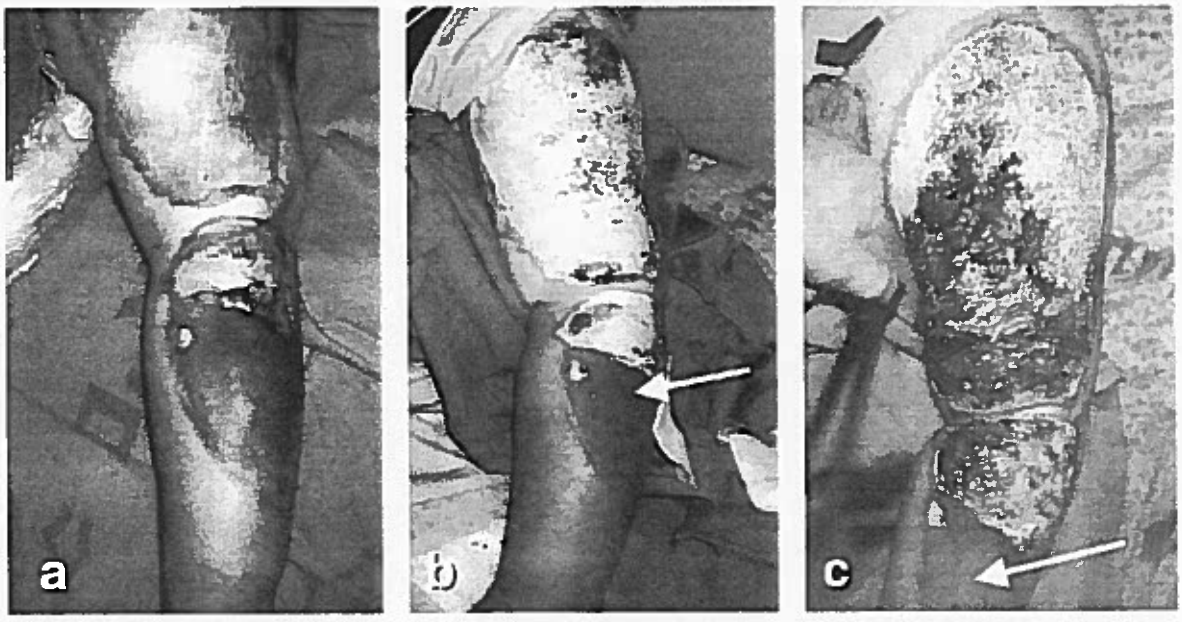

Fig. 2. (a) Patient suffering from a deep burn pretreated for 3 days by SSD. (b) First 4 h Debridase application produced only a good débridement with some remnants of the deeper eschar at the lower part of the debrided area. The clean bed at the upper arm has no eschar tissue but a whitish collageneous layer with few punctuate bleeders is seen that consists of the upper part of the healthy dermis. The lower part of the burned area is still covered with blister that prevented the contact of the eschar and Debridase resulting in an insufficient débridement (arrow). (c) A second 4 h of Debridase application cleaned entirely the exposed area. The blister was not removed even for the second application with the resulting failure of débridement (arrow).

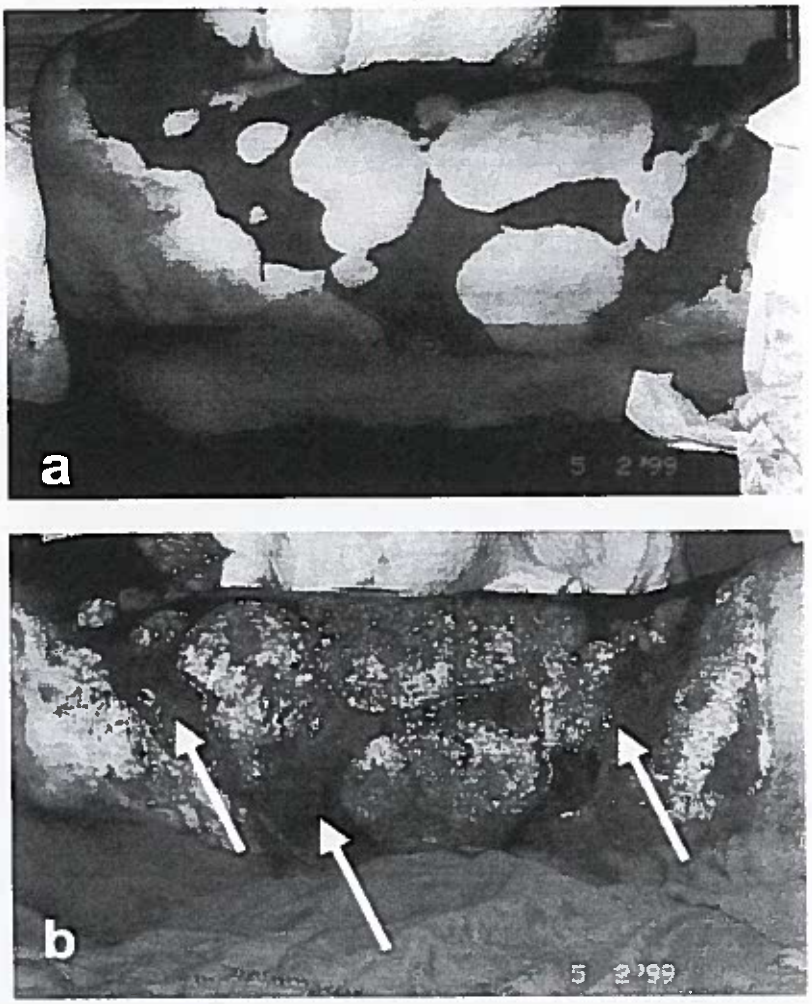

Fig. 3. (a) Deep burns of the trunk before Debridase application. (b) The charred blisters (arrows pointing at the dark areas) were not removed and were not affected by the Debridase, however, 4 h of its application resulted in an excellent débridement of the areas where the blisters were removed.

assessed using the amount of eschar that was removed in each application. Photographic documentation of all burns was performed and reassessments were made by two independent observers several months later.

All adverse events that occurred during hospitalization were recorded and their relationship to the treatment was judged according to their nature and timing in relation to the débridement. Based on past experience with other enzymatic debriding agents, assessment of fever and pain was especially important. Fever was defined as a temperature >38.5 C, and a rise in temperature of greater then 1 C within 48 h of débridement was considered as possibly related to the treatment.

3. Results

During the study period more than 250 consecutive patients were treated with Debridase, however, complete records were available for only 130 patients with 332 wounds. The patients' mean age was 18.6 ± 19.3, 42 (32.3%) were female, and 63 (48.5%) were children under age 18. Approximately half of all burns were caused by contact with fire or flame. Other etiologies included scalds (47), contact burns (17). Most burns (66%) covered less than 10% of TBSA. Burns covering 10–30% TBSA accounted for 27% of all patients while burns covering 31–50% and greater than 50% were seen in 3 and 4% of patients, respectively. Most burns were of mixed (deep dermal and full thickness) depth (64.9%) while 20.4% were of pure second degree (deep dermal) and 14.8% were third degree burns. The distribution of burns included 163 (50%) upper extremity burns, 126 (38%) lower extremity burns, 36 (11.8%) trunk burns, 5 (0.15%) neck burns and 1 burn each on the genitalia and head.

Debridase was applied once only in 241 (72.6%) of the 332 wounds, twice in 67 (20.18%) cases, three times in 12 (3.61%) cases, and four times in 2 (0.6%) cases only. The percentage débridement by number of applications was 89 ± 21% for one, 77 ± 27% for two, and 62 ± 27% for three

that necessitates additional surgical débridement. The repeated application of these agents has been followed in several cases by local and systemic infection due to bacteremia secondary to the repeated handling and occlusion of the contaminated eschar with exposure of the surrounding raw tissues to the contaminated and partially dissolved eschar [10,13].

The aim of the current study was to evaluate the efficacy of burn wound débridement using the Debridase enzymatic preparation as well as to evaluate the presence of any possibly related adverse events. Direct assessment of the débridement thoroughness (efficacy) and its safety was sought as the primary end points and not graft take as many factors besides the host bed influence the graft take. Another reason for not including graft take as a measure of débridement efficacy is the fact that selective enzymatic débridement removes only the necrotic tissues and deep but not full thickness burns may still heal by epithelialization of the surviving dermal bed from the epidermal adnexae without the need for transplantation surgery. This differs significantly from surgical débridement where in most cases the full thickness of the skin is sacrificed for the sake of débridement and transplantation of a skin graft is mandatory.

The study population is fairly typical of our burn unit population, though slightly more representative of adults since judicious inclusion of children in the study was encouraged. The mean BSA of the deep burns that required débridement and were treated by Debridase was less than 2% of BSA. The majority of burns were debrided using a single brief application of Debridase for 4 h (241 applications). In the remainder of cases for which two or more applications were required the wound was usually old, dry or saturated with silver sulfadiazine (SSD). In two cases, one a pressure-contact burn of the fingers and the other of an old SSD treated scald burn of the arm, four consecutive applications were required.

In most cases the débridement was completed in less than 24 h. In average, the first application removed nearly 90% of the entire eschar, the second (if needed) 77% and in the few cases in which a third application was used, 68% of the eschar was eventually removed. In nearly three-quarters of the cases a single 4 h application was sufficient to complete this phase of the treatment.

During the early phases of the study many of the debrided wound beds that had typical features of a non surgical debrided bed were misinterpreted only as partially debrided, skewing the results against Debridase. Once it became clear that this bed was clean and could heal spontaneously or support a skin graft the results "improved". In some difficult areas (such as on the trunk or on convex areas where the debriding gel could not be in close and continuous contact with the eschar) additional applications were required to complete the débridement of the entire intended area. Early on the importance of removing all the superficial burned keratin layer (blisters) that hinder the action of the enzymes was realized (Figs. 2 and 3). Dry and old eschars, especially if treated with SSD for several days, did not dissolve as well as fresh moist ones. Thus the efficacy of Debridase decreased after the 6th post burn day possibly due to the changing nature of the eschar following treatments such as SSD.

Five patients with extensive burns were treated several times, each time for no more than 15% TBSA of the burned area. In such cases Debridase dressings were applied sequentially after removing the previously debrided dressings.

Approximately one quarter of the burns were completely debrided within the first day with another half undergoing complete débridement within 2–3 days of injury. These results are even more impressive when one considers that in some cases (e.g., more extensive burns) sequential applications of Debridase were used. In all cases where enzymatic débridement with Debridase was complete, skin allografting, for biological, epithelialization enhancing cover or other topical covers were performed at the bedside with minimal pain and no bleeding. In cases of full thickness burns and an excellent Debridase débridement the grafting of an autograft could be done without a farther surgical débridement and the recipient bed prepared by scraping or dermabrasion. This is obviously of great benefit when compared to the pain and bleeding associated with surgical débridement. The selectivity of the preparation was demonstrated by the lack of effect on the healthy surrounding tissue and the preservation of remnants of unburned tissues (dermis and epidermis) (Fig. 1). Finally, unlike other non-surgical débridement techniques, Debridase achieved a thorough débridement in a single or double brief 4 h application offering a rapid and selective burn wound débridement method.

Many patients complained of various sensations at the treated area immediately on application of Debridase. These sensations ranged from a very mild tingling or discomfort, to a mild burning or itching with some 12% requiring oral analgesia mainly with the more superficial burns. Most of these complaints subsided within 30 min of Debridase application, but some patients complained of an itching or burning sensation for the entire duration of the treatment. Typically, the more intense sensations started to decrease after 15–20 min of treatment reaching a level of very mild irritation within 30 min of application. Prophylactic pretreatment of patients with analgesic agents (as is customary before dressing changes) usually was sufficient to keep the patients comfortable. None of our patients required sedation or general anesthesia for the treatment.

Fever was noted in nearly 80% of our patients, however, fever is common after thermal injuries and the exact relationship to the débridement is unclear. It should be noted that 2/3 of our patient population did not develop any fever beyond the first 2 days after injury when in general fever becomes more common. Also, we did not find that the temperatures of patients treated with Debridase were any higher than in our other burn patients during the study period that were not treated with enzymatic débridement. Only a

large prospective randomized comparative trial will help determine the relationship between enzymatic débridement with Debridase and the occurrence of fever. Such as study is currently underway at 22 burn sites worldwide.

Our study has several limitations that merit further discussion. Data was incomplete in a large number of patients introducing the possibility of inacuracies. Furthermore this was not a comparative trial, thus it is unclear what the exact impact of enzymatic débridement compared to the standard of care tangential excision was.

5. Conclusions

We present our preliminary results using the enzymatic debriding agent "Debridase" for deep burns. We found that in most cases complete débridement of the eschar was obtained after only one to two brief applications with minimal side effects and no blood loss. No specific Debridase-related morbidity or mortality was noted. The availability of a rapid, reliable and complication-free enzymatic debriding agent may open new horizons and provide a new treatment modality for burns.

Acknowledgments

The study was initiated in 1983 in the Soroka Burn Unit at the request of Drs. Klein and Houck who donated the Debridase enzyme. In 1992, the study GMP material was produced and donated by Biotechnology General LTD Israel (BTG Ltd.). None of the authors had any financial interests in the company at the time of the study (1983–1999). Since January 2002, the primary author (LR) acts as the Chief Medical Director of MediWound Ltd. that produces the new batches of Debridase under the name of "Debrase". Neither Dr. Rosenberg nor any of the other authors had any financial interest in the companies that produced the Debridase that was used in this study.

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