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ORIGINAL ARTICLE

Bromelain-based enzymatic debridement of chronic wounds: A preliminary report

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Sharp debridement is currently considered most effective for debridement of chronic wounds; however, some patients do not have access to or cannot be treated by surgical methods. This study was designed to provide a first impression of the safety and efficacy of bromelain-based enzymatic debridement of chronic wounds. Two consecutive single-arm studies assessing the enzymatic debridement efficacy of a concentrate of proteolytic enzymes enriched in bromelain in chronic wounds was conducted in 2 medical centres. Patients were treated with up to 11 consecutive 4-hour enzymatic debridement sessions and then treated until wound closure. Twenty-four patients with chronic wounds of different aetiologies were enrolled. All wounds achieved an average of 68% ± 30% debridement in an average of 3.5 ± 2.8 enzymatic debridement 4-hour sessions. Seventeen responding wounds (venous, diabetic, pressure, and post-traumatic aetiologies) achieved an average 85% ± 12% debridement in 3.2 ± 2.5 applications. Seven non-responding wounds (arterial and post-surgical aetiologies) achieved an average 26% ± 13% debridement in 4.3 ± 3.5 applications. No treatment-related serious adverse events were observed, and the only adverse event attributed to the enzymatic debridement was pain. These preliminary results indicate the potential safety and efficacy of bromelain-based enzymatic debridement in chronic wounds. Larger controlled studies are needed to further investigate this indication.

KEYWORDS

a concentrate of proteolytic enzymes enriched in bromelain, bromelain-based debridement, chronic wounds, enzymatic debridement

1 | INTRODUCTION

Chronic wounds are estimated to affect over 6 million people in the United States. Approximately 15% to 25% of individuals with diabetes develop a foot ulcer at some point in their lifetime, and an estimated 12% of those patients require lower extremity amputation.[1] Chronic wounds seriously affect the quality of life and productivity of patients and cause substantial burden to health care systems worldwide. Furthermore, the prevalence of chronic wounds is expected to increase as the population ages and as the number of individuals with obesity, peripheral vascular disease, and diabetes increases.

Chronic wounds are often characterised by the presence of hard eschar on the wound surface, devitalised tissue, or a slough that frequently hardens by desiccation. The presence of eschar can delay granulation and epithelialisation; its removal (debridement) facilitates healing and is therefore the first stage of wound care.[2] The choice of debridement method depends on the clinician, who considers wound characteristics, patient comorbidities, the time needed to achieve a clean wound bed, and the available skills and

Yaron Shoham and Yuval Krieger contributed equally to this study.

resources to safely manage the debridement process in the particular clinical setting.[3] Based on currently available studies, a positive influence on healing of chronic leg ulcers is best achieved with surgical wound debridement.[4] Non-surgical methods, however, cause less pain, less bleeding, less damage to surrounding healthy tissues, and do not require surgical skills, all valuable advantages in situations where physician availability may be limited, such as within the long-term care environment.[3]

Currently available non-surgical debridement agents, either enzymatic (eg, collagenase) or autolytic (eg, medicinal honey), are slow-acting, and there is little evidence to suggest that the use of any currently available debridement agent for chronic wounds is beneficial for wound healing when compared with traditional (saline soaking) or other control treatments. Bromelain-based debridement (BBD), performed with a concentrate of proteolytic enzymes enriched in bromelain (MediWound Ltd, Yavne, Israel), has been proven to be a rapid, efficient, and safe enzymatic debridement agent in burns, with the additional benefit of selectivity, that is, removal of non-viable tissue and preservation of viable tissue.[5–14] In light of the unmet need for a rapid and effective non-surgical debridement agent for chronic wounds and these positive results using BBD for burn eschar removal, 2 similar consecutive concept validation studies were conducted to provide a first impression of the safety and efficacy of BBD in chronic wounds.

Key Messages

- bromelain-based enzymatic debridement has been proven to be safe and effective in burns; the aim of this study was to provide a first impression of its safety and efficacy in chronic wounds
- a total of 24 patients suffering from chronic wounds of different aetiologies underwent up to 11 consecutive 4-hour applications of enzymatic debridement
- all wounds achieved an average of 68% ± 30% debridement in an average of 3.5 ± 2.8 applications
- the 17 responding wounds (venous, diabetic, pressure, and post-traumatic aetiologies) achieved an average 85% ± 12% debridement in 3.2 ± 2.5 applications

2 | METHODS

Study drug: Patients were treated with a 10% concentrate of proteolytic enzymes enriched in bromelain (MediWound Ltd, Yavne, Israel).

Ethical considerations: The study protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the institutions' human research review committees. Signed written informed consent was obtained from each patient.

Inclusion criteria: Age 18 to 80 years old; patients with at least 1 necrotic chronic wound (ie, venous insufficiency ulcers, diabetic foot ulcers, pressure ulcers in the heel, or arterial insufficiency ulcers post revascularisation) defined as non-healing and covered by eschar for >4 weeks or post-traumatic/surgical cutaneous necrotic wounds defined as non-healing and covered by eschar for >2 weeks; each target wound size area of at least 2 cm^2 and no greater than 40 cm^2 of necrotic tissue; patient available for 12 weeks of follow up; and patient is willing and able to adhere to the protocol regimen and wound care as prescribed by the investigator.

Exclusion criteria: Evidence of underlying osteomyelitis; patients with more than 2 necrotic wounds with an area greater than or equal to 2 cm^2; presence of acute severe clinical infection of target ulcer; continuous use of heavy metal dressings (ie, silver sulphadiazine, silver nitrate or iodine) within 1 week of the screening visit; target ulcer has purulent discharge; target ulcer has sinus tracts or tunnels extending under healthy tissue; patients undergoing renal or peritoneal dialysis; ABI index <0.7; recent history (less than 4 weeks) of myocardial infarction or concurrent acute injury or disease that could compromise the patient's welfare; evidence of significant haematological (severe pre-existing coagulation disorder), cardiovascular, liver, or neoplastic disease; other immediate life-threatening conditions; patients receiving, at any time within 1 month prior to the screening visit, any medications or treatments known to affect the wound-healing processes; history of allergy or atopic disease or a known sensitivity to pineapples; pregnant or nursing mothers; participation in another investigational drug trial within 30 days prior to the screening visit or anticipated participation while enrolled in the study; and concurrent use of non-approved drugs or alcohol abuse.

Study design: Two consecutive, exploratory, prospective, single treatment arm studies were conducted in 2 large university medical centres. Due to the exploratory nature of the studies, patients with different aetiologies of chronic wounds were enrolled. Patients were initially screened during a 2-week period to confirm that the wounds were not improving and were then treated as inpatients with up to 11 consecutive daily 4-hour BBD applications. Patients were then treated until wound closure according to the discretion of the investigators. Wound closure was confirmed by an additional visit scheduled 2 weeks after wound closure (Figure 1).

Study treatment: Prior to BBD application, wounds were rinsed with sterile saline and covered with Lidocaine gel 2% for 30 minutes. Vaseline petroleum jelly that serves as an adhesive barrier to contain the BBD within the treatment area was applied around the wound's perimeter. The lyophilised BBD enzymes were mixed with a vehicle gel just before application on the treated wound and covered with an occlusive dressing for the 4-hour treatment session

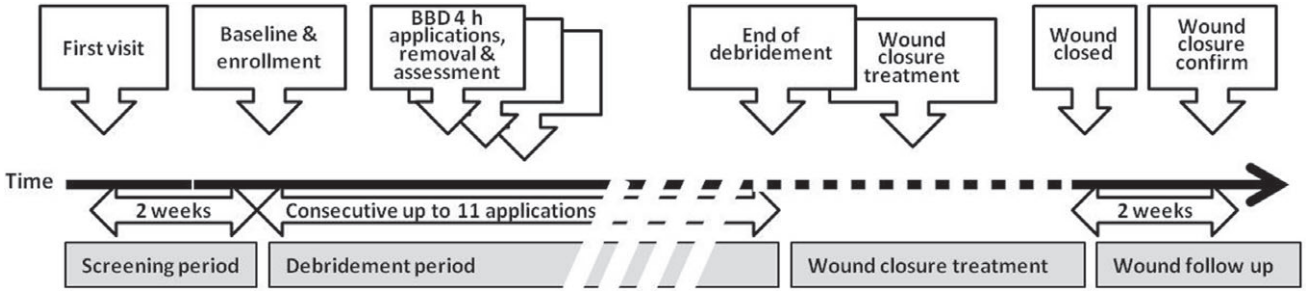

FIGURE 1 Study design

(Figure 2). After the 4-hour application, the wound was wiped clean and scraped with a wooden tongue depressor and assessed by the investigator. The wound was then dressed with saline-soaked gauze until the next day, when an additional BBD application was performed if the debridement was not yet complete. Complete debridement was defined as a clean wound bed without eschar, ready to be treated until closure.

Treatment was to be discontinued if no debridement progress was seen in any single application, or in case of an irreversible adverse event, or in case a patient wished to abort the treatment.

Endpoints: The endpoints included the number of 4-hour BBD applications needed to achieve an eschar-free wound bed, safety and efficacy parameters such as adverse events, change in the percentage of viable and non-viable tissue, and additional wound assessment and closure strategies.

Statistical analysis: Data were recorded on case report forms and converted to Microsoft Excel© sheets. Continuous variables are expressed as mean ± standard deviation, as calculated by Microsoft Excel© formula functions.

3 | RESULTS

A total of 24 patients with wounds of different aetiologies (diabetic ulcers, venous and arterial insufficiencies, pressure ulcers, post-surgical and post-traumatic wounds including a background of lymphedema and chronic steroid treatment brittle skin) were enrolled in both studies. The mean wound age was 3.9 ± 4.9 months. All wounds achieved an average of 68% ± 30% debridement in an average of 3.5 ± 2.8 BBD 4-hour applications (14 ± 11.2 BBD hours), range 1 to 11 applications. The 14 wounds treated in 1 centre (2 venous and 3 arterial insufficiency, 1 diabetic, 1 pressure, 1 post-surgical, and 6 post-traumatic ulcers) achieved 68% ± 34% debridement in 1.9 ± 0.6 applications (7.6 ± 2.4 BBD hours), and the 10 wounds treated in the second centre (4 venous and 1 arterial insufficiency, 3 post-traumatic, and 2 post-surgical ulcers) achieved 68% ± 23% debridement in 5.8 ± 2.9 applications (23.2 ± 11.6 BBD hours). Examples of BBD efficacy can be seen in a venous insufficiency ulcer (Figure 3) and in 2 post-traumatic wounds (Figures 4 and 5).

Wounds that did not demonstrate a substantial reduction in eschar within 3 BBD applications were defined as non-responders. A total of 17 responding wounds (6 venous, 1 diabetic, 1 pressure, and 9 post-traumatic ulcers) achieved an average 85% ± 12% debridement in 3.2 ± 2.5 applications (12.8 ± 10 BBD hours). A total of 7 non-responding wounds (3 post-surgical necrotic flaps, and 4 arterial insufficiency dry eschars) achieved an average 26% ± 13% debridement in 4.3 ± 3.5 applications (17.2 ± 14 BBD hours). A summary of debridement efficacy and average number of applications per aetiology in all patients can be seen in Figure 6.

Wound closure was performed by various methods. Skin grafting over granulation tissue was the most common method ($n = 13$), followed by a combination of spontaneous healing and skin grafting ($n = 6$), spontaneous healing alone ($n = 2$), primary closure ($n = 1$), flap closure ($n = 1$), and 1 patient was lost to follow up before completion of wound closure.

No BBD-related serious adverse events were observed, and there were only 2 types of adverse events reported as

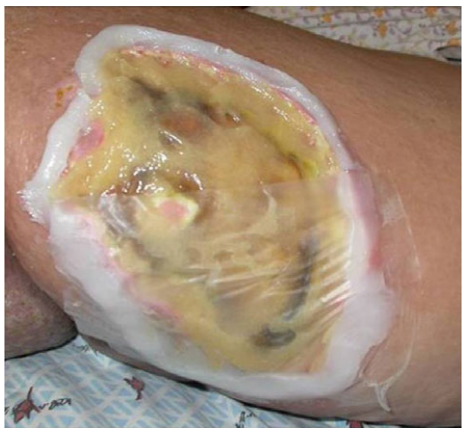

FIGURE 2 Bromelain-based debridement (BBD) applied on wound, surrounded by a Vaseline barrier, and partially covered by an occlusive dressing. A second occlusive dressing was then applied to cover the upper portion of the wound. The Vaseline layer in the lower part of the wound can be seen lightly smeared underneath the occlusive dressing, thus providing an effective adhesive barrier

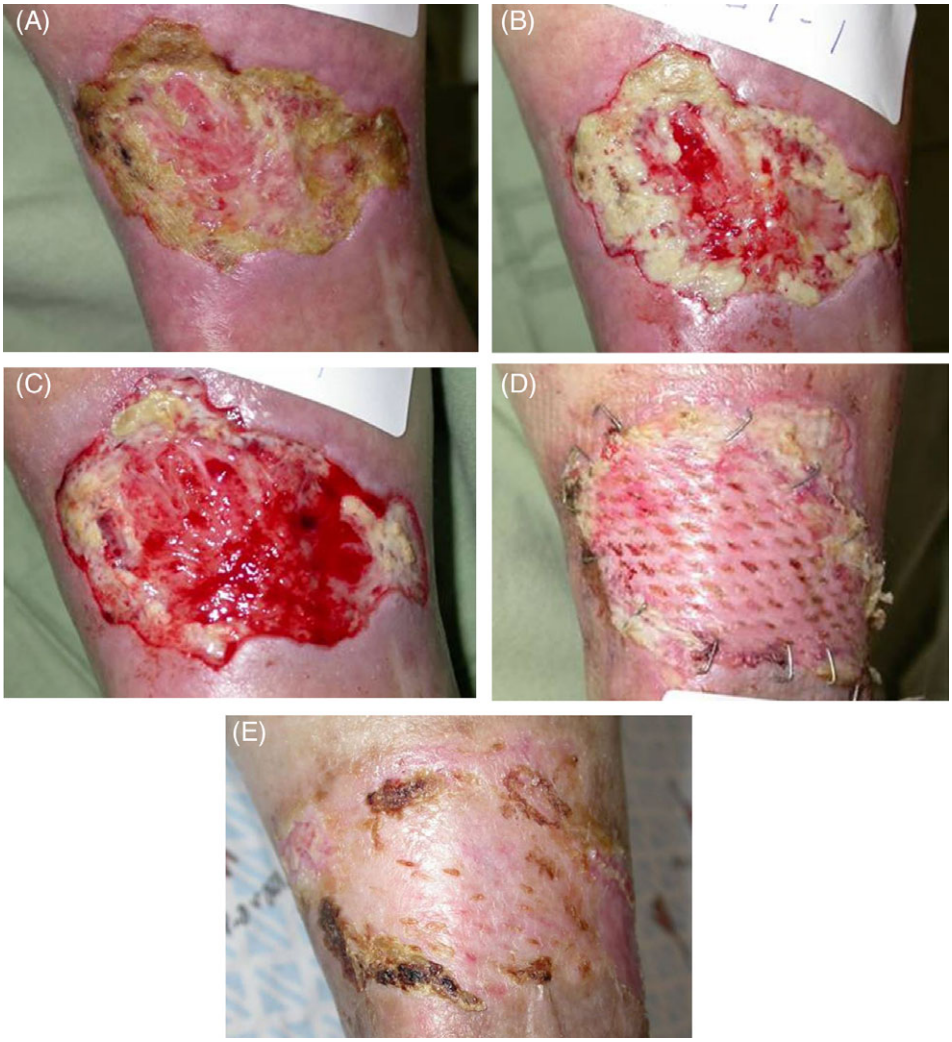

FIGURE 3 A, Venous insufficiency ulcer, pre-existing for 5 months. B, After first bromelain-based debridement (BBD) 4-hour application. C, After fourth BBD 4-hour application (16 hours total exposure to BBD). D, 1 week post-split-thickness skin grafting. E, 7 weeks post-split-thickness skin grafting

probably or definitely related to BBD. Peri-procedural pain was reported in 5 of the 24 patients (21%), and injury of the peri-wound skin was reported in 4 of the 24 patients (17%, see Figure 7). All 4 cases of injury of the peri-wound skin were among the first patients enrolled, and in all these cases, there was leakage of BBD from the treatment area to the peri-wound skin. A more accurate application of a thick Vaseline barrier in later cases prevented further recurrences of this adverse event, and the superficial damage in these 4 cases healed spontaneously under conservative treatment.

4 | DISCUSSION

Non-surgical debridement techniques (autolysis and available enzymes) are slow and inefficient. Surgical strategies that are effective are skill-dependent and painful and harbour the danger of surgically related additional trauma to the already compromised patient. Therefore, there is an unmet need for a safe and effective non-surgical debridement agent. We aimed to explore the possibility that BBD, already proven effective in selective burn wound

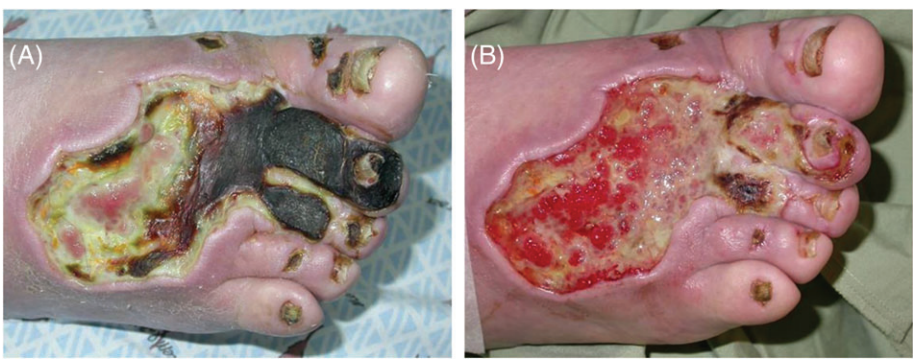

FIGURE 4 A, Post-traumatic dorsal foot wound (tire abrasion), pre-existing for 1 month. B, After fourth bromelain-based debridement (BBD) 4-hour application (16 hours total exposure to BBD)

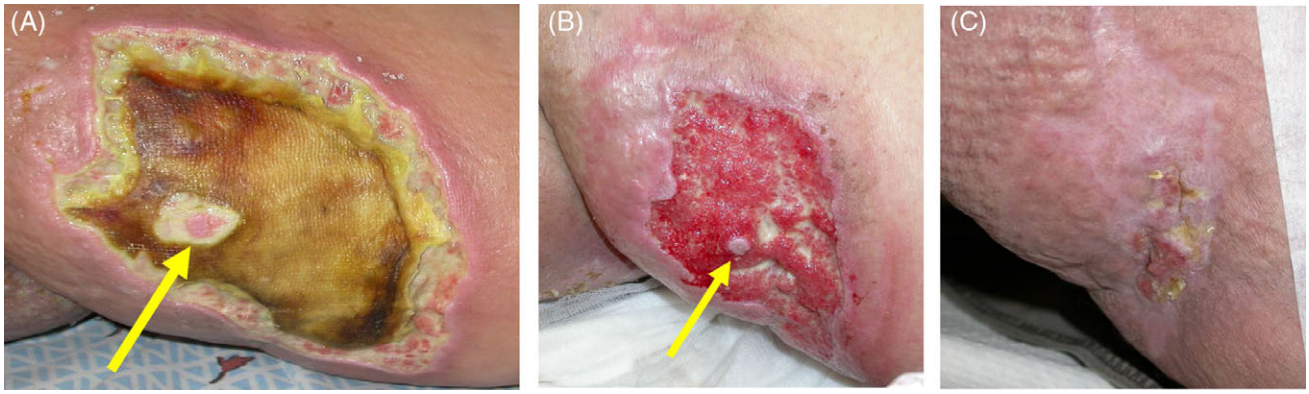

FIGURE 5 A, Post-traumatic leg wound, pre-existing for 2 months, in a patient suffering from severe lymphoedema. Note the arrow pointing to an area of intact epithelium. B, After fifth bromelain-based debridement (BBD) 4-hour application (20 hours total exposure to BBD); note the area of intact epithelium unharmed by BBD. C, 2 months post-split-thickness skin grafting

debridement, is useful in debriding a variety of chronic wound eschars, serving as a non-surgical alternative to surgical debridement. The combined results of these 2 feasibility studies, despite being preliminary and exploratory in nature, demonstrate that this concept appears to be valid. Unlike burn wounds where, in most cases, a single 4-hour BBD application dissolves all the eschar, the results of these studies demonstrate that chronic wound debridement necessitated longer exposure times and that not all types of eschars are equally susceptible to BBD dissolution. Different wound aetiologies and topical wound care agents used result in different eschar characteristics (hardness of eschar, adherence to viable wound bed, level of moisture, and saturation with prior topical medications). Enzymatic debridement may function in 2 separate or combined pathways: dissolution of the eschar itself and dissolution of the ties between the eschar and the wound bed. Assessing the characteristics of the debridement in these studies demonstrated that a sufficient debridement allowing for a treatment shift to wound closure strategies was achieved in moist wounds, where either the eschar itself or its interface with the wound bed was moist. Dry eschars, on the other hand, such as those present in arterial insufficiency ulcers and post-surgical dry necrotic flaps, were hardly dissolved.

The efficacy results in both medical centres were similar (68% average debridement); however, the average number of 4-hour BBD applications was quite different (1.9 vs 5.8). The similar efficacy results can be attributed to the similar ratio of hard dry eschars vs moist eschars treated in both centres. In 1 centre, there were 4 cases of arterial insufficiency and post-surgical dry necrosis out of a total of 14 wounds treated (29%), and in the second centre, there were 3 cases of arterial insufficiency and post-surgical dry necrosis out of a total of 10 wounds treated (30%). The reason for the difference in the average number of applications is not clear; however, it may be attributed to the differences in the investigators' prior experience with BBD in burns. The first centre had prior experience in the use of BBD in dozens of burn patients, whereas the second centre had no such prior experience. This prior experience may have led to better adherence with treatment protocol or to an earlier recognition of debridement efficacy and an understanding that further applications may not be necessary.

BBD of deep burns is associated with procedural pain, and this is to be expected as it has been shown to remove eschar as efficiently as surgery, which is painful to the patient as well if not managed appropriately. Therefore, it is not surprising that pain was reported as an adverse event attributable to BBD in these studies as well. However, in most cases, pre-treating the wounds with a local anaesthetic gel eliminated the procedural pain. In addition, one must consider the lack of a comparator surgical arm in these studies, where peri-procedural pain would have been most likely reported as an adverse event attributed to the procedure (sharp debridement) as well.

The injury of the peri-wound skin in several cases warrants discussion as well. The use of a Vaseline barrier to prevent leakage of BBD out of the treatment area was performed in a similar manner to the way it is performed when treating burns with BBD. It is the authors' experience that a thick layer of Vaseline applied evenly around the treatment

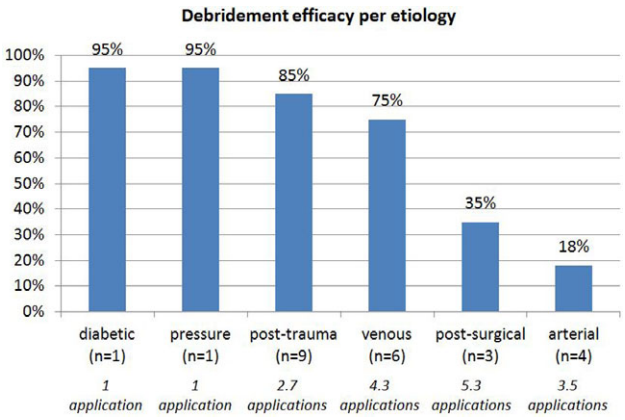

FIGURE 6 Average % debridement efficacy and average number of 4-hour bromelain-based debridement (BBD) applications per aetiology

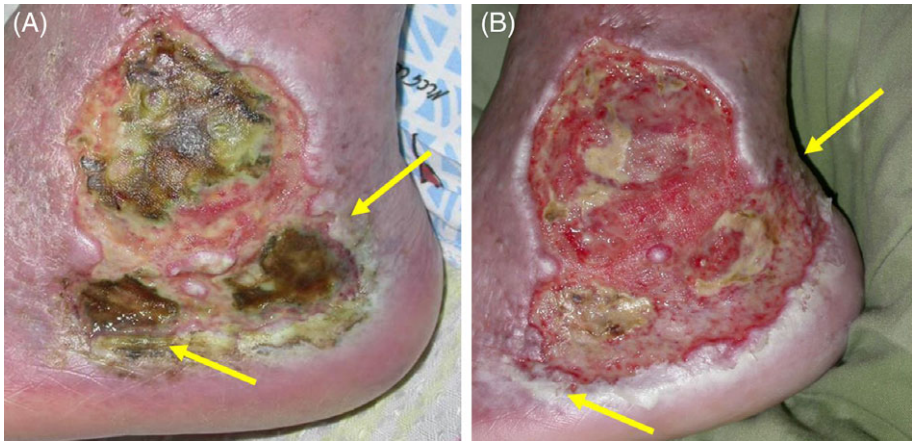

FIGURE 7 A, Venous insufficiency ulcer, pre-existing for 2 months; note arrows pointing to unhealthy peri-wound skin. B, After 10th 4-hour bromelain-based debridement (BBD) application (40 hours total exposure to BBD); note arrows pointing to maceration at wound edges and debrided peri-wound skin

area prevents leakage. However, it is important to state that, in burns, leakage does not injure the peri-wound skin as it is healthy and has an intact keratin layer that BBD does not penetrate. On the other hand, in chronic wounds, the peri-wound skin is usually not healthy (underlying pathology such as diabetes or venous/arterial insufficiency) and often does not have an intact keratin layer. Therefore, we believe that the application of an effective adhesive barrier in chronic wounds to contain BBD within the treatment area is crucial in order to prevent damage to the peri-wound skin.

5 | CONCLUSION

These preliminary results indicate the potential efficacy and safety of BBD in chronic wounds. BBD was found to be more effective in the debridement of relatively moist eschars and less effective in dry eschars. Larger controlled studies are needed to further investigate the efficacy of BBD in chronic wounds of different aetiologies.

Study strengths: These results serve as a proof of concept that BBD may be an alternative to sharp debridement in chronic wounds, perhaps adding an additional tool to the armamentarium of chronic wound care. To the best of our knowledge, this is the first report of this possible efficacy.

Study drawbacks: Small case series of multiple aetiologies with no control arm comparison allows only a preliminary impression of the potential efficacy and safety of BBD in chronic wound care.

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Conflict of interest

Financial relationships:

Yaron Shoham is the Director of Medical Affairs for MediWound Ltd.

Lior Rosenberg is the Chief Medical Officer for MediWound Ltd.

Josef Haik is a consultant for MediWound Ltd.

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