A Retrospective Review of an Off-label Bromelain-based Selective Enzymatic Debridement (Nexobrid®) in the Treatment of Deep, Partial, and Full Thickness Burns and Hard to Heal Wounds

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ABSTRACT: **Background:** Rapid and selective bromelain-based enzymatic debridement provides a non-surgical alternative for the eschar removal in deep burns, which allows for early debridement of large surface areas, accurate evaluation of burn and wound depth, and the need for skin grafting.

Objectives: To evaluate the efficacy of application of a bromelain-based selective enzymatic debridement (Nexobrid®) beyond the manufacturer's guidelines for use in burns › 48 hours as well as chemical, electrical, and pediatric burns, and chronic wounds.

Methods: This retrospective review included records collected between January 2017 and April 2019, from male and female patients aged 8 months to 99 years with deep burns or wounds treated with bromelain-based selective enzymatic debridement.

Results: Of the 33 patients who received the bromelain-based selective enzymatic debridement agent beyond the manufacturer's guidelines, 25 (76%) were observed to have successful debridement of the eschar, 8 (24%) were observed to have little effect on the burn eschar. Sixteen required further surgery after debridement. Clinical data on the use of bromelain-based selective enzymatic debridement agents are limited, but these results suggest the capacity to effectively debride burns › 48 hours (late presentation burns), use for pediatrics and for chemical and electrical burns, and apply to hard to heal full thickness chronic wounds.

Conclusions: Bromelain-based selective enzymatic debridement was found to be an effective treatment modality beyond the recommended guidelines including late presentation burns and chronic wounds. This debridement method warrants further consideration when making clinical decisions concerning burn and wound care.

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KEY WORDS: bromelain-based enzymatic debridement, burns, eschar, excision, wounds

The early removal of eschar is a foundational procedure [1], which is necessary in the treatment of deep burns and wounds to manage the bioburden of the wound. This debridement allows the early closure of the wound by either dressings or surgical skin grafting [2]. Removal of devitalized tissue often requires surgical debridement to facilitate granulation and epithelization or to permit early diagnosis of wound depth and consequently evaluate the need for grafting. Debridement of the wound bed may include methods such as surgical, sharp, or mechanical debridement. Other methods include biological debridement with maggot therapy and autolytic and enzymatic debridement. The standard of care for the treatment of severe burns is skin grafting [3] with the aim to preserve the viable dermis that is accompanied by early closure of the wound to reduce complications such as infection and scarring [2]. Tangential excision is often used to remove eschar, which is a non-selective method requiring costly hospital resources that can result in substantial blood loss and significant loss of body heat and viable tissue [4].

It is well established that early debridement of eschar is associated with shorter hospital stays, reduced infection rates, and improved patient outcomes [3]. Increasingly, evidence suggests that enzymatic debridement is an effective method in the removal of eschar from burns; thus reducing blood loss and the need for skin grafting and surgical excisions [2,5]. A technique commonly used in wound care is the implementation of selective enzymatic debridement [6]. There is strong evidence to suggest that bromelain-based selective enzymatic debridement is a safe and effective method for the treatment of deep burns reducing the necessity for surgical debridement [2,7]. A complex combination of protease that is extracted from a pineapple's stem and fruit, bromelain has been used in folk medicine for many years for its biochemical and pharmacological properties [8].

Rapid and selective bromelain-based enzymatic debridement provides a non-surgical alternative for the eschar removal in deep burns [9]. This solution allows for the early debridement of large surface areas, accurate assessment of burn and wound depth, and the need for skin grafting. Bromelain-based selective enzymatic debridement (Nexobrid®) has been approved in Israel for more than 3 years for use on adults with burns sustained no greater than 48 hours, but is not indicated for chemical, electrical, and pediatric burns or for chronic wounds.

There remains a notable absence of evidence for the use of bromelain-based selective enzymatic debridement greater than 48 hours in the treatment of burns and for use on the pediatric population, electrical and chemical burns, and for use on hard to heal chronic wounds. Manufacturer guidelines suggest that Nexobrid® should not be applied to burns older than 48 hours and to no more than 15% total body surface area (TBSA) [10]. It should also not be applied on chemical burns, contaminated wounds, and wounds where it may come into contact with foreign bodies or large blood vessels or the eyes [11]. In addition, the safety and efficacy for use in children and adolescents younger than 18 years of age has not yet been verified [11]. Moreover, there currently is no experience in the use of Nexobrid® on electrical burns [11]. This is an important issue as electrical burns are often deceptive as there is no association between the cutaneous damage and underlying structures [12].

The present study assessed the efficacy of the application of an enzymatic debriding agent (Nexobrid®) beyond the manufacturer's guidelines when clinically indicated. In this study, we focused on selective bromelain-based enzymatic debridement (Nexobrid®) beyond the recommended manufacturer's guidelines that included use on burns greater than 48 hours and in pediatric patients, chemical and electrical burns, or hard to heal chronic wounds.

PATIENTS AND METHODS

INTERNAL REVIEW BOARD

This retrospective, descriptive chart review was conducted at the National Burns Center, Sheba Medical Center in Israel [13]. The study followed the principles outlined in the Declaration of Helsinki and was approved by the ethics committee, Sheba Medical Center (SMC 1544-14).

STUDY PATIENTS

Charts from male and female subjects with partial to full thickness burns and chronic wounds, ranging in age from 8 months to 99 years, were reviewed as part of this study. Between January 2017 and April 2019, 417 hospitalizations for burn injuries were registered at the National Burns Center. Among them, 32 inpatients of differing ages presenting with partial and full thickness burns were treated with bromelain-based selective enzymatic debridement agent (Nexobrid®) beyond the manufacturer's guidelines and one case with a hard to heal chronic wound. Off label bromelain-based selective enzymatic debridement (Nexobrid®) was applied based on the clinical evaluation if the patient met the following criteria: late presentation of adult partial to full thickness burns greater than 48 hours or burns caused by chemical or electrical sources, pediatric burns, and hard to heal chronic wounds.

TBSA was estimated by the Rule of Nine for adults and the Lund and Browder chart that uses age-appropriate measurements [14]. After analgesia was provided in accordance with the pain protocol, petroleum jelly was placed on the edges of the wound to protect the viable skin and the bromelain-based selective enzymatic debridement agent was applied to the burn/wound with a spatula and then covered with a nylon wrap for a period of 4 hours. After 4 hours, the debriding agent was then removed using normal saline irrigation and gauze. Successful debridement was classified as a clean wound bed free of eschar ready to graft or dress appropriately if grafting was not required. Digital images were taken prior to the application, and after the removal of the debriding agent to assess the efficacy of eschar removal and to reassess the depth of the burn/wound. Demographic data was collected including mechanism of injury, gender, age, TBSA and depth, area debrided, and the time from injury to application [Table 1].

RESULTS

A total of 33 patients received the bromelain-based selective enzymatic agent (Nexobrid®) outside of the guidelines, including 5 pediatric patients. Fourteen sustained a partial to full thickness burn, 6 sustained a full thickness burn, 12 sustained a partial thickness burn, and one had a full thickness chronic wound. The average age was 44 years (range 8 months–99 years), and average TBSA was 12% (range TBSA 0.5–45%). The affected body surface area encompassed the upper and lower limbs including feet and hands, torso, neck, and face. From injury to treatment, the range was 8 hours to 15 days, and the average area debrided was 8% (range 0.5–36%). Of the 33 patients who received the bromelain-based selective enzymatic debridement agent beyond the manufacturer's guidelines, 25 (76%) were observed to have successful debridement of the eschar [Table 1] [Figures 1A, 1B, 1C, 1D, 1E, 1F), 8 (24%) were observed to have little effect on the burn eschar [Table 1] [Figure 1G, 1H]. Sixteen required further surgery post-debridement (i.e., skin grafting).

Of the six with either a chemical or electrical burn, five were reported to have had their burn successfully debrided. Little effect on the debrided area was noted for one patient with a chemical burn (battery acid) despite treatment within 8 hours of their injury as per manufacturer's recommendations. Of the five pediatric patients treated, no adverse effects were reported. Four patients had a surface area greater than the recommended 15% treated and no adverse effects were reported.

Table 1. Demographic and debridement data

	Mechanism of injury	Patient	Gender	Age, years	TBSA	Burn degree	Time from injury until treatment	Area treated	Debridement	Efficacy of debridement	Further surgery post-debridement	LOS (days)
Treatment later than 48 hours	Scald	1	Male	73	4%	PT	8 days	Both feet	4%	×	×	65
		2	Female	33	20%	PT	5 days	Right arm	4%	✓	✓	29
		3	Male	36	2%	PT	3 days	Both ankles	2%	✓	×	29
		4	Male	99	8%	FT	14 days	Right thigh	6%	×	✓	20
		5	Female	45	1.5%	PT	50 hours	Both ankles	1.5%	✓	×	7
		6	Male	40	3%	PT	15 days	Left foot	1.5%	×	×	14
		7	Female	42	5%	PT	6 days	Right thigh	5%	✓	×	15
		8*	Male	1.8	35%	FT	4 days	Chest, back, shoulder	15%	×	✓	42
		9*	Male	0.8	30%	FT	3 days	Chest, upper limbs	30%	✓	✓	30
	Cooking oil	10	Female	63	1%	PT	9 days	Left hand	1%	✓	×	33
		11	Female	89	2%	PT	5 Days	Right hand and forearm	2%	×	×	9
		12	Male	23	5%	FT	4 days	Left thigh	5%	✓	✓	25
		13	Male	49	2%	PT	3 days	Left hand and wrist	1.5%	✓	×	11
		14	Male	48	9%	PT	3 days	Right thigh	4%	✓	×	18
	Flame	15	Male	45	1%	PT-FT	8 days	Right hand	1%	✓	×	22
		16	Male	87	17%	PT/FT	5 days	Both lower legs	13%	×	✓	60
		17	Male	55	12%	PT/FT	49 hours	Both legs	11%	✓	✓	61
		18	Male	36	7%	PT/FT	4 days	Left arm, neck, chest	7%	✓	✓	21
		19	Male	22	8%	PT	3 days	Right arm	2%	✓	×	18
		20	Female	69	3%	PT/FT	53 hours	Right axilla and right hip	3%	✓	✓	29
		21*	Male	9	45%	PT/FT	5 days	Chest, abdomen upper limbs	32%	✓	✓	196
	Contact burn	22	Female	25	1.5%	PT/FT	4 days	Right lower leg	1.5%	✓	×	9
		23	Female	86	7%	PT/FT	6 days	Face and left arm	6%	✓	✓	29
		24	Female	82	2%	PT/FT	7 days	Right thigh	2%	×	✓	18
	Chemical burn injury	25	Male	32	38% (battery acid)	PT/FT	13 days	Right upper limb	8%	✓	×	36
		26	Male	46	40% (unknown source)	PT/FT	5 days	Upper limbs	18%	✓	✓	86
		27	Male	43	1% (phosphorus)	FT	7 days	Right palm	1%	✓	✓	25
Treatment within 48 hours		28	Male	23	38% (battery acid)	PT/FT	8 hours	Lower limbs	36%	×	✓	90
	Electrical burn injury	29	Male	33	0.5%	PT/FT	20 hours	Right hand and left forearm	0.5%	✓	×	6
		30	Male	40	18%	PT/FT	46 hours	Right hand and forearm and right thigh	6%	✓	×	18
	Contact burn	31*	Female	1	1%	FT	10 hours	Right hand	1%	✓	×	6
	Scald	32*	Male	4	15%	PT	1 day	Lower limbs	15%	✓	×	47
	Chronic wound	33	Male	72	8%	FT	N/A	Lower limbs	8%	✓	✓	36

*pediatric patients

FT = full thickness, PT = partial thickness, LOS = length of stay, TBSA = total body surface area

Of the burns sustained from hot oil (n=5), four patients had successful debridement initiated 3 days or more post-burn. For flame burns, successful debridement was initiated from day 3 up to day 8 days post-injury. Among the chemical burn group (with early and late debridement from battery acid and phosphorous), successful debridement was observed among the majority of patients regardless of the time since injury.

One patient with a chronic wound [Figure 1E] and significant co-morbidities including vasculitis, demonstrated successful debridement of the eschar after 60 days [Figure 1F].

DISCUSSION

The use of a bromelain-based selective enzymatic debridement agent is a non-surgical approach that is currently licensed for

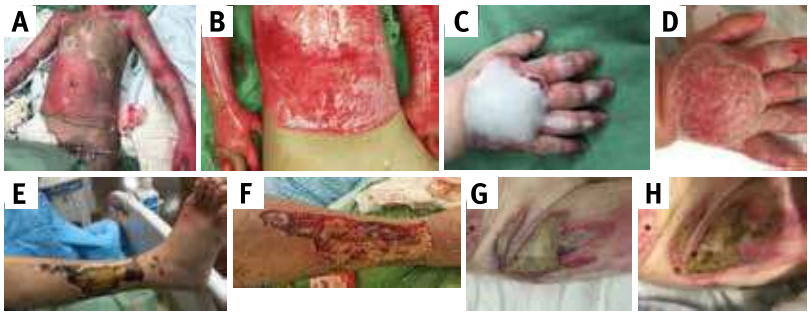

Figure 1. [A] 9-year-old child with 45% PT/FT flame burns to the chest, abdomen upper limbs; **[B]** 32% successful debridement with Nexobrid® at 5 days post-burn; **[C]** 1-year-old child with 1% FT contact burn to the right hand; **[D]** 1% successful debridement with Nexobrid® 10 hours post; **[E]** 72-year-old male with 8% FT chronic wound to the lower limb abdomen upper 8%; **[F]** successful debridement with Nexobrid® after 60 days; **[G]** 82-year-old female with 2% PT/FT to the right thigh; **[H]** unsuccessful debridement with the application of Nexobrid® 7 days post-burn

FT = full thickness, PT = partial thickness

the removal of burn eschar in the adult population for deep to full thickness cutaneous burns [15] and until now, the use has been limited to the adult population for immediate use limited to 15% TBSA. Furthermore, it is recommended that the use of bromelain-based selective enzymatic debridement agent be limited to use on scald, flame, and contact burns [2]. Nexobrid® was observed to be safe and efficient when used beyond the standard guidelines, with no adverse reactions reported.

In 2017, European consensus guidelines were published based on experience with the application of Nexobrid® that encompassed more than 500 adult and pediatric patients by the consensus group [2]. The aim of the guidelines was to provide recommendations for use of enzymatic debridement beyond the current available evidence in the peer reviewed literature [2]. Subsequently, this retrospective study aimed to demonstrate efficacy of bromelain-based selective enzymatic debridement beyond the recommended manufacturers guidelines.

Manufacturer's guidelines recommend that the bromelain based selective enzymatic debridement agent (Nexobrid®) should be applied within 48 hours post-burn. Our study demonstrated the safe and effective use of the bromelain-based selective enzymatic debridement agent beyond the recommended 48 hours suggested by the manufacturer with a 76% success rate. As for scald burns, we observed successful late debridement initiated up to 6 days from the injury for adult patients. This finding was supported by Hirche et al. [2] establishing that delayed application of greater than 72 hours is acceptable in selected patients that attained 100% consensus [2]. In a recent case study of a 61 year old male who sustained a severe burn of 95% TBSA, Krauss and colleagues [15]. reported the efficacy of delayed use of (Nexobrid®) on day 5. However, it is suggested that delayed presentation of burns with dry eschar may require the removal of the superficial layers and soaking of the eschar for a prolonged period to improve the efficacy of enzymatic debridement [2].

The use of bromelain-based selective enzymatic agent (Nexobrid®) is not recommended for use on chemical burns [2,11]. Chemical burns cause coagulative necrosis to both the epidermis and underlying tissue [16]. Hirche et al. [2] reported limited use in two burn centers encompassing five chemical burns with limited results when applied early. Subsequently, Hirche et al. [2] stated that due to the limited evidence and the unclear demarcation of chemical burn injury it is not recommended. Despite these findings, our study demonstrates positive results with three out of the four chemical burns sustained from battery acid and phosphorous treated, successfully up to 13 days post-burn.

It was reported that there was no experience of the use of bromelain-based selective enzymatic debridement on electrical burns [11]. Until now, to the best of our knowledge, there have been no reports of bromelain-based selective enzymatic debridement on chemical burns in the peer reviewed literature. Out of the 33 patients in our study, 2 had electrical burns that were successfully debrided.

The consensus guidelines developed by Hirche et al. [2] state that up to 30% TBSA burned can be treated with Nexobrid® based on an individual use and as such considered off-label use. Four of our 33 patients were treated with bromelain-based selective enzymatic debridement agent (Nexobrid®), greater than the recommended 15% with no adverse effects. Krauss et al. [15] reported fractional use of bromelain-based selective enzymatic debridement agent on 54% of the TBSA across three surgeries within a 4-day period with no adverse effects except for bleeding suggesting the need for monitoring of hemoglobin to avoid anemia. Hirche et al. [2] reported similar findings to our study with treating > 15% TBSA ranging up to 36% in one session; however, the researchers stops short of recommending greater than 30% TBSA in one debridement session. Important elements to consider when treating areas greater than the recommended 15% are the systemic effects due to loss of fluid requiring recalculation of fluid resuscitation and invasive monitoring [2].

Special focus should be given to the successfully treated chronic wound due to vasculitis. Although one case can be the exception, the fact that a chronic wound underwent viable enzymatic debridement suggests that further investigation should be conducted to explore the use in hard to heal chronic wounds. There has been limited reports of the use of bromelain-based selective enzymatic debridement for the treatment of chronic wounds [17,18]. Characteristics of chronic wounds are hardened

eschar, accompanied with devitalized tissue or slough that hardens by the process of desiccation [17]. Shoham and colleagues [17] treated 24 patients with chronic wounds using bromelain-based enzymatic debridement with up to 11 consecutive daily 4-hour treatments with Nexobrid®. Shoham et al. [15] reported that all wounds attained an average of 68% ± 30% debridement with an average of 3.5 ± 2.8 applications with no adverse events. Mataro et al. [18] also reported the use of bromelain-based enzymatic debridement in patients with chronic ulcers to the lower limbs with complete removal of necrotic tissue after one application for a period of 4 hours and within 24 hours. They reported complete debridement of the wound bed with no adverse events. However, at day 7, Mataro and colleagues reported partial recurrence of necrotic tissue. Both Mataro's group and Shoham's group reported patients with diabetic, venous, and arterial ulcers suggesting underlying chronic disease. Berner et al. [7] found that the use of Nexobrid® in the treatment of diabetic foot burns had poor results that resulted in the development of further eschar and the deepening of wounds that required further surgical debridement and grafting. Despite this, these studies support the potentially safe and effective use in chronic wounds. As highlighted by Shoham et al. what may be of significance to successful debridement with Nexobrid® is the moisture content of the wounds and whether that be the eschar or its connection with the moist wound bed, as dry eschar was poorly removed in patients with arterial insufficiency.

It is our impression that the optimal timeframe for effective use of bromelain-based selective enzymatic debridement is up to 5 days post-injury inclusive of electrical, chemical, pediatric burns and chronic wounds. It is our belief that the efficacy of bromelain-based selective enzymatic debridement is reduced after this period due to the lack of permeability of the eschar. However, histological studies are necessary to confirm this assumption. Subsequently, the introduction of bromelain-based selective enzymatic debridement immediately beneath the eschar for this cohort is to be considered.

The safety and efficacy of the bromelain-based selective enzymatic agent (Nexobrid®) in the pediatric and adolescent population younger than 18 years has yet to be established. The consensus guidelines introduced by Hirche et al. [2] clearly state that Nexobrid® can be applied in pediatric populations with pleasing results but is currently considered as off label use with no recommendation on a posology [11]. We had only five pediatric patients in our study and no notable adverse effects were observed. Rosenberg et al. [4,19] found that bromelain-based selective enzymatic debridement could be safely and successfully used on the pediatric population.

Currently there is a multicenter, international, randomized, controlled, open label study underway that aims to evaluate the efficacy and safety of Nexobrid® in children with burns compared the standard of care (https://clinicaltrials.gov/ct2/show/NCT02278718) and we await these results.

CONCLUSIONS

Evidence on bromelain-based selective enzymatic debridement mainly relates to the use for acute burns applied within 48 hours. To date clinical data on the use of bromelain-based selective enzymatic debridement are limited outside the manufacture's guidelines, but these results suggest that Nexobrid® has the capacity to effectively debride late presentation burns and chronic wounds and could be considered when making clinical decisions concerning burns and wound care. More data are required to adequately inform clinicians about use for late presentation burns, the pediatric population, electrical or chemical burns and chronic wounds so that the indications for use can be broadened.

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Conflict of interest

Josef Haik is a freelance consultant for MediWound Ltd.

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Capsule

Taking the bite out of diseases

Arthropods are the most abundant animals on earth and can transmit diseases such as dengue or West Nile virus to humans. **Bryden** and colleagues tried to manipulate the immune reaction at the site of mosquito bites to restrict viral dissemination. They found that local Toll-like receptor 7 (TLR7) activation shortly after infection dampened replication of a model alphavirus in mice. This finding held true for clinically relevant arboviruses and in human skin explants. Viral restriction was due to activation of skin macrophages and heightened type I interferon production. Topical TLR7 activation after mosquito bites could be a broad-acting approach to abrogate arboviruses.

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Eitan Israeli

Capsule

Influenza-induced monocyte-derived alveolar macrophages confer prolonged antibacterial protection

Despite the prevalence and clinical importance of influenza, its long-term effect on lung immunity is unclear. **Aegerter** and co-authors described that following viral clearance and clinical recovery: at 1 month after infection with influenza, mice are better protected from *Streptococcus pneumoniae* infection due to a population of monocyte-derived alveolar macrophages (AMs) that produce increased interleukin-6. Influenza-induced monocyte-derived AMs have a surface phenotype similar to resident AMs but display a unique functional, transcriptional, and epigenetic profile that is distinct from resident AMs. In contrast, influenza-experienced resident AMs remain largely similar to naive AMs. Thus, influenza changes the composition of the AM population to provide prolonged antibacterial protection. Monocyte-derived AMs persist over time but lose their protective profile. These results help to understand how transient respiratory infections, a common occurrence in human life, can constantly alter lung immunity by contributing monocyte-derived, recruited cells to the AM population.

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Eitan Israeli

Capsule

Elevated anti-citrullinated protein antibodies prior to rheumatoid arthritis diagnosis and risks for chronic obstructive pulmonary disease or asthma

Zaccarelli et al. investigated elevation of anti-citrullinated protein antibodies (ACPA) before RA diagnosis and risks for chronic obstructive pulmonary disease (COPD) or asthma. They analyzed 283 pre-RA women and 842 controls. Blood was donated mean of 9.7 ± 5.8 years before RA diagnosis. Fifty-nine women (20.8%) were pre-RA ACPA+. There were 107 cases of incident COPD and 105 incident asthma cases during 21,489 person-years of follow-up. Pre-RA ACPA+ was associated with increased COPD risk (hazard ratio [HR] 3.04, 95% confidence interval [95%CI] 1.33–7.00) after adjusting for covariates including smoking pack-years. Pre-RA ACPA+ had a HR for asthma of 1.74 (multivariable 95%CI 0.72–4.24), similar to the risk of asthma for pre-RA ACPA (HR 1.65, 95%CI 1.11–2.46). The authors concluded that women with elevated ACPA before RA diagnosis had increased risk for developing COPD compared to controls. Women who later developed RA were more likely to develop asthma, regardless of pre-RA ACPA status.

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