OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE

Burns

Enzymatic Debridement (Nexobrid) on Burned Hands: Retrospective Review from a Burn Referral Center in Spain

Zhan Q. Lin Wu, MD*
Antonio Bulla, MD*
Jon A. Aguirrezabala del Río, MD*
Danilo A. Rivas Nicolls, MD*
Jorge Aguilera Sáez, MD*
Jordi Serracanta Domènech, MD*
Juan P. Barret, MD, PhD*†

Background: In deep burns, the gold standard of treatment is surgical debridement and coverage, but in hands, this may lead to poor aesthetic and functional results due to the complexity of this anatomical area. Enzymatic debridement (Nexobrid) allows for the preservation of the dermal remnant and reduces the number of skin grafts when compared with surgical excision. The study aimed to analyze the patients with intermediate second-degree or deeper burns in hands who required surgical treatment after Nexobrid and those who avoided it.

Methods: A descriptive retrospective study of all patients who underwent Nexobrid following hand burns between May 2015 and April 2020 treated in Vall d'Hebrón University Hospital was conducted. After the enzymatic debridement, the burn unit team determined if the burn required conservative treatment or surgery, based on the characteristics of the wound bed.

Results: A total of 202 hands were collected. Most hands included in this study had deep second-degree burns (122; 60.4%). Almost half of the hands underwent surgery (99; 49%), and most had deep second-degree burns (61; 61.62%). During follow-up, 24 hands required surgery for sequelae (11.88%) and 62 did not undergo follow-up (30.69%). In the group that needed sequelae surgery, 21 needed surgery after Nexobrid and three of them were healed with conservative treatment after Nexobrid ($P < 0.001$).

Conclusions: Nexobrid decreases the number of surgical procedures in deep burns of the hand because more conservative attitudes are adopted. Also, it seems to reduce the need of surgery due to burn sequelae. *(Plast Reconstr Surg Glob Open 2024; 12:e5886; doi: 10.1097/GOX.0000000000005886; Published online 10 June 2024.)*

INTRODUCTION

Burns represent a significant burden on health care systems, necessitating prompt medical attention and often surgical intervention.[1–3] According to the World Health Organization, an estimated 180,000 deaths annually result from burns, with the majority occurring in lower-middle-income countries. Additionally, nonfatal burns contribute substantially to patient morbidity.[4,5]

*From the *Department of Plastic Surgery and Reconstructive Surgery, Vall d´Hebrón University Hospital, Barcelona, Spain; and †Department of Surgery, School of Medicine, Universitat Autónoma de Barcelona. Barcelona, Spain.*

Received for publication November 26, 2023; accepted April 24, 2024.

DOI: 10.1097/GOX.0000000000005886

The hands are a commonly affected anatomical region, with burn injuries affecting 30%–60% of burn patients.[6,7] Surgical management of deep hand burns presents unique challenges due to the intricate anatomy, which includes important structures such as ligaments, tendons, nerves, and vessels, all relatively superficial but crucial for hand function. Furthermore, the potential impact of scar formation on functional outcomes adds another layer of complexity to treatment.[7,8] Since 2004, numerous studies have investigated the use of Nexobrid (MediWound Ltd, Israel) for the enzymatic debridement of burns. Nexobrid is a concentrated solution containing proteolytic enzymes, primarily bromelain derived from pineapple stems. It aids in the targeted removal of necrotic burn eschar, reducing inflammation, and preserving viable tissue. By revealing the underlying healthy tissue, Nexobrid facilitates precise assessment of burn depth and enables effective treatment planning.[7,9–12] Following enzymatic debridement, the burn bed may

Disclosure statements are at the end of this article, following the correspondence information.

exhibit vascular patterns that assist in accurately diagnosing the depth of the burn, thus guiding its treatment effectively.[7,13]

The selective debridement of devitalized tissue with higher dermal preservation reduces the local inflammatory state and lowers the risk of infection, thus promoting the spontaneous healing of the burn. Consequently, burns initially deemed suitable for surgical debridement may, following Nexobrid treatment, exhibit sufficient dermal remnants to support spontaneous healing without the need for skin grafting. Nevertheless, this is a costly procedure that needs locoregional or general anesthesia to be performed and trained personnel to evaluate and follow the procedure.

In this scenario, the aim of this study is to investigate and describe the efficacy of Nexobrid in treating hand burns in a referral burn center in Spain, being the largest case series of hand burns treated with Nexobrid at the time of this article's publication.

Takeaways

Question: The standard of care for deep burns is debridement followed by an autograft, but in some complex anatomical areas such as the hand, it can cause poor aesthetic and functional results. The study aimed to analyze if enzymatic debridement could decrease the number of surgical procedures in hand deep burns.

Findings: We conducted a retrospective review of 202 hands treated with Nexobrid, and found that enzymatic debridement could reduce the number of surgical debridements in deeply burned hands.

Meaning: Enzymatic debridement may change the standard of care of the treatment for deep hand burns because the surgeons could take more conservative measures.

MATERIALS AND METHODS

The present study has been approved by our center's ethics and clinical research committee [EOM(AG)037/2022(6022)].

Patient Selection

We conducted a descriptive retrospective study encompassing all patients who underwent enzymatic debridement following hand burns from May 2015 to April 2020 at the Burn Unit of Vall d'Hebron University Hospital.

Patients with deep dermal or deeper hand burns involving at least 0.5% of the total body surface area (TBSA) were identified as candidates for enzymatic debridement with Nexobrid by senior surgeons in our burn team. Additionally, patients with superficial dermal burns on the hands but with Nexobrid-eligible deep dermal burns in the forearm also underwent enzymatic debridement on the hands, taking advantage of regional blockade. Exclusion criteria included chemical and electrical burns, pregnancy, and allergies to any components of the formula. There were no exclusions based on patients' age or other medical comorbidities.

Procedure

Enzymatic debridement followed our center's protocol and the manufacturer's guidelines, and was conducted within the first five days postinjury. Before enzymatic debridement, we removed blisters and mechanically cleared devitalized skin, covering the wound with an occlusive moist dressing containing Prontosan (B. Braun, Germany) for at least two hours. Pain control included sedoanalgesia or regional nerve blocks.

At the beginning of the procedure, the wound dressing was removed, and the burn area bordered with sterile petrolatum. Nexobrid was applied in a 1.5- to 3-mm layer, followed by an occlusive dressing. After 4 hours, the dressing was removed, and the product was cleansed with physiological saline and a spatula. Subsequently, the area was covered again with a moist dressing containing Prontosan for at least 6 hours until the postdebridement wound evaluation, typically during the next morning round.

Following the 2017 Spanish consensus guideline on enzymatic debridement in burn injuries,[14] the medical team assessed whether the burn required conservative treatment, with a potential for spontaneous epithelialization or surgery (Table 1 and Fig. 1). If conservative treatment was chosen, the wound bed was covered with Suprathel (PolyMedics Innovations GmbH, Filderstadt, Germany) and Urgotul (Laboratoires URGO, Dijon, France). Conversely, if spontaneous healing was deemed unlikely, the wound was covered with Mepitel (Mölnlycke Health Care, Gothenburg, Sweden) plus nitrofurazone 0.2% (Furacín, SEID S. A., Barcelona, Spain) or Mepilex Ag (Mölnlycke Health Care, Gothenburg, Sweden) and scheduled for surgery involving surgical debridement plus skin grafting.

Follow-up

We conducted a follow-up of patients for a minimum period of 2 years after the complete healing of the burn. Patients who did not complete our 2-year follow-up were considered lost to follow-up.

All patients initiated active hand mobilization three days after enzymatic debridement and five days after surgery (if required). In case of signs of hypertrophic scarring, compression therapy was initiated.

Table 1. Wound Bed Diagnosis and Prognosis of Resolution and Treatment after Enzymatic Debridement

Wound Bed	Appearance	Type of Burn	Attitude
IIA	Abundance of small pin-point bleeders (uniform shades of red)	Superficial partial thickness	Wound care
IIB	Sparse pattern of larger diameter bleeders in white bed	Mid/deep partial thickness	Wound care
IIC	Same as IIB plus depression of the wound bed	Deep partial thickness	Surgery
III.	Subdermal fatty tissue	Full thickness	Surgery

Modified with permission from *Cir Plást Ibero-Latinoam* 2017;43:193–202. Martínez-Méndez et al.[14]

Fig. 1. Post enzymatic debridement wound bed according to the classification shown in Table 1. A–B, Display of the wound bed after enzymatic debridement that will epithelialize spontaneously (IIA–IIB postdebridement evaluation respectively). C–D, Display of those that will need surgical debridement (IIC–III postdebridement evaluation respectively).

Data Collection Parameters

1. Age
2. Sex
3. Burn etiology
4. TBSA of the burn
5. Percentage of burn affecting the hands
6. Laterality (whether the burn affected the dominant or nondominant hand)
7. Time intervals: (a) Duration from the time of burn injury to administration of Nexobrid, (b) duration from administration of Nexobrid to surgery (if surgery was required), (c) duration from the time of burn injury to complete healing
8. Follow-up duration (minimum of 24 months after complete healing)
9. Incidents or complications during the follow-up period
10. Whether sequelae surgery was required

Endpoints

The primary endpoint of the study is to determine whether the clinical assessment of the burn is a reliable predictor of the need for surgery following the introduction of Nexobrid treatment, as well as to evaluate whether the use of Nexobrid reduces the incidence of unnecessary surgical procedures in patients who, in a traditional scenario, would have been considered candidates for early surgical intervention.

The secondary endpoints include assessing demographic and burn-related factors, evaluating treatment timelines, documenting follow-up duration and complications, identifying factors linked to sequelae surgery, and assessing long-term functional and cosmetic outcomes.

Statistical Analysis

The statistical analyses were conducted using RStudio, version 2022.12.0 + 353 (2022.12.0 + 353).

Descriptive statistics, such as frequencies, percentages, medians, and quartiles, were generated to summarize patient demographics and burn characteristics. Hypothesis testing methods, including chi squared tests, Fisher exact test, and Wilcoxon rank sum tests, were used to compare categorical and continuous variables between groups and assess associations. Statistical significance was determined at $\alpha = 0.05$.

RESULTS

Data of 139 patients were collected from the medical records, comprising 108 male and 31 female individuals (77.7% versus 22.3%). The median age was 40 years (min 17, first Qu. 30, third Qu. 53.5, max 87).

Of these patients, 76 had unilateral hand involvement, whereas 63 had bilateral involvement (54.7% versus 45.3%), resulting in the analysis of 202 hands. Right hand involvement occurred in 109 cases (53.96%), with left hand involvement in 93 cases (46.04%).

The majority of hands included in this study (Fig. 2) exhibited deep second-degree burns (122; 60.4%), followed by mid-dermal (71; 35.15%), third-degree (7; 3.47%), and superficial second-degree burns (2; 0.99%). The primary burn etiology was flame-related (89 cases; 64.03%), followed by scald (27 cases; 19.42%), electrical flash (19; 13.67%), contact (2; 1.44%), and electric (2; 1.44%).

The median TBSA burned was 7.5% (min 0.5, first Qu. 3.5, third Qu. 17, max 85), with the median TBSA debrided with Nexobrid at 1.25% (min 0.25, first Qu. 1, third Qu. 2.5, max 3). The median day of Nexobrid application postburn was day 1 (min 0, first Qu. 1, third Qu. 2, max 5). Approximately half of the hands underwent skin graft surgery (99 cases; 49%). The median time to complete healing was 32 days (min 12, first Qu. 24, third Qu. 43, max 212).

During follow-up, 24 hands required surgery for sequelae (11.88%), whereas 116 did not (57.43%), and 62 did not undergo follow-up (30.69%). Surgical interventions included commissuroplasties, two arthrodeses of the second and fifth fingers, and one scar removal and coverage with a groin flap.

Among the group with deep second-degree burns (122 hands), 61 (50%) underwent conservative management, whereas 61 (50%) underwent surgery. Fisher exact test revealed a significant association between surgery and the development of scar hypertrophy or scar retraction ($P = 0.0004433$, odds ratio: 5.149183, 95% CI: 1.906348–14.762473). No significant association was found between skin graft surgery and secondary scar surgery ($P = 0.07808$, odds ratio: 3.37896212, 95% CI: 0.7864106–20.6121266). Refer to Table 2 for further details.

A Wilcoxon rank sum test with continuity correction showed a statistically significant difference in healing time scores between the two groups ($W = 1249$, $P = 0.03343$). The median healing time after skin graft surgery was 34 days (min 15, first Qu. 24, third Qu. 43, max 116),

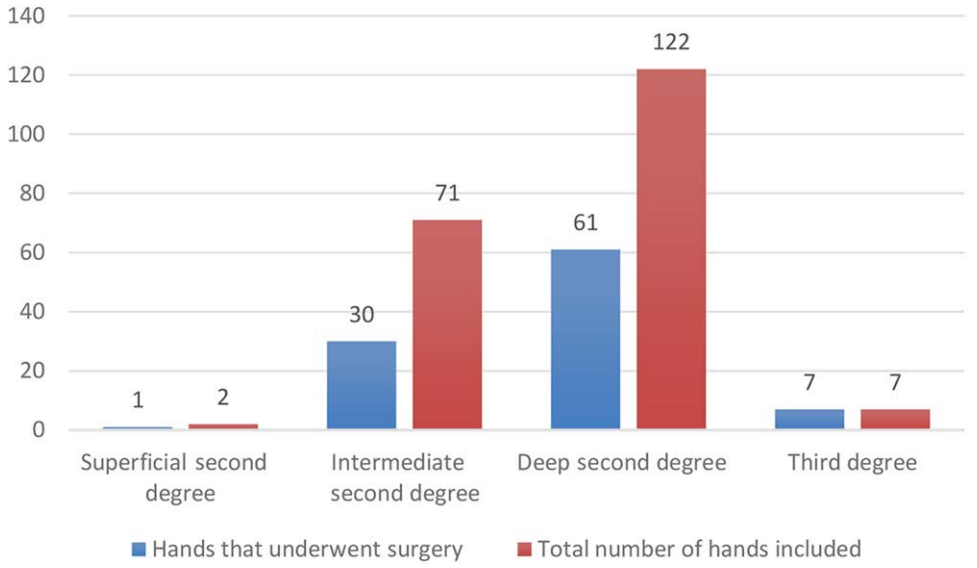

Fig. 2. Graphical data of the hands that underwent surgery after enzymatic debridement.

Table 2. Descriptive Statistics of Second-degree Deep Burns Group Revealing Significant Differences in % TBSA, and the Development of Hypertrophic/Retraction Scars

	Total No.	Sex	Median Age	Median % TBSA	Healing Time	Hipertrophy	Secondary Surgery
Conservative treatment	61	90.2% M 9.8% F	43 y IQR: 21	6% IQR: 8	31 d IQR: 19	35%	7.3%
Surgical treatment	61	75.4% M 24.6% F	37 y IQR: 25	17% IQR: 26	34 d IQR: 19	73.9%	21.27%
Mean (*P*) and statistical significance		$P = 0.5322$	$P = 0.1508$	$P = 0.00002421$ *	$P = 0.3343$	$P = 0.0004433$ *	$P = 0.7808$

No significant association was found between surgical treatment group and secondary revision surgery. IQR, interquartile range; M, male; F, female.
*$P < 0.05$ (statistical significance).

compared with 31 days (min 17, first Qu. 30, third Qu. 49, max 212) with conservative treatment. Four cases of deep dermal burns managed conservatively with Nexobrid are illustrated in Figures 3–6.

DISCUSSION

Historically, various debridement methods have been used for burns, with plant-derived products tracing back to 1600 BC.[15] Bromelain, the active ingredient in Nexobrid, is a proteolytic enzyme derived from pineapple fruit, initially described by Heinicke et al.[16] Nearly 30 years later, Klein et al[17] conducted the first randomized clinical trial on the enzyme's use for burn debridement, whereas Boswick et al[18] published a multicenter study investigating the efficacy of enzymatic debridement with bromelain the same year. However, results varied, potentially due to the lack of standardization in the product composition,[15] leading to uncertainty about the actual proportion of bromelain present and the discovery of up to four different proteolytic enzymes.[19]

In December 2012, Nexobrid, a bromelain-based product with standardized composition (0.09 g of bromelain per gram of product), received approval in Europe. The first multicenter study on its efficacy was published by Rosenberg et al,[11] which demonstrated faster debridement with reduced blood loss compared with tangential debridement. Additionally, Nexobrid minimized the need for skin autografting by selectively debriding while preserving more healthy dermis. Since then, Nexobrid has become an indispensable tool in burn centers for the early debridement of burn eschar, particularly in intermediate (mid-dermal) and second-degree deep burns.[20]

One of the anatomical areas frequently affected by burns is the hands and upper limbs,[21] posing a significant surgical challenge despite their limited contribution to the TBSA. This is due to the vital role of the hand in daily functionality, necessitating the preservation of proper mobility. It is essential to prioritize restoring hand mobility rather than solely focusing on wound closure, as hand contractures frequently develop due to burn trauma.[6,8,22] Since the widespread adoption of enzymatic debridement with Nexobrid for burns, it has become a standard practice in burn referral centers globally, including our own. However, the current standard of care (SOC) for burns typically involves tangential debridement followed by autografting. This conventional approach is nonselective and may inadvertently remove healthy dermis or dermis with healing potential, resulting in increased patient morbidity.[20] Consequently, there is a growing trend toward performing less-invasive procedures to minimize patient discomfort and optimize outcomes.[9] In our series, all Nexobrid debridements were 100% effective, successfully removing burn eschar and enabling precise examination of the burn bed. In our view, particularly in delicate areas like the hand with thin dermis and closed angles, preserving the dermal remnant as much as possible is crucial. This approach enhances the likelihood of spontaneous epithelialization, leading to improved aesthetic and functional outcomes.[7,23,24]

The majority of included hands in this study were categorized as second-degree deep burns (122, 60.4%). Before implementing Nexobrid in our center, patients with such burns were typically scheduled for early debridement and skin grafting (SOC), as we considered them to require early surgical debridement because it reduces the proinflammatory state and reduces the risk of infection due to the removal of devitalized tissue.[25–27] However, only 50% of these patients underwent intervention, indicating that enzymatic debridement could provide more accurate information about the dermal remnant in the burn bed.

This insight enables us to consider a conservative strategy whenever possible, thus avoiding tangential excision, which might unintentionally remove viable tissue and increase the depth of the burn. Our results revealed a significant association between surgery and the development of scar retraction ($P < 0.05$, OR: 5.149). Therefore, in our previous clinical practice, we would have performed 50% more tangential debridement in patients initially classified as second-degree deep burns, increasing the risk of scarring and morbidity. This would have led to a higher likelihood of revision surgery due to scar retraction.

When dealing with mid-dermal burns, assessing their potential for spontaneous healing during the initial evaluation can be challenging,[25] with some evolving favorably without the need for surgical treatment or on the contrary, requiring surgery for healing. In our series, mid-dermal burns accounted for 35.1% (71 hands), and 42.2% eventually underwent surgery (30 cases).

At present, the management of mid-dermal burns is uncertain, but it is known that deep second-degree and third-degree burns benefit from early debridement because it reduces the proinflammatory state and reduces the risk of infection due to the removal of devitalized tissue.[25–27] While some may heal without intervention, others

Fig. 3. Patient with initial assessment of deep dermal burns on both hands (A–B). Postdebridement with Nexobrid showing a bed with IIB (C–D) characteristics, so conservative measures are adopted. Hands fully healed without the need for surgical treatment (E–F).

Fig. 4. Patient with deep dermal burns on the dorsum of both hands and fingers with extension to the dorsum of both wrists (A–B). Assessment after Nexobrid showing an IIB bed, so conservative treatment is adopted (C–D). Epithelialization of the burn without the need for surgical treatment after 4 weeks (E).

Fig. 5. Patient with deep dermal burn in the left hand (A) with post enzymatic debridement wound evaluated as IIB (B) that underwent conservative treatment with Suprathel. Complete epithelialization after 4 weeks (C). Good aesthetic and functional results after 1 year follow-up (D).

may require surgery. Studies suggest that early debridement of mid-dermal burns could accelerate healing by removing the eschar, thus reducing infection risk and halting the proinflammatory cascade, facilitating cell migration and resulting in accelerated healing rates. However, these have shown no improvement in resulting scars.[28] Another study published in 2011 by Singer et al, in which enzymatic debridement was performed with Debrase (now Nexobrid, MediWound Ltd, Israel) on mid-dermal burns in pigs, showed faster epithelialization of these burns.[29] Before Nexobrid's introduction, mid-dermal burns were typically managed conservatively in our center, allowing them to evolve over 2–3 weeks, sometimes extending to 4 weeks based on clinical criteria, to maximize epithelialization.[24,30] The integration of Nexobrid into our protocol has changed our approach to mid-dermal burns. Following enzymatic debridement, we assess the burn bed to determine conservative or aggressive management. In our series, mid-dermal burns accounted for 35.1% (71 hands), with only 42.2% eventually requiring surgery (30 cases). In summary, 42.2% of mid-dermal burns and 50% of deep dermal burns required surgery. This underscores the potential for error during the clinical judgment of the precise depth of hand burns. Enzymatic debridement may serve as a diagnostic tool, preserving viable dermis that would otherwise be debrided in tangential excision by the surgeon.

In our series, we observed two cases of superficial second-degree hand burns treated with enzymatic debridement. Although Nexobrid is not typically indicated for

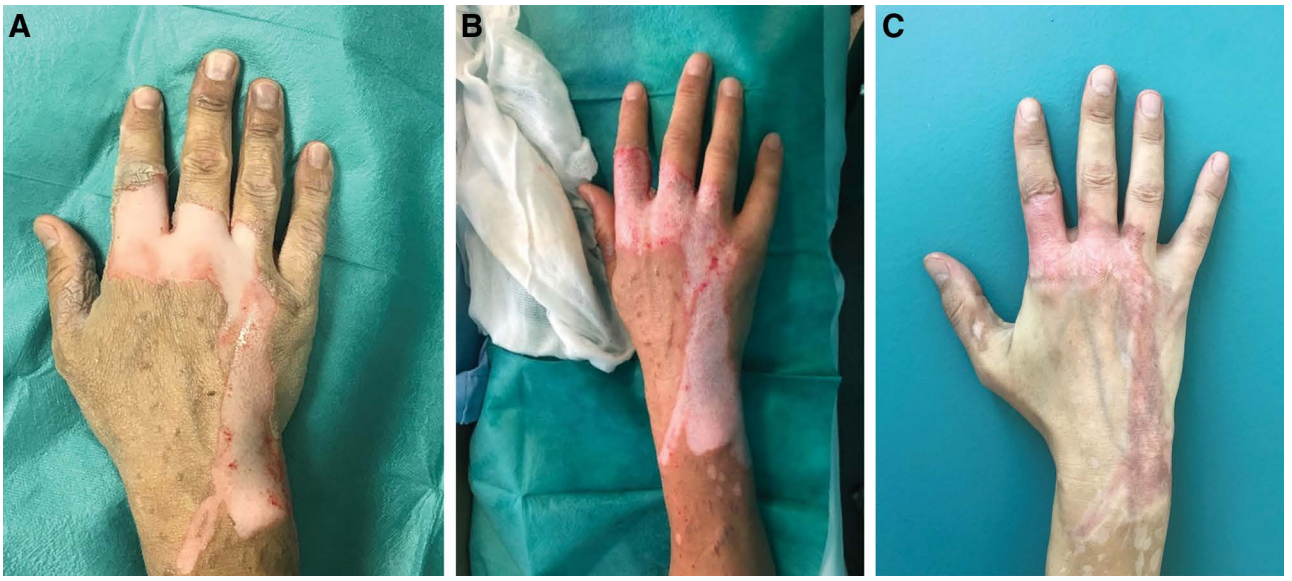

Fig. 6. Deep dermal burn on the right hand (A), which, after enzymatic debridement, shows a IIB bed (B) with correct epithelialization without the need for surgical treatment (C).

superficial second-degree burns, these patients underwent enzymatic debridement due to the presence of mid-dermal or deep burns on the upper limb that were being treated with Nexobrid. Following locoregional blockade, the product was also applied to the hand. However, one of these cases eventually required surgery due to a wound infection.

For effective enzymatic debridement, the product must be applied in a moist environment, which can pose challenges in cases of third-degree eschar, where proper penetration of the debriding agent may be hindered. However, the 2017 European consensus on Nexobrid usage[31] and its 2020 update[20] stipulated that enzymatic debridement could be considered in third-degree burns, especially in technically challenging areas with thin subcutaneous layers like the hands. The goal is to preserve structures deeper than the dermis, resulting in less aggressive surgical intervention.

In our series, all seven cases of third-degree burns underwent surgery as expected. Among them, five cases did not experience aesthetic or functional compromise after debridement and skin grafting. However, one case required commissuroplasties due to scar retraction. Another case was lost to follow-up.

In summary, growing evidence supports the efficacy of enzymatic debridement in refining our assessment of burn depth, enabling a more conservative therapeutic approach and potentially yielding superior healing outcomes, especially in mid-deep dermal burns, thereby enhancing the aesthetic and functional rehabilitation of hand burns.[6,13] In our study, 24 hands underwent surgery for scar sequelae of burns. Among these, 21 (87.5%) were in the group that received both enzymatic debridement with Nexobrid and subsequent surgery, whereas the remaining three were in the group treated with Nexobrid only, resulting in spontaneous epithelialization. Most of the procedures involved commissuroplasties (21 cases, 18 in the Nexobrid and surgery group, and three in the Nexobrid-only group), followed by two instances of finger arthrodesis and one case of groin flap for scar replacement on the dorsal side of the hand. Krieger et al[32] conducted a controlled animal study affirming that enzymatic debridement (Debridase, later Debrase, and now Nexobrid, MediWound Ltd, Israel) significantly reduced intracompartmental pressure in circumferential burns on the legs of the animals included in the study within 30 minutes of product application, thereby reducing burn induced compartmental syndrome. Subsequently, some authors corroborated these findings in patients treated with Nexobrid on their hands and upper limbs, performing an escharotomy using the enzymatic debriding agent to release intracompartmental pressure.[24,33] The 2017 European consensus on the guidelines for enzymatic debridement with Nexobrid[31] and its subsequent 2020 update,[20] along with the 2021 Italian[34] and 2022 Spanish updates,[30] strongly advocate for the use of enzymatic debridement to prevent burn induced compartmental syndrome. However, these recommendations do not extend to cases where burn-induced compartment syndrome is already established, or to high-voltage burns.

In our study, no hand required surgical escharotomy. Our experience supports the notion that surgical escharotomies can be circumvented if enzymatic debridement is applied in thermal burns, notably reducing tension at the level of the affected limb.

LIMITATIONS

Our study has several limitations that warrant consideration. Firstly, it is a retrospective observational study based on a database of collected patient data, introducing potential biases inherent to this study design. Additionally, the absence of a control group undergoing SOC, such as

surgical debridement and autografting, prevents us from conducting a prospective randomized comparative study. However, since 2015, our center has exclusively used enzymatic debridement as the primary approach for mid-dermal grade or deeper burns on the hands, resulting in negligible utilization of SOC in these cases. Another limitation is the loss of follow-up in some patients, with 62 hands (30.69%) lost to follow-up. This loss may impact the accuracy of our findings regarding the percentage of procedures for sequelae, as the outcomes could differ if all patients had been consistently followed up.

CONCLUSIONS

This study presents the largest series of burned hands enzymatically debrided using Nexobrid to date. Our findings suggest that enzymatic debridement can significantly reduce the number of procedures required for hand burns initially classified as deep by clinicians, which might otherwise have been deemed for early surgical debridement with an SOC approach. Out of the 122 burns clinically classified as deep, only 61 (50%) necessitated surgery. This decreased need for surgical intervention can be attributed to the surgeon's enhanced accuracy in assessing burn depth following eschar removal and wound bed evaluation, thus identifying burns that can heal spontaneously. Enzymatic debridement also improves the healing process by reducing the proinflammatory state and the risk of infection through selective eschar removal, allowing for a longer waiting time during the proliferation phase. Our findings indicate a decreased need for surgery to address burn sequelae after enzymatic debridement. In our study, only 24 hands underwent sequelae surgery, with most of them (21, 87.5%) being among the group that needed surgery after Nexobrid treatment, whereas only three (12.5%) were among those treated conservatively ($P < 0.001$).

Zhan Q. Lin Wu, MD
Passeig de la Vall d´Hebrón 119-129
Barcelona 08035, Spain
E-mail: zhanpacqiao@outlook.com

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

REFERENCES

1. Hettiaratchy S, Papini R. Initial management of a major burn: II—assessment and resuscitation. *BMJ.* 2004;329:101–103.
2. Papini R. Management of burn injuries of various depths. *BMJ.* 2004;329:158–160.
3. Barret J, Gomez P, Solano I, et al. Epidemiology and mortality of adult burns in Catalonia. *Burns.* 1999;25:325–329.
4. World Health Organization. Burns. Available at https://www.who.int/news-room/fact-sheets/detail/burns. Published 2018. Accessed March 24, 2022.
5. García-Díaz A, Durán-Romero AJ, Carbajal-Guerrero J, et al. Trends in burn injury mortality in Spain (1979–2018): sex-specific age-cohort-period effects. *Burns.* 2021;47:714–720.
6. Krieger Y, Bogdanov-Berezovsky A, Gurfinkel R, et al. Efficacy of enzymatic debridement of deeply burned hands. *Burns.* 2012;38:108–112.
7. Rivas-Nicolls D, Aguilera-Saez J, Gallardo-Calero I, et al. Does enzymatic debridement allow us to perform conservative treatment on clinically deep hand burns? A retrospective review. *Ann Burns Fire Disasters.* 2020;33:239–244. PMID: 33304215
8. van Zuijlen PP, Kreis RW, Vloemans A, et al. The prognostic factors regarding long-term functional outcome of full-thickness hand burns. *Burns.* 1999;25:709–714.
9. Cherubino M, Valdatta L, Baroni T, et al. Selective enzymatic debridement for the management of acute upper limb burns. *Ann Burns Fire Disasters.* 2021;34:328–333. PMID: 35035327
10. Rosenberg L, Shoham Y, Krieger Y, et al. Minimally invasive burn care: a review of seven clinical studies of rapid and selective debridement using a bromelain-based debriding enzyme (Nexobrid). *Ann Burns Fire Disasters.* 2015;28:264–274. PMID: 33304215
11. Rosenberg L, Krieger Y, Bogdanov-Berezovski A, et al. A novel rapid and selective enzymatic debridement agent for burn wound management: a multi-center RCT. *Burns.* 2014;40:466–474.
12. Rosenberg L, Lapid O, Bogdanov-Berezovsky A, et al. Safety and efficacy of a proteolytic enzyme for enzymatic burn debridement: a preliminary report. *Burns.* 2004;30:843–850.
13. Palao R, Aguilera-Sáez J, Serracanta J, et al. Use of a selective enzymatic debridement agent (Nexobrid) for wound management: learning curve. *World J Dermatol.* 2017;6:32–41.
14. Martínez-Méndez J, Serracanta-Domènech J, Monclús-Fuertes E, et al. Guía clínica de consenso en el uso de desbridamiento enzimático en quemaduras con NexoBrid [Consensus guideline about the use of enzymatic debridement in burn injuries with Nexobrid]. *Cir Plást Ibero-Latinoam* 2017;43:193–202.
15. Heitzmann W, Fuchs PC, Schiefer JL. Historical perspectives on the development of current standards of care for enzymatic debridement. *Medicina.* 2020;56:706.
16. Heinicke R, Gortner W. Stem bromelain—a new protease preparation from pineapple plants. *Econ Bot.* 1957;11:225–234.
17. Klein GK. Historical development of bromelain in the treatment of burn wounds. In *Care of the Burn Wound.* Karger Publishers; 1985:90–96.
18. Boswick JA. Clinical experience with a new enzymatic debriding agent. In *Care of the Burn Wound.* Karger Publishers; 1985:97–100.
19. Rowan A, Christopher C, Kelley S, et al. Debridement of experimental full-thickness skin burns of rats with enzyme fractions derived from pineapple stem. *Burns.* 1990;16:243–246.
20. Hirche C, Kreken Almeland S, Dheansa B, Fuchs P, et al. Eschar removal by bromelain based enzymatic debridement (Nexobrid) in burns: European consensus guidelines update. *Burns.* 2020;46:782–796.
21. Smith MA, Munster AM, Spence RJ. Burns of the hand and upper limb—a review. *Burns.* 1998;24:493–505.
22. Schneider JC, Holavanahalli R, Helm P, et al. Contractures in burn injury part II: investigating joints of the hand. *J Burn Care Res.* 2008;29:606–613.
23. Krieger Y, Rubin G, Schulz A, et al. Bromelain-based enzymatic debridement and minimal invasive modality (MIM) care of deeply burned hands. *Ann Burns Fire Disasters.* 2017;30:198–204. PMID: 27857653
24. Schulz A, Shoham Y, Rosenberg L, et al. Enzymatic versus traditional surgical debridement of severely burned hands: a comparison of selectivity, efficacy, healing time, and three-month scar quality. *J Burn Care Res.* 2017;38:e745–e755.
25. Palao Domenech R. *Quemados. Valoración y Criterios de Actuación.* 1st ed. Barcelona, Spain: Marge Medica Books; 2009.
26. Barret JP, Herndon DN. Effects of burn wound excision on bacterial colonization and invasion. *Plast Reconstr Surg.* 2003;111:744–50; discussion 751.

27. Ziegler B, Fischer S, Pieper D, et al. Evidence and trends in burn wound debridement: an evidence map. *Plast Surg*. 2020;28:232–242.
28. Macri LK, Singer AJ, McClain SA, et al. Immediate tangential excision accelerates wound closure but does not reduce scarring of mid-dermal porcine burns. *Ann Burns Fire Disasters*. 2016;29:54–61. PMID: 27857653
29. Singer AJ, Taira BR, Anderson R, et al. Reepithelialization of mid-dermal porcine burns after rapid enzymatic debridement with Debrase. *J Burn Care Res*. 2011;32:647–653.
30. Serracanta J, Baena J, Martinez-Mendez JR, et al. Bromelain-based enzymatic burn debridement: Spanish multidisciplinary consensus. *Eur J Plast Surg*. 2022;46:271–279.
31. Hirche C, Citterio A, Hoeksema H, et al. Eschar removal by bromelain based enzymatic debridement (Nexobrid) in burns: an European consensus. *Burns*. 2017;43:1640–1653.
32. Krieger Y, Rosenberg L, Lapid O, et al. Escharotomy with an enzymatic debridement agent for treating experimental burn-induced compartment syndrome in an animal model. *J Trauma Acute Care Surg*. 2005;58:1259–1264.
33. Fischer S, Haug V, Diehm Y, et al. Feasibility and safety of enzymatic debridement for the prevention of operative escharotomy in circumferential deep burns of the distal upper extremity. *Surgery*. 2019;165:1100–1105.
34. Ranno R, Vestita M, Maggio G, et al. Italian recommendations on enzymatic debridement in burn surgery. *Burns*. 2021;47:408–416.