

# MINIMALLY INVASIVE BURN CARE: A REVIEW OF SEVEN CLINICAL STUDIES OF RAPID AND SELECTIVE DEBRIDEMENT USING A BROMELAIN-BASED DEBRIDING ENZYME (NEXOBRID®)

## SOINS MINI-INVASIFS AUX BRÛLÉS: REVUE DE SEPT ÉTUDES CLINIQUES PORTANT SUR LA DÉTERSION RAPIDE ET SÉLECTIVE AU MOYEN D'UN ENZYME LYTIQUE DÉRIVÉ DE LA BROMÉLAÏNE (NEXOBRID®)

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**SUMMARY.** Current surgical and non-surgical eschar removal-debridement techniques are invasive or ineffective. A bromelain-based rapid and selective enzymatic debriding agent was developed to overcome these disadvantages and compared with the standard of care (SOC). The safety and efficacy of a novel Debriding Gel Dressing (DGD) was determined in patients with deep partial and full thickness burns covering up to 67% total body surface area (TBSA). This review summarizes data from seven studies, four of which were randomized clinical trials that included a SOC or control vehicle. DGD eschar debridement efficacy was >90% in all studies, comparable to the SOC and significantly greater than the control vehicle. The total area excised was less in patients treated with DGD compared with the control vehicle (22.9% vs. 73.2%,  $P < 0.001$ ) or the surgical/non-surgical SOC (50.5%,  $P = 0.006$ ). The incidence of surgical debridement in patients treated with DGD was lower than the SOC (40/163 [24.5%] vs. 119/170 [70.0%],  $P < 0.001$ ). Less autografting was used in all studies. Long-term scar quality and function were similar in DGD- and SOC-treated. DGD is a safe and effective method of burn debridement that offers an alternative to surgical and non-surgical SOC.

**Keywords:** burns, enzymatic debridement, NexoBrid®, enzymatic escharotomy, debriding gel dressing, DGD

**RÉSUMÉ.** Les protocoles actuels de détersion d'une brûlure, chirurgicaux et non chirurgicaux, sont soit invasifs soit inefficaces. Un enzyme détersion rapide et spécifique, dérivé de la bromélaïne, a été développé dans le but de palier à ces 2 inconvénients. Il a été comparé aux techniques usuelles (TU). L'efficacité et l'innocuité d'un Gel Topique Détersion (GTD) ont été évaluées chez des patients souffrant de brûlures intermédiaires et profondes atteignant jusqu'à 67% de la Surface Corporelle Totale (SCT). Cette revue compile les données de 7 études cliniques, dont 4, randomisées, faisaient appel aux TU ou à un groupe contrôle. La détersion obtenue avec GTD était toujours > 90%, comparable aux TU et meilleure que dans le groupe contrôle. La surface relative excisée totale était moindre après GTD que chez les contrôles (22.9% VS 73.2%,  $p < 0,001$ ) ou les patients sous TU (50.5%,  $p = 0,006$ ). Le nombre de patients ayant eu besoin de chirurgie a été inférieur dans le groupe GTD que dans le groupe TU (40/163 [24.5%] VS 119/170 [70%],  $p < 0,001$ ). Le recours aux greffes était moins fréquent dans toutes les études. Les qualités cicatricielle et fonctionnelle à distance étaient comparables après TU et GTD. GTD est une technique de détersion efficace et sûre qui offre une alternative au TU, chirurgical ou non.

**Mots clés:** brûlure, détersion enzymatique, NexoBrid®, excision enzymatique, Gel Topique Détersion, GTD

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## Introduction

Burns are common and often devastating injuries that can result in significant morbidity and mortality. Unlike other wounds, burns are characterized by the presence of a denatured protein necrotic eschar that covers the injured skin, inducing an inflammatory reaction, delaying healing and increasing the risks of infection and subsequent scarring. As a result, removal or debridement of the burn eschar is a cornerstone of modern burn care. Traditionally, the burn eschar is removed by non-surgical means (autolysis) or surgical, excisional debridement. While effective, surgical excision is invasive and traumatic, requiring specialized personnel and facilities. In addition, surgical excision of the eschar results in significant blood and heat loss. Due to poor selectivity, surgical excision often sacrifices viable skin together with necrotic tissue.<sup>1</sup> Significant dermal losses decrease the ability of partial thickness and mixed depth burns to heal spontaneously, requiring the use of autologous skin grafts or other permanent wound covers. Non-surgical debridement involves an inflammatory/infectious process with local and systemic complications. In such a process, complete debridement may be achieved after up to two weeks. However, this process results in significant local and systemic complications, including extension of the burn depth by transformation of the zones of hyperemia and stasis into a zone of necrosis, and the development of granulation tissue that leads to deforming scars.

Rapid and selective chemical/enzymatic debridement has the potential to offer an alternative to both surgical and non-surgical methods of eschar removal. However, currently approved agents, such as collagenase, are limited by their slow action and poor efficacy.<sup>2</sup> Debriding gel dressing (DGD) is a bromelain-based enzymatic medical grade agent derived from the stems of pineapples that results in rapid and selective debridement of the necrotic eschar. This agent has been evaluated in several pre-clinical and clinical studies.<sup>3-11</sup> Numerous in-vivo studies have demonstrated that DGD removes the entire eschar without harming viable tissue, exposing a clean wound bed of viable dermis or the subdermal tissue.<sup>9, 11-14</sup> Enzymatic debridement with DGD also reduces elevated interstitial compartment pressures in circumferential extremity burns, functioning as a non-surgical method of escharotomy.<sup>5</sup>

We reviewed the results of seven consecutive clinical studies, assessing the efficacy and safety of DGD on burns and its possible impact on burn care. If confirmed to be safe and effective, enzymatic debridement with DGD may provide a new, minimally invasive alternative modality to the present surgical and non-surgical eschar removal strategies.

## Methods

### *Study design and population*

All participants provided written, informed consent, with consent obtained before any study-specific procedures were undertaken. All studies were approved by the participating Institutional Review Boards and were conducted in accordance with national and international guidelines. A summary of the study designs is presented in *Table I*.

**Table I** - Summary of the seven studies

Study No.	Design	Patients	Inclusion criteria	Comparator(s)
1	Open-label	154	Age 5m-82yrs TBSA<67%	None
2	Blinded RCT	20	Age 18-70yrs TBSA<15%	1, 2, 4 gm DGD
3	Open-label, RCT	140	Age 18-70yrs TBSA<30%	DGD, vehicle, SOC
4	Open-label, RCT	30	Age 18-65yrs TBSA<10%	DGD, vehicle, SOC
5	Open-label	33	Age 4-70yrs TBSA 4-30%	None
6	Open-label, RCT	156	Age 4-55yrs TBSA 5-30%	DGD, SOC
7	Assessor- blinded RCT, no drug	89	Age 4-55yrs TBSA 5-30%	DGD, SOC

### *Study 1 (1985-2000)*

This was an open-label, prospective, single arm, non-comparator study that included retrospectively-collected data on 154 patients aged 5 months to 82 years, admitted to a single burn unit with deep partial or full thickness burns covering up to 67% TBSA, treated with DGD as a part of the burn care routine of this burn unit. The primary endpoints were percentage of eschar removed and time to wound closure.

### *Study 2 (2002-2005)*

This was a randomized, controlled, blinded, dose-ranging study aimed at evaluating the safety and efficacy of three doses of DGD (1, 2, or 4 grams in 20 ml of gel per 1% TBSA) in 20 hospitalized burn patients aged 18-70 with deep partial or full thickness burns covering up to 15% TBSA. The primary outcome in this study was time to >95% wound closure or reepithelialization. Secondary outcomes were number of debridement procedures and percentage debridement of the burn eschar.

### *Study 3 (2003-2005)*

This was a randomized, open-label, Food and Drug

Administration (FDA) controlled investigational new drug (IND) study in 18 burn centres (in eight countries), that included 140 patients aged 18-70 with deep partial or full-thickness burns covering up to 30% TBSA. Patients were randomized in a 2:1:1 ratio to DGD (2 gm/1% TBSA), gel vehicle, or standard of care (surgical or non-surgical). In this study, facial and hand burns were excluded and only a single anatomical area ("target wound") was treated with DGD.

#### *Study 4 (2006-2007)*

This was a randomized, open-label, FDA controlled IND study that compared treatment with DGD (n=10), gel vehicle (n=9) and SOC (n=11) in healthy adult patients aged 18-65 with deep partial or full thickness burns of up to 10% TBSA. In this study, facial and hand burns were excluded from treatment with DGD.

#### *Study 5 (2009-2013)*

This is an open-label, single arm, safety and efficacy study that mainly evaluates the systemic absorption of DGD using a specially formulated ELISA kit in patients aged 4-55 with partial and full thickness burns of 4-30% TBSA. This study is still ongoing, with data available for 33 patients.

#### *Study 6 (2006-2010)*

This was a phase three, European Medicines Agency (EMA), confirmatory, randomized, controlled, open-label study assessing the safety and efficacy of DGD in comparison with SOC in patients aged 4-55 with deep partial and full thickness burns of 5-30% TBSA.<sup>11</sup> In this study, hand burns were included but facial burns were excluded. Of all patients enrolled, 75 were randomized to DGD, and 81 were randomized to SOC. In addition, one patient in each centre, the first patient enrolled (26 in total), served as a training patient. These training patients had only their safety data included in the analyses.

#### *Study 7 (2011)*

This was a multi-centre, assessor-blinded study designed to evaluate the long-term (2-4 years from wound closure) scar quality in patients that participated in Study 6. Of the 182 participants in Study 6, 89 patients (54 treated with DGD and 35 with SOC) could be traced and assessed for long-term follow-up data. Scar quality was assessed by blinded assessors using the Modified Vancouver Scar Scale (MVSS), which includes scar vascularity, height, pigmentation, pliability, pruritus and pain.<sup>14</sup>

#### *Study interventions*

In all controlled studies, data collection was performed using an electronic, computerized instrument (eCRF Target Health Ltd., New York, NY) and treatment allocation

was assigned by a computerized randomization program. All burns were cleaned with soap and water, remaining blisters were removed and a bulky, saline-soaked dressing was applied to the wound to prevent desiccation. After removal of the dressing, an experienced burn surgeon assessed the burn depth based on visual inspection. While laser Doppler imaging (LDI) is more accurate, it is rarely used in clinical sites, including those in the studies. Furthermore, LDI is only accurate after 3-5 days, while the clinical assessments in the study were often made much earlier since the debriding agent is intended to be used as early as possible after injury.

#### *DGD arm*

The burns were covered with a 1-3 mm thick layer of DGD (2 gm enzymatic powder in 20 ml gel vehicle per 1% TBSA of an adult). The area was then covered with a sterile polyurethane occlusive sheet that was sealed to the surrounding normal skin with sterile petrolatum ointment to contain the DGD for a period of four hours. After noting that DGD application was painful in some patients, the study protocols were adjusted to include administration of an analgesic 10-15 minutes prior to application of DGD. The analgesic agent, dose and administration route were similar to those given during extensive burn dressing changes and at the discretion of the treating physician. Four hours after application, DGD was removed and the wound was scrubbed with an abrasive sponge soaked in normal saline or with a blunt wooden tongue depressor until the appearance of a clean, bleeding wound bed. The wounds were then further dressed with "wet-to-dry" dressings containing saline and antibacterial agents (e.g., hypertonic saline, 3% Mafenide acetate, 0.1 % chlorhexidine) for another two hours to remove any remaining DGD and dissolved eschar. The efficacy of eschar removal was assessed only after the removal of these "wet to dry" soakings.

*Care of the debrided wound bed:* when debridement was considered complete and there was enough residual viable dermis with a potential for spontaneous reepithelialization and healing, further topical treatment was aimed at preserving the viable dermis (mainly preventing desiccation) and promoting healing. If debridement was complete yet there was a large full-thickness defect, the area was autografted as early as possible. If autografting was not an option, or had to be delayed, a temporary skin substitute was used to cover the defect. If debridement was complete, leaving a mixed wound bed of viable dermis and areas of deep dermal and full-thickness defects, the wound was covered with a skin substitute for up to three weeks to exploit the reepithelialization potential, followed by autografting of any remaining non-epithelialized areas.

### SOC arm

The current standard method for burn eschar removal is either surgical or non-surgical debridement, depending mainly on the initial diagnosis of burn depth. Burns diagnosed as “deep” (i.e., deep partial and full thickness burns that were unlikely to heal spontaneously without scar formation) were surgically excised as early as possible followed by permanent wound closure (e.g., autograft or Integra). Surgical excisional debridement (mainly tangential excision or dermabrasion/hydrosurgery) is the only available debridement method that can remove the offending eschar as early as the diagnosis of a deep burn is made and as soon as surgery is possible. In most cases, surgically debrided burns lose most or all of their dermis, necessitating autografting or other permanent wound coverage to heal the wound with acceptable scarring. Autografts were harvested from patients’ healthy donor sites that were treated conservatively until spontaneous healing occurred. Since grafts only “take” on a completely debrided and clean wound bed, the goal of graft “take” biases surgical debridement towards sacrificing the deeper wound bed in order not to lose the graft.<sup>1</sup> As a result, though graft “take” is often considered the hallmark of a thoroughly debrided and viable wound bed, one should be aware of the fact that other factors may cause graft failure (e.g., fluid collection, sheering, insufficient stabilization, excessive pressure, swelling and edema following hydrostatic pressure or vacuum, infection or trauma).

Burns diagnosed as more superficial, partial thickness, judged to have a thick dermal layer under the eschar, were usually treated by slow non-surgical debridement, using daily dressings, topical medications, scrubbing, bathing and soaking until the eschar macerated (“autolysis”) and sloughed after 10-20 days. During this period, superficial burns start to epithelialize, while deeper ones develop granulation tissue that needs to be surgically excised and grafted rapidly in order to reduce scarring. Full thickness defects, if diagnosed early, were closed by autografting or other permanent skin substitutes after excision, but often grafting was performed on a granulating bed leading to less than optimal results.

In burns where the diagnosis was unclear (“indeterminate”), treatment usually started with several days of non-surgical dressings until a clearer diagnosis could be made. The more superficial burns were managed with non-surgical care whereas the deeper ones were excised as soon as possible. This indeterminate group was the largest group of burns, including burns of all depths in different proportions. Due to their heterogeneity and objective difficulty in assessing the different depths, an early diagnosis-based treatment was often impossible.

### Outcomes and measures

Based on the individual study, various combinations

**Table II** - Endpoints

Endpoint	Study
Efficacy of eschar removal	All studies
Time to complete debridement	All studies
% wound excised, % wounds autografted	Studies #2, #6 (phases 2&3)
Time to wound closure	All studies
Hand burns and escharotomy	Studies #1 (retro), #6
Cosmesis & function (QOL) at 2-4 years	Study #7 (Phase 3b)

of the following outcomes were measured (*Table II*): (1) efficacy of eschar removal; (2) time to complete (>90%) burn debridement; (3) incidence of surgical excision; (4) percentage area of burn surgically excised; (5) incidence of autografting and area autografted; (6) need for escharotomy in hand/foot burns; (6) time to complete wound closure; and (7) long-term scar quality.

The primary outcome in most studies was the efficacy of debridement, defined as the percentage of the original eschar that was removed after application of the study agent. The need for surgical excision served as a surrogate marker for debridement efficacy and was measured as the incidence and percentage area of burns requiring any surgical excisional debridement. The incidence and total wound area requiring autografting after excision were surrogate markers for debridement selectivity, as the more selective the eschar removal the more viable dermis remains, allowing for spontaneous epithelialization with a reduced need for grafting. A reduction in the total wound area requiring autografting is not only an indicator of selectivity but is also of major clinical benefit if the physician indeed decides to wait for spontaneous epithelialization. Additional measures were the rate of successful graft “take” and time to complete wound reepithelialization or closure. Adverse events were monitored in all studies.

Data management was performed by Target Health LTD (New York, NY) or Medistat LTD (New Hyde Park, NY) and statistical analyses for all studies were performed by MediWound LTD (Yavneh, Israel). All the studies were carefully reviewed by the EMA or the FDA.

### Statistical Analyses

Efficacy analyses used the intention-to-treat principle. Continuous data are presented as means with standard deviations and compared among groups with analysis of variance (ANOVA) or pair-wise t-tests. Binary data are presented as the percentage frequency of occurrence and compared with  $X^2$  or Fisher’s exact test as appropriate. Data analysis was performed with SPSS for Windows (SPSS Inc., Chicago, IL).

### Role of the funding source

The last five studies were funded by MediWound

(Yavneh, Israel), the manufacturer of DGD (under the name of Debrase or NexoBrid). All authors had full access to the data, and the corresponding author had the final decision to submit for publication.

## Results

The demographic and clinical characteristics of the study patients are summarized in *Table I*.

### *Efficacy of eschar removal*

Debridement data from the first study was available in 388 of 400 wounds. Complete debridement was achieved in 91.8±/17.5% of the areas exposed to DGD in a single four-hour application. In 329 wounds (61.6%) a debridement level of greater than 90% was achieved, and in 98 wounds (25.3%) a debridement level of greater than 65% was attained. In the second, dose-ranging study, all the patients required only one application of DGD, and debridement efficacy was similar in all three groups (1 gm 98.9%, 2 gm 100%, and 4 gm 99.1%). Data from the third and fourth comparative studies demonstrated that the eschar was successfully removed from 92.5% of the treated wound area in the DGD group as compared to 94.7% in the SOC group (P=NS). Burns treated with the vehicle gel demonstrated negligible if any eschar debridement (2.8% eschar removed in one patient). In the fifth study, successful eschar removal was achieved in 97.7% of cases. Following termination of the four-hour treatment with the gel vehicle, patients in this group were all treated by the SOC. A second application of DGD was required in 14.3% of the wounds in the third study and in none of the wounds in the fourth study.

Data from the phase three RCT demonstrated that 90.5% (67/74) of the DGD-treated patients had successful removal of the eschar compared with 90.1% (73/81) of the SOC-treated patients (P=NS).

### *Time to complete eschar removal*

Data from the third, comparative study shows that there was no significant difference in time to initiate the initial debridement procedure between the DGD and control groups (1.6 vs. 1.7 days respectively, P=0.81). However, there was a significant difference between DGD and SOC groups in the time to complete the initial debridement procedure (1.6 vs. 14.3 days from injury, respectively, P<0.001). Data from the sixth RCT shows that the time to achieve successful eschar removal was significantly shorter in the DGD vs. the SOC group (2.2 vs. 8.7 days from injury, respectively, P<0.001).

### *Incidence of excision and area of wound excised*

In the first, non-comparative study, surgical excision was required in 35/397 (8.8%) patients treated with DGD.

In the second, dose-ranging study, surgical excision was not required in any of the patients treated with DGD. In the third, phase two comparative study, the total area surgically excised was significantly lower in DGD-treated patients compared with patients treated with the gel vehicle (22.9% vs. 73.2%, P<0.001) or with the SOC (50.5%, P=0.006). In the sixth, phase three RCT the rate of surgical excision was significantly lower in DGD-treated patients compared to patients treated with the SOC (40/163), 24.5% vs. (119/170) 70.0%, (P<0.001). The total area surgically excised was also significantly lower in DGD-treated patients compared with patients treated with the SOC (13.1% vs. 56.7%, P<0.001).

### *Area of wound autografted*

In the first study, a total of 171/397 wounds (43.1%) that were treated with DGD and required skin grafting were assessed for %TBSA grafted; all of these wounds were mixed dermal or third degree burns. The mean area of all the wounds was 2.7 + 1.9 %TBSA pre-debridement vs. 0.8 + 1.5 %TBSA grafted. Thus, only 30% of the original burns that were debrided required grafting. This difference was statistically significant (p<0.001).

In the fifth study, the incidence of grafting was 26.5% (9/34) and the mean percentage of the burn area that was autografted was 14.2 ± 32.9%.

In the sixth, phase three study, the wound area autografted was evaluated in deep partial thickness wounds. Wounds that were entirely full thickness or had full thickness areas were excluded from the analysis of percentage of wound area autografted as such wounds require autografting regardless of the debriding method. In this study, the incidence of deep partial thickness wounds that were autografted was 17.9% (19/106 wounds) compared to 34.1% (30/88 wounds) in the SOC group. Moreover, these deep partial thickness wounds also had significantly less wound area autografted in the DGD group (8.4%) compared to the SOC group (21.5%; P=0.005). In the subset of children, the incidence of deep partial thickness wounds that were autografted was 21.7% in the DGD group (5/23 wounds) compared to 31.8% (7/22 wounds) in the SOC, and the area autografted was also lower in the DGD group (6.1%) compared to the SOC group (24.5%).

### *Time to wound closure*

Time to wound closure depends more on the wound closure strategy (fast autografting or slower epithelialization) than on the debridement phase. Wound closure was used mainly as a safety measure in order to exclude a negative influence of DGD on this process. In the first study, dates of complete wound closure were recorded per wound for all patients, if known. Data were available for 135 patients (87.7%); however, there was no information for 19 patients (12.3%). The mean time to wound closure was

25.7 ± 19.5 days. Approximately 70% of all the wounds achieved wound closure within 30 days from the last debridement. The remaining 30% of the wounds closed between 30-130 days.

Of the DGD debrided, operated (grafted) wounds, approximately 25% reached wound closure by day 10 compared to 10% of the non-operated wounds, probably due to early skin grafting. Between days 10-15, there was a change in this trend and more non-operated wounds reached wound closure before the operated ones, probably due to delayed skin grafting.

In the second study, the primary efficacy endpoint was wound closure as measured by >95% closure (spontaneous epithelialization or graft take). The mean time to >95% epithelialization (for all wounds) from last debridement was 21.6 ± 2.4 days, 12.6 ± 5.1 days and 19.1 ± 8.1 days respectively, for the 1g, 2g and 4g DGD treatment groups. The median time to >95% epithelialization from last debridement was 20.0, 14.0 and 16.0 days respectively for the 1g, 2g and 4g DGD treatment groups.

In the third, phase two study, the mean time from injury to complete wound closure was 34.7 days for the DGD group, 37.0 days for the vehicle group and 32.4 days for the SOC (P = 0.675).

In the fourth study, the mean time to complete wound closure from the date of randomization was 42.5 ± 6.9 days for the DGD group, 30.6 ± 10.8 days for the vehicle and 30.4 ± 10.2 days for the SOC treatment groups. However, this data was skewed by a single patient in the DGD group (the very first one) in whom wound closure took 56 days. Similar results were seen in the fifth study. The mean time to complete wound closure from signing of informed consent was 31.8 ± 22.7 (n=68 wounds) days for the DGD group. In the sixth study, based on a per-wound analysis, the difference in time to wound closure was neither statistically nor clinically significant; the mean time to wound closure was 31.3 ± 16.9 days in the DGD group compared to 27.4 ± 15.9 days in the SOC group.

In a post-hoc analysis, a positive correlation was found between autografts performed (Yes/No and % wound area autografted) and time to wound closure in the DGD group but not in the SOC group. When wound closure results were adjusted for % wound area autografted as well as the interaction between the groups, there was no significant difference between the groups in time from randomization to wound closure based on a per subject analysis.

The positive correlation between autografting and time to wound closure is in line with the expected wound closure time by autografting. Among adult subjects, the time from randomization to complete wound closure was longer in the DGD group (mean 37.8 days) vs. the SOC group (mean 27.9 days). In contrast, among children (≤18 years), mean time to wound closure was 29.9 days in the DGD group compared to 32.1 days in the SOC group.

#### *Blood loss*

During the sixth study, changes in hemoglobin and hematocrit over the 24 hours before and after debridement were recorded. The drop in hemoglobin was lower in patients treated with DGD vs. SOC (0.52 ± 0.96 vs. 1.04 ± 1.03 gm/L respectively). The drop in hematocrit was also lower in patients treated with DGD vs. SOC (3 ± 6% vs. 5 ± 5% respectively).

#### *Long-term scar assessment*

In the seventh study, cosmetic outcome based on the modified VSS was similar in patients treated with DGD vs. SOC (3.12 ± 2.55 vs. 3.38 ± 2.56 respectively). The use of pressure garments or silicone sheets for scar management as well as the need for surgical scar revision were lower among patients treated with DGD vs. SOC (27.8% vs. 34.3% and 3.7% vs. 8.6% respectively); however these differences were not statistically significant. There were less donor site scars among patients randomized to DGD vs. SOC (40% vs. 68%, P = 0.01). There were no differences in quality of life in patients treated with DGD vs. SOC measured with the Short Form 36 in adults (51.3 ± 11.5 vs. 52.3 ± 11.5 respectively) or the Burn Outcomes Questionnaire in children (118.7 ± 7.6 vs. 121.6 ± 13.0 respectively).

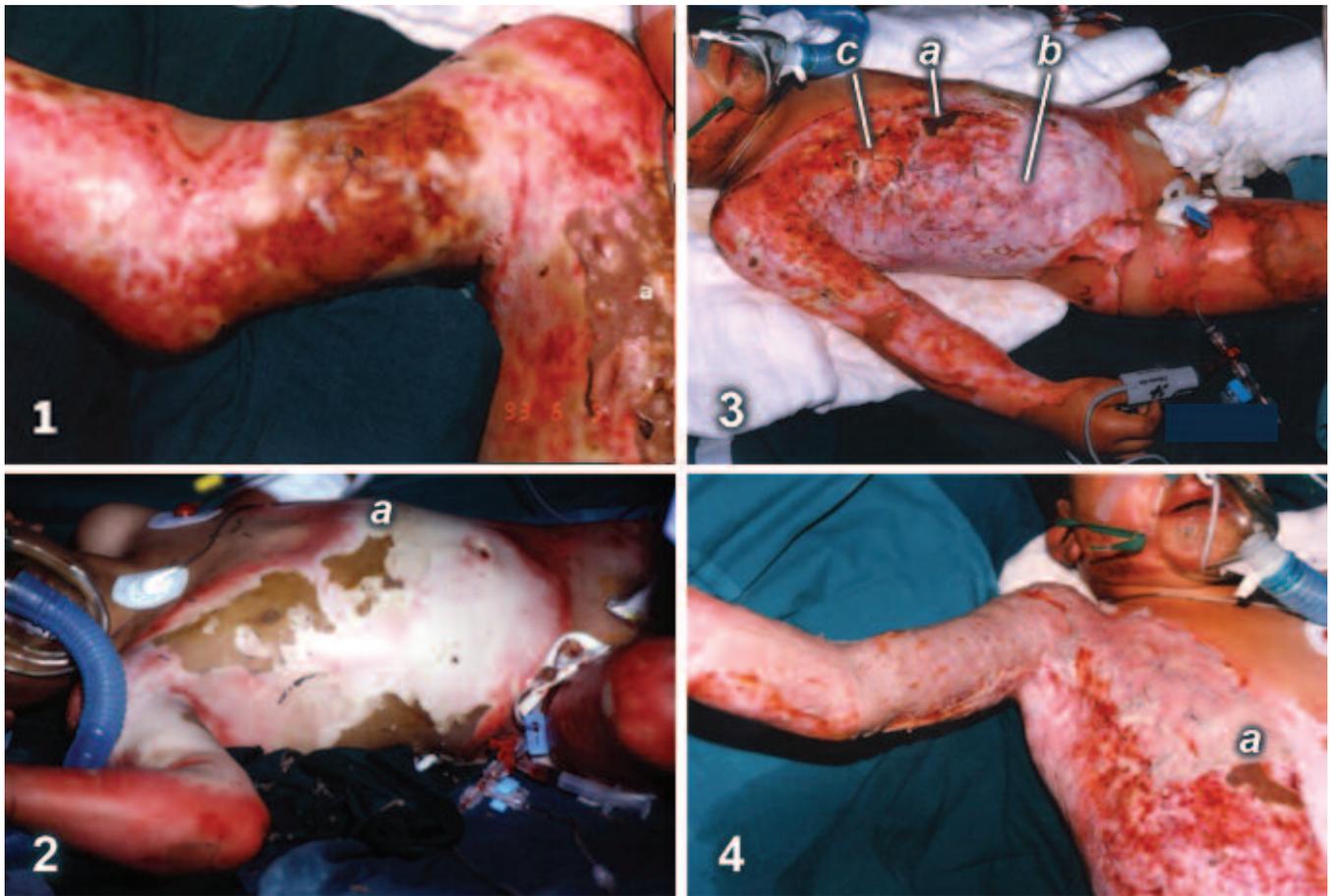
#### *Hand burns: need for escharotomy and excision in hand wounds*

In the first and sixth studies, DGD was used to treat 163 hand burns in 101 patients, of which 33 were children. While none of the DGD-treated hand burns required an escharotomy to relieve elevated compartment pressures, 4/41 (9.7%) of hand burns treated with the SOC required an escharotomy.

In the phase three RCT, 31 hand burns in 24 patients were treated with DGD while 41 hand burns in 28 patients were treated with the SOC. Autografting of the hand burns was significantly reduced in burns treated with DGD (of which 5 had full thickness burns) compared with SOC (of which 7 had full thickness burns): 6/31 [19.3%] vs. 23/41 [56.1%] respectively.

#### *Results in children (age <18 years)*

Of the 154 patients in the first study, 77 were children. In this subgroup, results were slightly better than in adults. Regarding efficacy of debridement, 92.0% of the treated area was successfully debrided in children vs. 90.3% in adults. Time to wound closure was 21.4 ± 16.5 days in children and 22.9 ± 16.2 days in adults. Among the 156 randomized patients in the sixth study, 31 were children (15 were treated with DGD and 16 with the SOC). In this study as well, results were better in children. Complete debridement was achieved in 100% of the children vs. 93.8% of the adults treated with DGD. Time to complete de-



**Fig. 1** - A 6-year-old boy with 67% TBSA deep flame burns. Before (1) and after (2) cleansing. Note remaining charred blisters (a). Following initial DGD debridement under analgesia and sedation (2). All eschars were completely removed except the small area covered with the blister where poor contact with DGD resulted in incomplete debridement (3a and 4a). Full thickness burns demonstrate underlying exposed fat (3c). Deep dermal burns appear white and glistening (3b).

bridement was significantly shorter in children treated with DGD vs. the SOC ( $1.9 \pm 0.8$  vs.  $8.1 \pm 6.3$  days respectively). The need for surgical excision was significantly reduced in children treated with DGD vs. SOC (20.7% vs. 78% respectively). Time to wound closure was shorter in children randomized to DGD vs. SOC ( $29.9 \pm 14.3$  vs.  $32.1 \pm 18.9$  days respectively,  $p=NS$ ). The reduction in hemoglobin levels was also slightly improved in children treated with DGD vs. SOC though it did not reach statistical significance, most probably due to the smaller population size ( $0.56$  vs.  $1.38$  gm./L respectively). Long-term cosmetic outcome (Modified VSS) was slightly better in children randomized to DGD vs. SOC ( $3.14 \pm 2.59$  vs.  $4.05 \pm 2.82$  respectively,  $p=NS$ ).

#### Adverse Events

No differences were noted between patients treated with DGD or SOC in the incidence of adverse events in

any of the studies, and the overall incidences were lower than those reported in the literature. There were 5 deaths among the 386 patients treated with DGD vs. 1 death among the 127 patients treated with the SOC (1.3% vs. 0.8%;  $P=0.65$ ). Upon review by independent data safety monitoring boards, all deaths were considered to be unrelated to the study treatment. A representative case study is presented in *Figs. 1-4*.

#### Discussion

This paper summarizes the experience gained in the use of DGD during nearly 30 years in different studies that included burn patients, burn centres and investigators across four continents. The results of these studies demonstrate that early use of DGD in deep burns results in rapid, selective, safe, and effective eschar removal with increased preservation of the uninjured dermis compared with the



**Fig. 2** - Before (1) and after (2) DGD application to lower extremity burn. Incomplete debridement due to poor contact with DGD. Complete debridement after second DGD application (3 and 4) with exposed fat typical of full thickness burn (3). Autografts harvested and transplanted to debrided burn. Appearance of leg 4 years later (5).



**Fig. 3** - 2.5 days after admission, the patient is sitting up in bed after all of the burns have been debrided and covered with allografts (small area on right lower leg autografted).

SOC. This preserved dermis can epithelialize spontaneously, reducing the need for surgical excision and grafting. The non-inferior eschar removal efficacy of DGD compared with surgical debridement does not prolong hospitalization and may reduce the need for blood transfusion. While relatively safe, debridement with DGD can result in procedural pain that usually resolves within the first hour after application, and generally can be managed by pre-treatment with oral or parenteral analgesics without the need for sedation or general anaesthesia. When applied to old and/or contaminated eschars, DGD may result in a systemic febrile response, probably due to a debridement-induced bacteremia. This effect, however, is not limited to enzymatic debridement and is also seen after surgical excision or even after dressing changes of old or contaminated eschars. Pyrexia has been traditionally seen with enzymatic debridement where many dressing changes were required.<sup>2</sup> The reason for fever, besides multiple handlings of contaminated wounds, has been attributed to the use of large occlusive dressings for extensive periods that prevented heat dissipation in these studies.<sup>2</sup> In contrast, the incidence of febrile episodes with DGD was similar to the SOC, probably as a result of a very short application time (four hours) as well as the use of post-debridement soaking.

Since early debridement of deep burns with DGD can preserve uninjured dermis and reduce the need for and extent of surgical debridement and grafting, we now refer to this modality of burn therapy as the Minimally Invasive Modality (MIM). The MIM, based on enzymatic debridement with DGD, is relatively simple, however there is a learning curve associated with its use. While mixing of the NexoBrid and its application is simple and straightforward, interpretation and management of the exposed wound bed



Fig. 4 - Long-term appearance of burns 12 years after injury. Back (1), front (2) and side (3) views.

requires some experience. It is important to realize that the wound bed that is left after application of DGD differs from traditional surgically or non-surgically debrided wound beds. The wound bed that remains after selective debridement (referred to as the “interface layer”) is the upper layer of the non-coagulated tissue. At the beginning of our first study, this enzymatically debrided dermal bed with its exposed whitish collagen stroma and spurious punctate bleeding points was perceived as incomplete debridement (Fig. 1). As a result, many of the earlier patients received an additional application of the debriding agent or were taken to the operating room for surgical debridement and skin grafting. However, careful histological examination of the tangentially excised enzymatically debrided beds revealed a healthy dermal or sub-dermal surface in such cases, confirming the debriding efficacy and selectivity of DGD. Indeed, this underestimation of the success of debridement in the earlier stages of our study may have biased our results against the debriding agent. Since the appearance of the enzymatically debrided wound bed differs from the surgically debrided or the non-debrided granulating wound bed, it is not always easy to determine whether it is still covered with dissolved eschar remnants. Additional soaking of the wound bed with saline or other water-based solutions (“wet-to-dry dressing”) helps remove these residues and greatly improves the wound bed’s appearance.

After realizing that the interface layer is not a full thickness burn and consists of viable dermal or sub-dermal adnexae remnants, we refrained from excising it but continued to autograft it with good initial take. In many cases, these wounds healed by epithelialization *under* the

autograft that served as a very efficient (yet costly) biological dressing and either later peeled off or became an overgraft. In other cases of deep and large dermal debrided burns where surgery was delayed and wounds were covered by allografts and/or concomitant topical medications such as silver sulfadiazine, we found that these deep burns epithelialized over the salvaged native dermis, and in the end healed spontaneously without any grafting. Eventually, we treated the interface layer as exposed healthy dermis (such as a split thickness skin graft donor site), aiming for spontaneous epithelialization from epithelial foci within the dermal remnant’s adnexae and from the wound edges. We found that this epithelializing dermis generally healed without excessive and abnormal scars. Modulation of granulation tissue by short courses (2-4 days) of topical corticosteroid ointment is an important component of the wound care. Topical application of a steroid ointment on the developing granulation tissue (~2 weeks after epithelialization begins) reduces granulation and allows epithelialization over the dermis. The ointment also helps preserve wound moisture that is important for the healing process.

Assessment of final long-term scar quality is important in order to demonstrate that the MIM, based on epithelialization of the remaining dermis (which is often a longer process than excision and autografting), does not result in worse scarring. The skin of the healed debrided wound has a different appearance compared to that of intact skin or the result of successful autografting. It is thinner, smoother, and may contain less hair and fewer sebaceous and sweat glands. The healed skin is typically flexible, without contracting scars, but is thinner due to loss

of part of the dermis and may have areas of discoloration depending on the thickness of the dermis and survival of melanocytes in the depth of the skin. For all practical considerations, this healed dermis has been found to be at least as good (functionally and aesthetically) as autografted areas that involve invasive surgical excision and grafting, with the drawbacks of surgical scars at the graft's edges and sites of incisions (for draining and meshing) as well as donor-site sequelae. In all cases, the end result is superior to that of healing by secondary intention (i.e., uncontrolled scarring). These results provide insight into the wound healing process. Even if wound closure is slightly delayed with DGD (since it requires epithelialization of exposed dermis), scarring can be controlled by modulation of any granulation tissue with topical steroids. This is supported by the well-known healing process of donor sites that is so different from the healing of partial thickness burns of similar depth. Thus healing of enzymatically debrided wound beds with residual yet viable dermis is unlike classical healing by secondary intention with scarring and contracture.

Application of DGD was not effective in all cases. In such cases, incomplete debridement was due to technical problems, such as the presence of a residual keratin layer or blister, or the result of shifting of the DGD dressing, disrupting contact of the enzyme with its substrate, the eschar. The more stubborn eschars were the old, desiccated, silver sulfadiazine (SSD) or povidine-iodine saturated eschars that did not respond well to enzymatic dissolution. Old, macerating, and partially sloughing eschars can be debrided by DGD, however handling (mechanically or enzymatically) the infected eschar may result in febrile episodes or even transient bacteremia and sepsis, probably from the contaminated eschar and the catabolic components that are present there. Similar phenomena can be seen with surgical and mechanical debridement as well as after dressing changes or even bathing of older, more contaminated eschars. The early, single application and very short debriding period of DGD "enzymatic surgery" seem to be part of the reasons for its rather benign course compared to previous reports of long application periods of other chemical/enzymatic debriding agents.<sup>2</sup>

An early, fast, selective, non-surgical debridement method that also resolves or prevents burn-induced compartment syndrome (BICS) has the potential to alter the strategy for handling burn mass casualty incidents. Such "enzymatic surgery" that does not require surgical teams and facilities can be used as a first line intervention by first responders, not specifically trained burn specialists, even while still in the pre-hospital setting following initial triage and resuscitation. This possibility for very early eschar removal has the potential to prevent or release any BICS, decrease the local and systemic inflammatory response, allow early visual diagnosis of burn depth, and fol-

lowing application of a biological cover, transfer of the victims to a secondary treatment centre where many of the wounds will have the potential to heal spontaneously. Wounds that require autografting can be operated on later without the need for surgical excision in most cases. Such a treatment strategy would allow better exploitation of rare surgical resources, thus increasing surge capacity in mass casualty incidents. Enzymatic debridement with NexoBrid can also be utilized in low and middle-income countries where burn care and facilities may be less developed, since mixing of the NexoBrid and its application are very simple and could be done by any personnel that normally perform wound dressing changes. Treatment of the underlying wound bed can be performed in any facility that generally cares for wounds non-surgically by application of topical agents or dressings. The minority of patients with full thickness wounds will still require excision and grafting, however this will be made easier after the eschar is removed by enzymatic debridement.

#### *Strengths of this study*

This review summarizes the results of multiple studies that included a large number of patients, study centres and physicians across the globe, thus increasing its generalization and external validity. Some of the studies were designed and regulated with the assistance of regulatory agencies such as the EMA and FDA, thus enhancing their quality and scrutiny. All the data were reviewed by the EMA or the FDA as part of the product development process. This review gives an insight into the process of the development of a treatment strategy based on the knowledge gained during the development of the debriding tool.

#### *Weaknesses of this study*

Not all of the studies were comparative or randomized, introducing potential selection bias. Due to the obvious differences between enzymatic, surgical and non-surgical debridement, it was impossible to mask the patients and investigators to the treatment arm, thus introducing the potential for observer bias. However, when long-term scar quality was assessed, the observers were masked to the original study treatment.

### **Summary and conclusions**

Current standard burn care may be surgical or non-surgical, depending on many factors (e.g., difficulty of early diagnosis, methods of non-selective eschar removal, availability of surgical facilities). The SOC surgical excisional debridement intends to remove the offending eschar as early as the diagnosis of a deep burn is made and as soon as surgery is possible. Besides the systemic trauma inflicted by the SOC surgical debridement, the debrided bed, usually a full thickness one, requires autografting, thus

causing additional trauma, pain (often described as stronger than the one caused by burn), wound care and scarring. The non-surgical SOC consists of application of topical medications until spontaneous eschar sloughing occurs, usually after 10–20 days. By this time, inflammation and infection may deepen the wound, sometimes converting partial thickness burns into full thickness ones, in addition to the development of local and systemic eschar-related complications. During this period, superficial burns will start to epithelialize, while the deeper ones develop granulation tissue that needs to be removed and grafted rapidly

in order to reduce scarring, often unsuccessfully.

In most cases, DGD-based enzymatic surgery achieved a clean wound bed very early after injury, replacing traditional surgery but leaving enough dermal remnants that epithelialized without the need for additional surgery and grafting, with similar, if not better, long term results. Thus, DGD enzymatic surgery offers a safe, effective, early and selective minimally invasive burn care modality. This modality in many cases offers the option of reducing surgery (excision and grafting) and utilizing spontaneous epithelialization of the salvaged dermis for wound closure.

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