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Review

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State of the art in enzymatic debridement

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Abstract

Surgical treatment of deep partial thickness to full thickness burn wounds by knife has been the undisputed standard of care and was one key point in surgical burn medicine for decades. Recently, it gets more and more challenged by Bromelain-based enzymatic burn wound debridement (ED) as technique for non-surgical, selective eschar removal. Although the literature on ED is increasing constantly it cannot comprise the rapid progress that is made in clinical application of ED. To outline the current state of art in ED, recent literature as well as clinical experience is summarized and the main steps in clinical application including indications, wound preparation, application of the enzyme, wound bed assessment and further treatment after ED are discussed. Initial indications and limitations in application of ED could be gradually extended to increase versatility of ED as tool in burn surgery. Several randomized controlled trials compared ED to standard of care (SOC). They could show significant shorter time to complete burn wound debridement and wound closure, reduced need for surgery, reduced blood loss, reduced area of burns that needed surgical excision and need for autograft as well as an improved scar quality. Further research is necessary to justify an extensive use of ED as tool for burn eschar removal. Especially a robust comparison to surgical burn wound excision by knife as SOC is required to facilitate evidence-based burn surgery.

Keywords: State of the art, enzymatic debridement, Nexobrid, eschar removal, burns

INTRODUCTION

Effective removal of necrotic burned tissue is a key step in the treatment of all deep partial thickness and full thickness burn wounds. It aims to promote wound healing, reduce bacterial colonization and infection, is the

basis for optimal wound bed conditioning, and thus prevents devastating scarring. Especially in severely injured patients with a high extent of burned surface, early eschar removal is as important as optimal intensive care treatment to optimize outcomes and reduce complications[1].

To date the conventional method of tangential excision by knife as introduced 50 years ago[2] is still the most applied technique of eschar removal worldwide. Nevertheless, several further techniques have been developed and became popular in the past decades. Hydrosurgery as most established additional technique for example enables the surgeon to achieve a more selective debridement of the burn wound by an adjustable water jet[3].

In the last decade, most progress has been achieved in enzymatic burn wound debridement (ED)[4]. This technique promises the effective eschar removal and uses bromelain-based enzymes extracted from pineapple stems in the most frequently applied medication (Nexobrid®). After preparation of the burn wound by pre-soaking the eschar, the product promotes selective eschar removal from burn wounds within 4 h even in full thickness burns, while viable dermal tissue is preserved. Due to encouraging reports and growing evidence in literature, including benefits like lower blood loss and fewer need for consecutive skin grafting[5], ED continues to increase in popularity. While the group of users is growing continuously, indications are widened and the technique of application is constantly refined.

To catch up with these developments, this article tries to give an overview on the current state of art on indications, implementation and post-treatment in the use of ED with Bromelain-based Nexobrid®.

INDICATIONS

According to its approval, ED can be used on all burn wounds up to 15% total burned surface area (TBSA) in adult patients per application. Effective and safe treatment of children has been reported and is practiced in pediatric surgery[5], but has to be considered as off-label use until further approval studies are evaluated. Likewise, the treatment of a TBSA up to 30% per session can be performed with reasonable risks although it is also regarded as off-label. Treatment of more than 30% TBSA in one session of ED cannot be recommended due to risks of increasing blood loss and hemodynamic instability. In addition, further systemic effects of ED in extra-large surfaces > 30% remain unknown.

The advantages in preserving more viable dermis compared to conventional excision is most important in delicate regions with high function and relatively thin subcutaneous tissue, like on the hands, feet, genitals, perineum, axilla or in the face. Application in these regions revealed good results and can be further encouraged[6-9].

In deep circumferential burns at the extremities, the early application of ED can release tissue pressure by timely removing the constrictive eschar, reduce inflammation-associated edema and thus may prevent patients from the need for surgical escharotomy and its possible complications and invasiveness. Despite the successful implementation in specialized burn centers, it is mandatory to re-evaluate the wound frequently and verify entire tissue release thoroughly and be prepared to perform additional surgical escharotomy or even fasciotomy if necessary in case of burn induced compartment syndrome[10-12].

As a bedside procedure, ED has the potential to shift early eschar removal to the patient ward and thus can spare valuable resources in the operating room. In that way ED can be especially advantageous in mass casualty incidents where a higher patient count can benefit from optimal and timely treatment[13].

PREPARATION

Prior to the application of ED, a sufficient analgesia must be ensured. For treatment of single extremities,

regional anesthesia (e.g., plexus anesthesia) has been used successfully and is favorable due to its little side effects[7]. To perform treatment of large surfaces including the trunk or the head, general anesthesia in an intensive care setting is recommended.

Because the enzymes can only process moist tissue, a wound condition have to be prepared by pre-soaking with crystalloid or anti-infective fluids for at least 2 h, and even longer in burns with delayed application of ED[10]. Some users report better outcomes of ED after prolonged pre-soaking for up to 12 h, but there is yet no evidence to support this approach - nevertheless it might help overcome logistical deficiencies at the burn center if being more flexible in the time of post-soaking. On the other hand, when a patient is presented immediately after burn trauma, the burn wounds should be still moist enough to skip pre-soaking phase and start with ED immediately - which is mandatory for emergency ED to prevent surgical escharotomy in circumferential burns

APPLICATION

For ED procedure itself, the prepared enzyme gel is calculated with 2 g of enzyme powder per treated % BSA, which is applied on the wound after rehydration. Unburned skin, mucosa and especially cornea and tympanic membrane must be protected thoroughly from contact with the gel by stoma paste or vaseline gauze. The active gel for ED is fixed with an occlusive dressing in order to increase the contact surface. To ensure removal of entire eschar, the gel should be placed on the wound for at least 4 h. In the absence of adverse effects of longer contact time, the enzyme can be safely left on the wound beyond the 4 h recommended by the producer[10].

After removal of the enzyme gel including debris and mechanical cleaning, wound bed evaluation is necessary with regard to the bleeding pattern, followed by a post-soaking phase to remove further remnants of debris and enzyme gel. Post-soaking again can be performed with saline or anti-infective solutions while a superiority could not be shown by now for any agent. Duration of post-soaking should be at least 2 h, but some users report superior results with a prolonged post-soaking of up to 12 h.

WOUND BED ASSESSMENT

One key point in treating burn wounds with ED is the postprocedural wound bed assessment. It should be performed prior to the post-soaking phase and after mechanical removal of gel remnants and debris. Photography of the wound is recommended to archive the results and as basis for further professional decision in case of late-night application. At this time, depth of the burn injury and the need for further surgical procedures should be estimated by assessment of wound bed color and bleeding patterns. A uniform pink wound bed or a uniform white wound bed with pin-point, small and dense, punctate bleeding pattern represent a high chance for spontaneous healing of the debrided burn wound putting the patient on a track for healing in-between 21 days. On the other hand, a wound bed with large diameter red circles or oval patterns, distant from each other, indicates a prolonged healing time with increased risk for necessary grafting. Exposure of subdermal tissue like fat or blood vessels indicate a full thickness burn injury and requires grafting[10].

Figure 1 shows an exemplary case of a deep partial thickness burn wound treated with ED that healed without split-thickness skin grafting.

POST TREATMENT

After ED, the burn wound is vulnerable and needs to be protected against wound infection and desiccation by a suitable dressing. Some authors report the use of epidermal substitutes like Suprathel or even allografts to cover the wound bed after ED in order to promote spontaneous reepithelization without instable scar-

Figure 1. The case of a 27-year-old male patient suffering a deep partial thickness burn due to flame burn at his right hand is shown. A: After admission to hospital right after trauma; B: two days after ED; C: two weeks after ED; D: one year after ED

ring[14], while other authors prefer conventional antiadhesive wound dressings with polyhexanide gel[7]. If wound bed assessment indicates a deep dermal wound with expected prolonged healing time or instable scarring, early surgical coverage - eventually accompanied by additional debridement - by split-thickness skin grafting (STSG) should be considered. As in every burn wound, development of hypergraulation tissue prevents primary wound healing and can lead to hypertrophic scarring. Topical administration of potent steroids (e.g., clobetasol) can be recommended to treat occurring hypergranulation tissue in the wound management phase[15]. If spontaneous healing is absent 21 days after ED or a sticky layer, called pseudo-eschar, which does not peel off after 14 days, surgical intervention and STSG should also be taken into account[10].

DISCUSSION

Bromelain-based ED is more than a new technique, it includes a new concept of selective eschar removal without the necessity to schedule OR for this initial step. Due to encouraging results, the technique and its concept behind has been implemented in the leading burn centers in Europe since 2013. With experience of treating many hundreds of burn victims with ED, results could even be improved and are stable enough to use ED in routine patient treatment[10]. Despite the growing experience, the literature offers seven publications on studies with a high level of evidence proving ED's advantages with certain issues over standard of care (SOC), which is remarkable for literature in burns. Loo *et al.*[16] investigated literature on ED from 1986 to 2017 and reported seven prospective studies including four randomized controlled trials in a recent review. The largest available randomized-control trial by Rosenberg *et al.*[5] compared 74 cases of ED with 81 cases treated by SOC and could show a significant shorter time to complete eschar removal, a lower number of wounds requiring surgical excision and STSG as well as a significant lower blood loss in in the ED group. No significant difference could be shown in time to wound closure and scar quality. While these results could be confirmed by other authors[6,7] one group even reported a reduced time to wound closure and an improved scar quality in comparison to historical control groups[8,9]. Further encouraging results could be

Table 1. Overview of literature

Study	Patients (IG/CG)	Intervention	Comparison	Outcomes (IG/CG)	Study type	Country/ setting	LoE
Rosenberg *et al.*[5]	Deep burns Age (mean): 32.4/29.3 Female: 23.8%/24.7% TBSA: 11.3%/11.0%	*n* = 74 Enzymatic debridement with NexoBrid	*n* = 81 Excisional debridement followed by autografting	• Time to complete eschar (mean, days): 2.2/8.7 ($P < 0.0001$) • Wounds requiring surgical excision 24.5%/70.0% ($P < 0.0001$) • Autograft: 17.9%/34.1% ($P = 0.0099$) • Time to complete wound closure (days): 32.8/29.2 ($P = 0.1197$) • Blood loss-change in hemoglobinc (mean, mmol/L): 0.52/1.04 ($P = 0.0061$) • Scar quality (mean, Modified Vancouver Scar Scale, 2-4years): 3.12/ 3.38 ($P = 0.88$) • Scar revision/reconstructive surgery (2-4years): 3.7%/8.6% ($P = 0.6547$) • General health (mean SF-36, 2-4years) – physical score (patients) 51.1 /51.3 ($P = 0.68$) • Adverse events: ns differences	RCT	Israel	2
Schulz *et al.*[19]	Partial thickness and deep dermal burn wounds of the face age (mean): 39/48 years male: 84.6%/76.9% TBSA: 16%/34%	*n* = 13 Enzymatic debridement with NexoBrid	*n* = 13 historic control group treated with SOC	• Time of initial debridement (days after admission): 0.92/4.92 • Autografting (wounds): 15%/77% • Time to complete healing after first debridement (days): 18.92/35.62	Prospective trial with historic control	Germany, burn center	3
Schulz *et al.*[8]	Partial thickness and deep dermal burn wounds of the hands age (mean): 41/45.5y. male: 95/85% TBSA: 10.1/31%	*n* = 26 Enzymatic debridement with NexoBrid	*n* = 20 historic control group treated with SOC	• Autografting (wounds): 15%/95% • Time to complete healing after admission (days): 24.2/35.8 • Number of surgeries until complete wound closure (includes debridement): 1.15/1.7	Prospective trial with historic control	Germany, burn center	3
Cordts *et al.*[7]	Full-thickness upper extremity burns Age (mean): 47.8 Females: 31.2 % TBSA: 20.1%	*n* = 16 Enzymatic debridement	NA	• Pain (3 months, patient-related) • Wrist Evaluation Score: 23/100 • Disabilities of the shoulder, arm and hand: 22/100 • Scar quality (3 months, Vancouver Scar Scale): 6/14 • Side effects (during hospital stay): 0 • Wound infections (during hospital stay): 0	Case series	Germany, burn intensive care unit	4
Schulz *et al.*[14]	Partial thickness and deep dermal burn wounds of the hands age (mean): 43y. male: 85% TBSA: 15.67%	*n* = 20 Enzymatic debridement with NexoBrid	NA	• Time to complete healing after admission (days): 29.15 • Efficiency of debridement (%): 90% • Autografting (wounds): 30%	Case series	Germany, burn center	4
Krieger *et al.*[6]	*n* = 69 Deeply burned hand TBSA: 1.4%	Selective enzymatic debridement	NA	• Complete wound closure (mean, days): 17 (surgery), 23 (no surgery) • Surgical escharotomy: 0 • Permanent damage: 0	Case series	Israel, hospital (burn unit)	4
Rosenberg *et al.*[4]	*n* = 130 Deep second degree and third degree burns Age (mean): 18.6 Female: 48.5% TBSA < 10%: 66%	Enzymatic debridement with Bromelain-derived debriding agent	NA	• Significant adverse events: 0	Case series	Israel, hospital	4

shown by Osinga *et al.*[17] who presented a series of 12 cases. While ED is most commonly used within 72 h after trauma the group of Osinga treated their patients with ED up to 19 days after burn trauma and still reported to avoid STSG even in deep burns in the majority of their cases[17]. Edmondson *et al.*[18] recently reviewed the literature from 1946 to 2017 for comparison of different tools of eschar removal. While sharp excision by knife was found to be the predominantly used technique, a robust comparison to newer tools like ED or Hydrosurgery (VersaJet®) is lacking[18]. Table 1 summarizes the latest literature on ED with given outcomes and level of evidence.

To provide detailed user-orientated guidelines and recommendations based on available literature as well as on the growing amount of experience with ED in Europe, a European Consensus Workshop was held in January 2017. As a result, 68 consensus statements based on the combined experience of > 500 patients treated by the panelists from 10 European burn centers could be generated. Various aspects of ED were discussed including indications, timing of application, preparations and application technique, pain management, blood loss, post ED wound diagnosis and management including skin grafting, scar prevention, training strategies and areas of future research. The degree of consensus was remarkably high, with a consentaneous agreement on 60 of the 68 statements (88.2%). The consensus statements contain detailed recommendations aiming to align current and future users and prevent unnecessary pitfalls. and may serve as preliminary user-orientated recommendations for the use of ED until further evidence is available[10].

CONCLUSION

Although the number of patients in analogue with the experience increases in literature, further research is necessary to prove further issues of superiority of ED in comparison with SOC, especially in the field of cost-efficiency to justify the progressive use of the technique in large surfaces > 15% TBSA. In addition, for large-surface areas, the potential systemic impact of ED in the severely burned patients should be addressed. Nonetheless, Bromelain-based ED is a valuable tool, technique and concept in the armamentarium of burn surgery.

DECLARATIONS

Authors' contributions

Conception and design: Ziegler B, Kneser U, Hirche C
Data analysis and interpretation: Ziegler B, Hundeshagen G, Cordts T
Data acquisition: Hundeshagen G, Cordts T
Administration, technic, material, and revision: Kneser U, Hirche C

Availability of data and materials

Not applicable.

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Conflicts of interest

Ziegler B is a speaker for Mediwound, Germany. Hundeshagen G and Cordts T reports no disclosures. Kneser U is a consultant and speaker for Mediwound, Germany. Hirche C is a consultant and speaker for Mediwound, Germany and member of the advisory board, KCI, Acelity, Wiesbaden, Germany.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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