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Open label randomized controlled trial of the efficacy and safety of NexoBrid compared to standard of care in children with burns

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ABSTRACT

Objectives: This study evaluated the safety and efficacy of an enzymatic bromelain-based debridement (BBD) agent (NexoBrid®) in children with deep thermal burns.
Methods: We conducted a multicenter, open-label, parallel design, randomized controlled trial at 36 burn centers in Europe, US, Israel and India. Main eligibility criteria included children 0–18 years old, suffering from deep thermal burns covering 1–30 % of their total body surface area. Patients were randomized to either BBD or standard of care (SOC) eschar removal methods. Primary endpoints included time to complete eschar removal (superiority), percentage of wound area surgically excised (superiority) and blinded 12 months follow-up assessment of cosmesis and function using the Modified Vancouver Scar Scale (MVSS, non-inferiority).
Results: One hundred and forty-five children were enrolled between 2015 and 2020 (last patient completed 12-month follow-up on April 2021); 72 were randomized to BBD and 73 to SOC. All three primary endpoints of the study were met. The median time to complete eschar removal was significantly lower in the BBD arm (1 vs. 6 days, $P < 0.001$). The mean [SD] percentage of wound area surgically excised was also significantly lower in the BBD arm (1.5 % [12.1 %] vs. 48.1 % [46.6 %], $P < 0.001$). Mean [SD] 12-month MVSS scores were 3.8 [2.9] and 4.9 [3.3] in the BBD and SOC arms, respectively (non-inferiority demonstrated at $P < 0.001$). The incidence of adverse events was similar between the groups, and there were no significant safety issues or deaths during the trial.
Conclusions: BBD was demonstrated to be safe and effective in children. Its use lead to a shorter time to complete eschar removal, a reduction in excisional surgery and non-inferior cosmesis and function results as compared to SOC eschar removal methods.

1. Introduction

More than half a million burn injuries occur in the USA annually [1]. Despite major advancements in burn care over the last half century that account for a 50 % decrease in the mortality of major burns in children, pediatric burn injury continues to be a top 10 cause of unintentional

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death and injury in children [2]. Early surgical excisional debridement of deep burns is among these major advancements and is considered a cornerstone of modern burn care. Early excision of the thermally injured tissue (the burn "eschar") has been shown to significantly reduce burn morbidity and mortality in children [3–5].

In her introduction of the concept of early surgical tangential excision and grafting over half a century ago, Dr. Janzekovic stressed the importance of preservation of viable dermis by the tangential, layer by layer excision of non-viable tissues, until reaching a viable wound bed [6]. This attempt to preserve viable dermis is especially important in children, due to their thinner skin [7]. In parallel to the groundbreaking work of Dr. Janzekovic and her colleagues, other researchers were working on a different concept for selective debridement that included chemical and enzymatic debridement agents [8,9]. One of these enzymatic agents was based on Bromelain, found in pineapples [10], but the process of learning how to properly extract the enzymes into a stable product that could be developed, clinically tested and approved for use lasted several decades [11–14].

In 2012 the European Medicines Agency (EMA) approved a pineapple stem derived Bromelain based concentrate of proteolytic enzymes (NexoBrid®, MediWound Ltd, Yavne, Israel) for debridement of deep thermal burns in adults [15]. The approval was based on the results of 7 clinical trials and a plethora of pre-clinical studies [16–21]. Bromelain based debridement (BBD) has been shown to lead to a complete eschar removal rate of $>$ 90 % with significantly reduced need for surgical debridement, significantly reduced time to complete debridement, significantly reduced debridement related blood loss, and a comparable safety profile to standard of care [16,22]. Additionally, it has been demonstrated to provide a selective eschar removal, without harming viable dermis [19]. Most of the patients treated with BBD in the clinical trials were adults, however the results of 110 children that participated in the trials pointed to similar safety and efficacy outcomes [23]. European consensus guidelines and publications also reported early positive results in the treatment of children, however a successful pediatric dedicated RCT was needed to gain regulatory approval of BBD use in children [24,25].

The objectives of this study were to demonstrate the safety and efficacy of bromelain-based debridement in children with deep burns as compared to the standard of care (SOC) eschar removal techniques. We hypothesized that enzymatic debridement would result in a shorter time to complete eschar removal and reduce the need for surgical excision compared to SOC while achieving similar time to wound closure as well as 12-month cosmesis, function, and quality of life.

2. Methods

2.1. Design and Setting

We conducted this multicenter, open-label, parallel design, randomized controlled trial at 36 burn centers in Europe, US, Israel and India. The trial was initially discussed with the EMA as part of the NexoBrid pediatric investigational plan in the EU and was thus registered with EudraCT (# 2014–003066–24). After the trial was initiated, it was also discussed with the FDA as part of the regulatory plan for approval in the US. A separate US protocol was thus developed and the ClinicalTrials.gov (# NCT02278718) registration was updated according to the US protocol. The study design and interventions were identical in both protocols, with some differences in study endpoints according to the different demands of the EMA/FDA (see below). This manuscript follows the EU protocol.

2.2. Participants, recruitment, and enrollment

Children (ages new-born to 18 years) with deep partial or full thickness thermal burns covering 1–30 % of their total body surface area (TBSA) were eligible to participate if informed consent could be obtained within 84 hours of injury. Informed consent for experimentation with human subjects was obtained for all the study participants from parents or legal guardians by study staff who randomized patients to either intervention (enzymatic debridement with BBD) or control (surgical and non-surgical SOC) arm in a 1:1 ratio using a computer-generated randomization stratified by center geographic location (e.g. US, India etc.), depth and size of burn, and age group. Patients with burns caused by chemicals or electricity as well as those with burns on the face, genitals and perineum were excluded. Patients with significant co-morbidities or weighing less than 3 kg were also excluded. A complete list of eligibility criteria can be found in the supplementary material.

2.3. Intervention and control

Intervention arm patients were treated with BBD within 84 hours of injury (NexoBrid®, by MediWound Ltd, Yavne, Israel), which is comprised of two components: a sterile lyophilized concentrate of proteolytic enzymes enriched in Bromelain extracted from the stem of pineapples as a powder and a sterile gel vehicle. Prior to BBD application, the wound was soaked with an antibacterial solution (e.g., sodium hypochlorite 0.25 % solution) and any blisters or adherent keratin were removed. Immediately prior to application, a dose of 2 g BBD sterile powder was mixed with 20 g sterile gel vehicle to cover 180 cm^2 burn surface area. The mixture of powder and gel was applied to the burn with a sterile wooden tongue depressor. The BBD was contained onto the burn area by applying petrolatum ointment to the normal skin immediately surrounding the burn and covering it with a sterile occlusive film dressing and an overlying loose gauze dressing. The BBD was left on the burn for four hours and then wiped away with another sterile wooden tongue depressor. The wound was then soaked for another two hours. BBD was not applied to more than 15 % TBSA at any one session and could be applied for a second time on the same area if eschar removal was incomplete.

The control group received SOC eschar removal methods initiated within 84 hours of injury, including surgical and/or non-surgical treatments such as antimicrobial ointments/creams or silver dressings. Surgical treatments included tangential excision, dermabrasion, or removal with hydromechanical means. The choice of SOC eschar removal methods was at the investigators' discretion and in line with their standard practice. Study treatment was not blinded due to obvious visual differences between BBD and the control surgical or non-surgical treatment. A treatment scheme can be found in the supplementary material.

Following removal of the burn eschar in both arms, the debrided wound bed was treated towards wound closure at the discretion of the treating physician including autografting, topical agents or dressings. After wound closure, patients were followed up for at least 12 months.

2.4. Data collection and outcomes

Baseline patient and burn characteristics were collected using standardized data collection forms. The primary outcomes were the time to complete eschar removal from randomization, the percentage of wound area surgically excised for eschar removal, and the Modified Vancouver Scar Scale (MVSS) scores at12 months following wound closure as assessed by blinded assessors (non-inferiority analysis). The MVSS ranges from 0 to 18 from best to worst [26]. Secondary endpoints included the incidence of surgical excision performed to complete eschar removal, blood loss related to complete eschar removal as measured by the Actual Blood Loss (ABL) formula [27], the incidence of autografting and percentage area autografted in deep partial thickness (DPT) wounds, and the MVSS scores at 24 months following wound closure as assessed by blinded assessors.

Safety endpoints included systemic and local treatment-related adverse events, time to complete wound closure, and long term (12

months) function and quality of life (QoL). Function was measured using the lower extremity function scale (LEFS) for burns of the lower extremity [28], the disabilities of the arm, shoulder and hand QuickDASH questionnaire for burns of the upper extremity [29], and range of motion for burns covering joints. QoL was measured by the EQ-5D and BOQ questionnaires. Exploratory endpoints included hospitalization duration, incidence of surgical escharotomies, incidence of pressure reduction to < 25 mmHg in circumferential burns, incidence and area of donor sites, and POSAS scores at 12- and 24-months follow-up. As previously mentioned, the US protocol endpoints differed, the main difference being only one primary endpoint which was the time to complete eschar removal.

Study treatment randomization was not blinded due to the visual differences between NexoBrid and surgical and non-surgical SOC. Eschar removal and wound closure assessments were also not blinded assessments. Long term cosmesis, function and QOL were assessed by an assessor blinded to the original treatment arm.

2.5. Statistical analyses

Categorical variables were summarized as numbers and percentages. Continuous variables were summarized as means or medians together with standard deviations or 95 % confidence intervals (95 % CI). We used one-way analysis of variance and tests of proportions to compare baseline characteristics. Time to complete eschar removal is presented graphically using Kaplan-Meier curves. Median time to complete eschar removal was estimated for each treatment arm together with 95 % confidence intervals.

A hierarchical testing procedure for the primary endpoints was used in which time to complete eschar removal was tested first using a two-tailed superiority test at the significance level of 0.05. A sample of 72 patients in each of the two study groups was adequate to detect with 90 % power a difference on each of the primary endpoints. Additional information about statistical tests used can be found in the study endpoints table. All data were analyzed with SPSS Version 27.0 for Windows (IBM Inc., Armonk, NY, USA).

3. Results

Of 153 patients screened for enrollment, 145 were randomized to BBD (n = 72) or SOC (n = 73). Of the 145 randomized patients, 139 were treated with BBD (n = 69) or SOC (n = 70). There were six patients that were randomized but did not receive study treatment. Of the patients treated, 132 (66 in the BBD and 66 in the SOC) completed the 12 weeks post wound closure follow up visit and 129 patients (66 in the BBD and 63 in the SOC) completed the 12 month follow up visit. A patient flow diagram including reasons for drop-out can be seen in Fig. 1. The first study patient was enrolled in May 2015 and the last patient completed 12-month follow-up in April 2021.

3.1. Baseline characteristics

The mean (SD) age of the 145 randomized patients was 5.8 (4.9) years and 90 (62.1 %) were males. Of all patients, 45 (31.0 %) were ages 0–23 months, 30 (20.7 %) were ages 2–3 years, 50 (34.5 %) were ages 4–11 years, and 20 (13.8 %) were ages 12–18 years. Mean (SD) time from injury to randomization was 41.0 (18.5) and 37.3 (18.0) hours in the BBD and SOC groups respectively (NS). Of all patients, 110 (75.9 %) had only deep partial thickness, 26 (17.9) had mixed depth and 9 (6.2 %) had only full thickness burns. Overall mean (SD) percentage of TBSA of treated target wounds were 7 (4.9) and 6.2 (4.8) in patients treated with BBD and SOC respectively. The burns were located on the

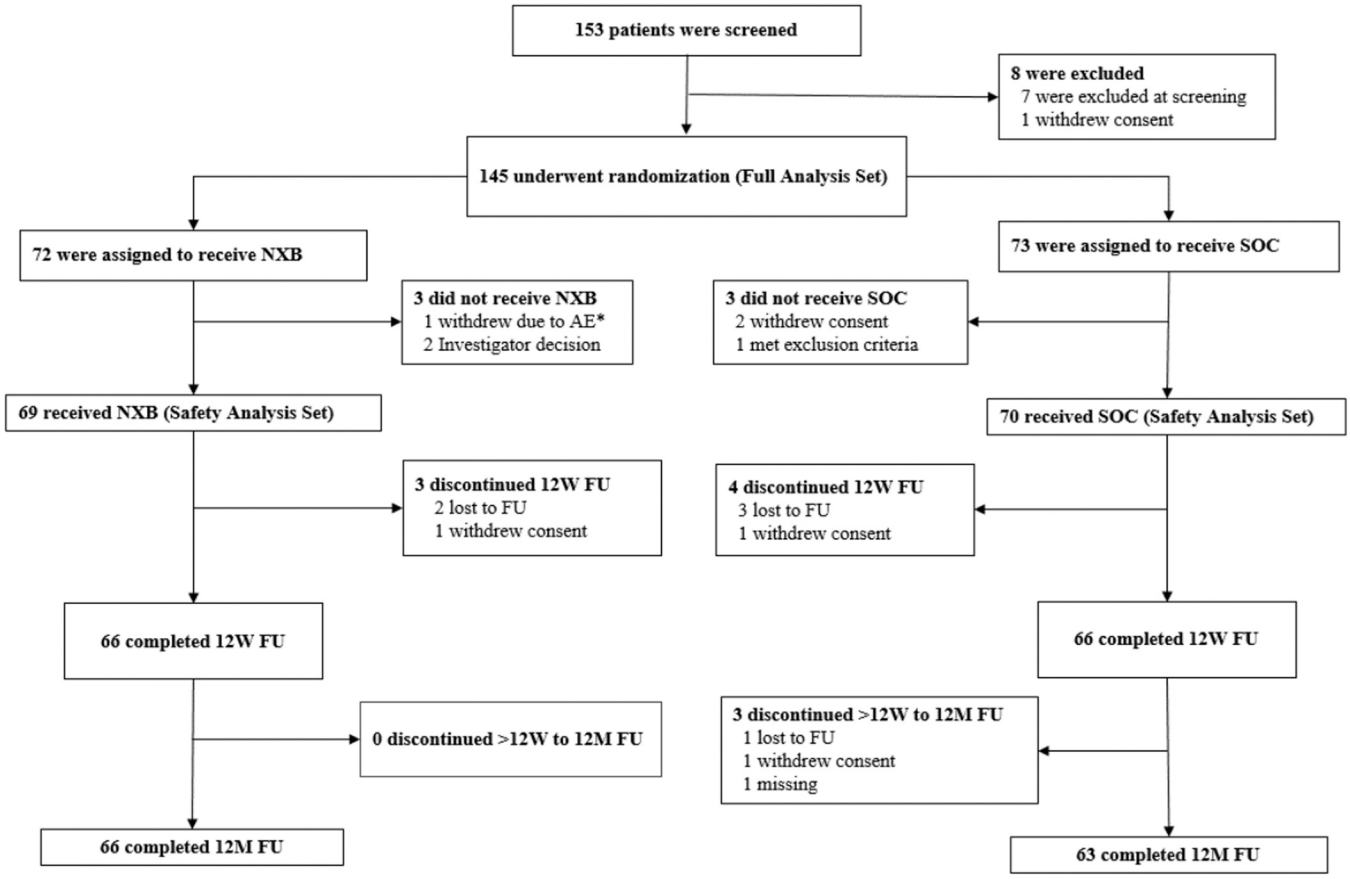

Fig. 1. Patient flow diagram. NXB – NexoBrid. SOC – Standard of Care. FU – Follow Up. AE* - Adverse Event (wound infection prior to study treatment).

lower extremities (28.6 %), trunk (27.1 %), upper extremities (15.1 %), buttock (0.5 %) or in multiple locations (28.6 %). Overall, baseline characteristics and randomization stratification groups were similar among the treatment groups (Table 1).

3.2. Primary outcomes

All three co-primary endpoints were met. The median (95 % CI) time to complete eschar removal in patients treated with BBD or SOC was 0.99 (0.88–1.04) and 5.99 (2.71–9.84) days respectively ($P < 0.001$). Fig. 2 presents the Kaplan-Meier curves for time to complete eschar removal. The mean (SD) percent wound area surgically excised for eschar removal was 1.5 (12.1) in patients randomized to BBD and 48.1 (46.6) in patients randomized to SOC ($P < 0.001$). Mean [SD] 12-month MVSS scores in BBD treated patients (3.8 [2.9]) were non inferior compared to patients treated with SOC (4.9 [3.3.]); mean difference, −2.8 (95 % CI, −3.7 to −1.8, $P < 0.001$). A representative case of a child's forearm burn that healed spontaneously after being treated with BBD can be seen in Fig. 3.

3.3. Secondary outcomes

The proportion of patients treated with BBD requiring surgical excision for eschar removal was significantly lower than in patients treated with SOC (8.3 % vs. 64.4 % respectively, $P < 0.001$; odds ratio (OR) 0.025 [95 % CI, 0.007–0.09]). The mean (SD) estimated blood loss in the BBD arm was 32.2 (284.8) vs. 202.6 (409.1) ml in the SOC arm ($P = 0.14$). The incidences of autografting in patients treated with BBD and SOC were 25.9 % and 37.8 % respectively ($P = 0.054$), OR 0.41 (95 % CI, 0.16–1.1). The percentages of wound area autografted in patients in the BBD and SOC arms were 15.9 (43.7) and 22.8 (43.7) respectively ($P = 0.50$). The estimated median (95 % CI) duration of hospitalization was 12 (9−16) days in the BBD arm and 10 (8−14) days in the SOC ($P = 0.09$).

Table 1
Baseline Characteristics.

	BBD (n = 72)	SOC (n = 73)
Age in years, mean (SD)	5.7 (4.8)	5.8 (4.9)
Age stratification groups, No. (%)		
0–23 months	23 (31)	22 (30.1)
24–36 months	15 (20.8)	15 (20.5)
4–11 years	25 (34.7)	25 (34.2)
12–18 years	9 (12.5)	11 (15.1)
Males, No. (%)	42 (58.3)	48 (65.8)
Females, No. (%)	30 (41.7)	25 (34.2)
Geographic location group, No (%)		
Western Europe	19 (26.4)	22 (30.1)
Eastern Europe & Israel	26 (36.1)	20 (27.4)
United States	12 (16.7)	16 (21.9)
India	15 (20.8)	15 (20.6)
Total burn area, % TBSA (SD)	7.0 (4.9)	6.2 (4.8)
TBSA stratification groups, No. (%)		
1 to ≤ 15 %TBSA	68 (94.4)	70 (95.9)
> 15–30 %TBSA	4 (5.6)	3 (4.1)
Target wounds area, %TBSA (SD)	5.9 (4.4)	5.3 (4.3)
Target wound depth, No. (%)		
Deep partial thickness	58 (80.6)	52 (71.2)
Full thickness	4 (5.6)	5 (6.8)
Mixed	10 (13.9)	16 (21.9)
Target wounds' full thickness depth area stratification groups, No. (%)		
Assessed as < 20 % full thickness	62 (86.1)	63 (86.3)
Assessed as ≥ 20 % full thickness	10 (13.9)	10 (13.7)
Burn etiology, No. (%)		
Scalds	49 (68.1)	48 (65.8)
Flame	18 (25.0)	19 (26.0)
Contact	5 (6.9)	5 (6.8)
Multiple	0	1 (1.4)
Burn location, No. of TW (%)	n = 98	n = 94
Upper extremities	14 (14.3)	15 (16.0)
Lower extremities	25 (25.5)	30 (31.9)
Trunk	25 (25.5)	28 (29.8)
Multiple	34 (34.7)	21 (22.3)

BBD: bromelain-based debridement, SOC: standard of care, SD: standard deviation.

3.4. Safety outcomes and adverse events

The estimated median (95 % CI) time to complete wound closure in the BBD and SOC arms was 32 (25−41) vs. 34 (28−38) days respectively (test for non-inferiority, P = 0.015). There were no significant differences between the arms in lower extremity (LEFS) and upper extremity (QuickDash) function assessments throughout 12 months of follow up. There were also no significant differences in joint range of motion assessments and EQ-5D quality of life scores at 12 months.

The incidence of treatment related adverse events was similar in both treatment arms. In the 12 weeks following study treatment, 31/69 (44.9 %) BBD treated patients, and 29/70 (41.4 %) SOC treated patients reported at least 1 treatment emergent adverse event (TEAE). In the 12 weeks to 12 months follow-up period, 7/69 (10.1 %) BBD patients and 8/70 (11.4 %) SOC patients reported at least 1 TEAE. In general, most of the TEAEs were mild to moderate. Overall, in the 12 month follow up period from start of treatment, no events of wound infection were reported in the BBD arm vs. 2 events reported in 2 SOC treated patients (2.9 %). One event of cellulitis was reported in each arm (1.4 %). All wound infections and complications were reported as mild or moderate. There were no deaths in the study. Fig. 4 shows the most common adverse events, those with an incidence higher than 4 % in any of the arms.

The rate of hospital readmission was assessed as a safety outcome. Overall, planned and unplanned hospital readmission rates were generally low in both the BBD and SOC arms and no statistically significant differences were observed between the arms. At least one hospital readmission was reported for 8 patients in each arm (11.6 %). The majority of these were planned hospital readmissions. Unplanned hospital readmissions were reported for 2 patients in each arm (2.9 %). The durations of hospitalizations for these unplanned hospital readmissions were 2 days and 9 days for the BBD patients and 1 day and 6 days for the SOC patients.

3.5. Additional outcomes

While the incidence of complete eschar removal was not an endpoint in the study, we find it important to report that 65 of the 69 children (94.2 %) treated with BBD achieved a complete eschar removal. Additionally, subgroup analyses based on patient age demonstrated similar efficacy and safety results across all age groups. The median hospitalization duration was 12 days in BBD patients and 10 days in SOC patients (p = 0.09). There were also no significant differences between the study arms in the other exploratory and safety endpoints results.

4. Discussion

In this randomized trial of children with deep partial and full thickness burns covering 1–30 % TBSA, treatment with BBD (NexoBrid®) as compared to SOC resulted in a significantly shorter time to complete eschar removal, a significantly reduced incidence of excisional surgery, and non-inferior 12 months follow up cosmesis and function. Thus, all three co-primary endpoints of the study were successfully met. The first secondary endpoint, the incidence of surgical eschar removal, was also significantly lower in the BBD arm. All these significant results are in line with those of previous enzymatic debridement RCTs [22,30].

Eschar removal related blood loss was numerically lower in the BBD group, however, this difference was not statistically significant in this study, as opposed to results of the recently published DETECT adult

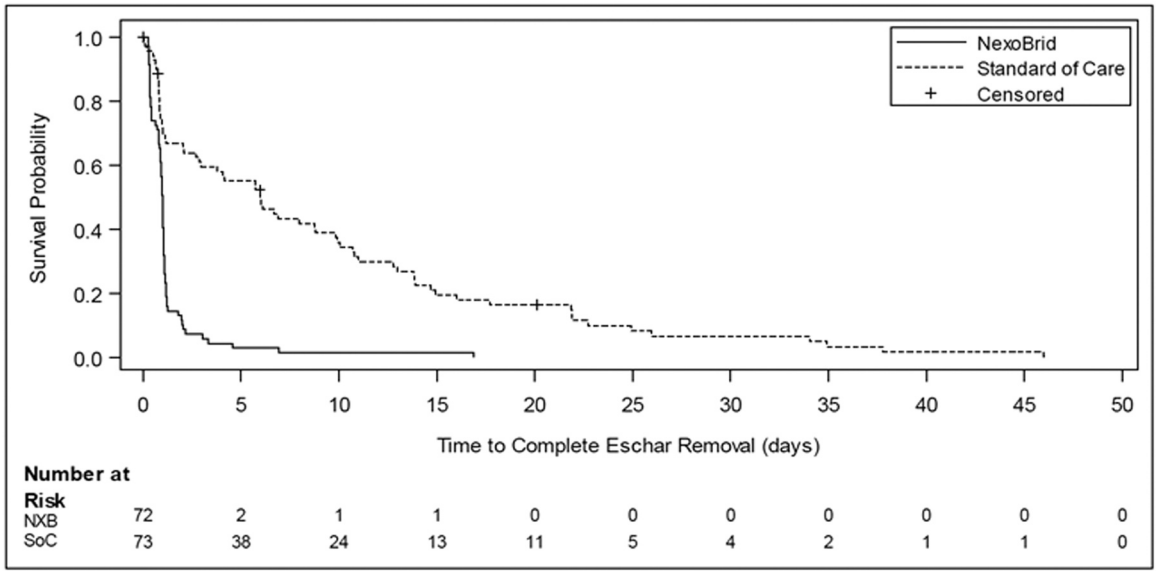

Fig. 2. Kaplan-Meier curves for time (in days) to complete eschar removal.

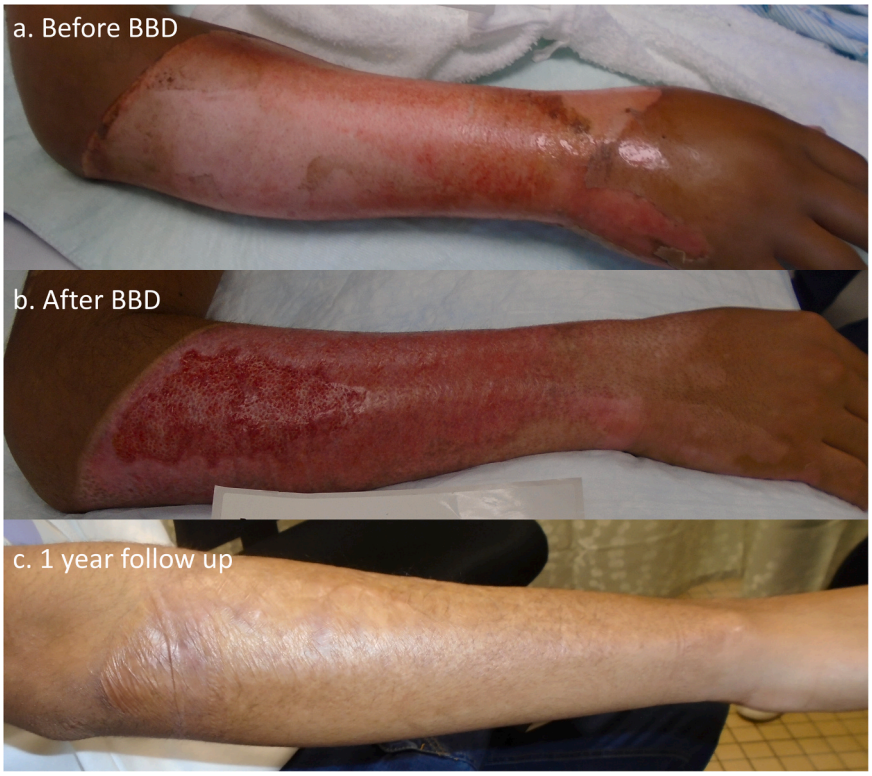

Fig. 3. Deep partial thickness forearm burn (a) before and (b) immediately after BBD treatment and 2-hour post-soaking, that healed under conservative treatment without surgery, and (c) after 1 year of follow-up.

enzymatic debridement multicenter RCT where a significant decrease was seen [30]. The reason for this difference may lie in the lower numbers of patients who had sufficient blood samples taken to perform the analysis in this study (42 in the BBD arm, 24 in the SOC arm). The incidence of autografting performed in DPT wounds was also numerically lower in the BBD arm, and was close to but did not reach statistical significance ($P = 0.0545$). Perhaps a larger sample size will have the power to demonstrate this outcome.

This study, as well as multiple others in both adults and children, supports enzymatic debridement with BBD as a minimally invasive, non-surgical eschar removal alternative to SOC. A major advantage of enzymatic debridement is the significant earlier eschar removal with the reduction in the need for excisional surgery, thus minimizing the exposure of burned children to the trauma associated with major surgery and anesthesia.

Despite the significantly shorter time to complete eschar removal in the BBD arm, there was no significant difference in the duration of hospitalization. This may be explained by the fact that the duration of hospitalization is a subjective decision, at the discretion of the investigators. As many of the investigators were initially less familiar with

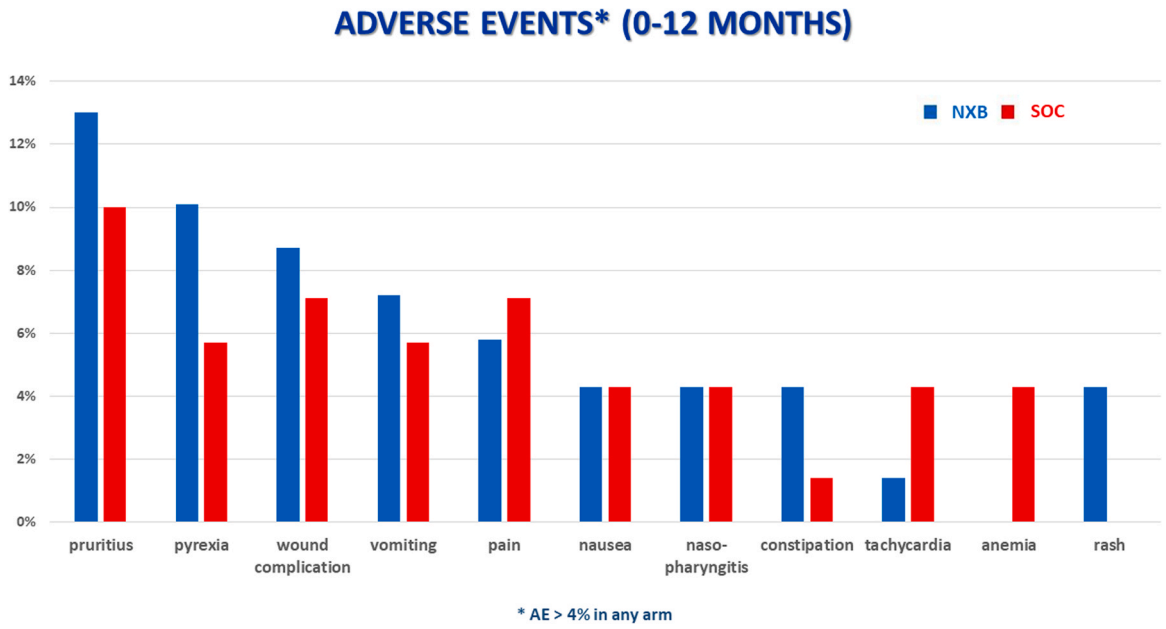

Fig. 4. Incidence of main adverse events (over 4 % incidence in any arm).

the different appearance of a post BBD wound bed, they may have tended to keep the patients hospitalized longer to witness the healing progression. This explanation is supported by the similar time to complete wound closure seen in the study, however, we acknowledge there is no evidence in this study to demonstrate a learning curve or quantify how investigator hesitancy influenced hospital stay decisions. Additionally, while not demonstrated in this study, preliminary studies suggest that enzymatic debridement is more cost effective than SOC, mostly due to a reduction in surgery related costs, reconstructive surgery costs, and intensive care following surgery [31,32]. These findings and a significant reduction in hospitalization duration in patients treated with BBD were also demonstrated in an economic analysis study recently published by a center that had already experienced an initial learning curve with BBD [33].

BBD did not have a deleterious effect on long term functionality and quality of life, and there were no significant safety issues in the study. The adverse event profile of BBD seems acceptable and in line with previous study results. While pain levels were not higher than in the SOC group, it is important to remember that SOC burn care is also painful, often necessitating general anesthesia. Similarly, it is important to understand that though BBD application is not a surgical procedure it is associated with pain, especially during the first hour of application, which needs to be managed with adequate parenteral analgesics and sedatives, regional anesthesia, or at times even general anesthesia [34–36].

A single previous retrospective study reported that BBD may not be as effective in scalds as compared to flame burns [37]. However, the results of our RCT demonstrate that BBD is highly effective in both burn etiologies. We find it important to address this issue as scalds are the most common type of pediatric burn [38].

4.1. Study strengths and weaknesses

To the best of our knowledge, this study is the largest, multicenter RCT of children with burns reported in the literature. This contributes to the generalizability of our findings to other settings where a burn unit is present. The study also followed patients for at least one year, which is rarely done in most burn studies. However, our study is not without limitations. Due to the nature of the interventions, patients and providers could not be blinded to study intervention. This introduces the potential for performance and detection bias with regards to the primary outcome (time to complete eschar removal), which may have been influenced by the investigators, whether consciously or unconsciously. In an effort to mitigate bias the assessment of complete eschar removal was standardized in accordance with the American Burn Association definition [39]. Additionally, the assessment of long-term outcomes was performed by observers blinded to treatment assignment. Study patients were treated in burn centers and by burn providers and may not generalize to settings where a burn center and burn specialists are not available. Another limitation is that while early eschar removal is clinically meaningful from a regulatory and clinician's perspective, the study does not connect this endpoint to direct patient-centered benefits, such as reduced hospital stay, fewer infections, or improved quality of life.

In conclusion, this randomized controlled trial demonstrates that enzymatic debridement with NexoBrid® is safe and results in more rapid eschar removal and a reduction in need for surgery in children with deep partial and full thickness burns, as compared to those treated with SOC. The results of this trial contributed to the recent regulatory approvals of the use of NexoBrid® in children by the EMA in the EU and the FDA in the US.

Ethical approval

All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committees of all the centers participating in this multicenter trial. The trial was registered with ClinicalTrials.gov (Identifier: NCT02278718) and EudraCT (Number: 2014–003066–24).

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Table 2
Summary of study endpoint results.

Endpoints	Outcomes BBD n = 72	SOC n = 73	Treatment effect (95 % CI)	p-value
Primary				
Time to complete eschar removal from randomization (median days)	0.99 (95 % CI: 0.88–1.04)[a]	5.99 (95 % CI: 2.71–9.84)[a]	Median Difference = −4.99 (95 % CI: −7.95, −2.04)[b]	P = 0.0008[c]
Percentage of wound area surgically excised for eschar removal	1.5 % (SD=12.13 %)	48.1 % (SD=46.58 %)	Adjusted difference = (−45.5 %)[d] (SE=6.83)	P < 0.0001[d]
MVSS score at 12 months from wound closure (assessed by blinded assessors)	3.83 (SD=2.88)	4.86 (SD=3.26)	Adjusted difference = (−2.76) (95 % CI; −3.67, −1.85)[e]	P < 0.0001[e] (non-inferiority)
Secondary				
Incidence of surgical excision performed for eschar removal	8.33 %	64.38 %	Odds Ratio = 0.025 (95 % CI: 0.007–0.090)[f]	P < 0.0001[f]
Blood loss related to eschar removal (milliliter, measured by ABL formula)	32.26 (SD=284.76) (n = 42)	202.55 (SD=409.15) (n = 24)	Adjusted Difference = (−47.13)[g] (SE= 32.14)	P = 0.14[g]
Incidence of autografting performed in DPT wounds	25.93 % (21/81 DPT wounds)	37.68 % (26/69 DPT wounds)	Odds ratio = 0.414 (95 % CI: 0.163 – 1.054)[h]	P = 0.0545[h]
Percentage of area of DPT wounds autografted	15.9 % (SD=38.57 %)	22.8 % (SD=43.72 %)	Adjusted difference = (−3.7 %)[i] (SE=7.6)	P = 0.5045[i]
MVSS score at 24 months from wound closure (assessed by blinded assessors)	3.21 (SD=2.78)	3.80 (SD=2.83)	Adjusted difference = (−2.39) (95 % CI; −3.25, −1.52)[e]	P < 0.0001[e] (non-inferiority)
Key exploratory /safety endpoints				
Duration of hospitalization (median days)	12 (95 % CI: 9–16) [j]	10 (95 % CI: 8–14) [j]	Median Difference = 2.00 (95 % CI: −2.66, 6.66)[b]	P = 0.0857[j]
Time to complete wound closure (median days from randomization)	32 (95 % CI: 28–42) [k] (n = 98 wounds)	34 (95 % CI: 28–38) [k] (n = 94 wounds)	Hazard ratio = 2.86 (95 % CI: 1.23–6.67) [l]	P = 0.0149[l] (non-inferiority)

[a] Median and 95 % CI estimated using Kaplan Meier method.
[b] 95 % CI for the median difference was calculated using the bootstrap method with 10,000 replications.
[c] Stratified generalized Wilcoxon-Gehan Test, p-value calculated using the re-randomization test.
[d] Estimated in 3 steps: Missing values were imputed using multiple imputations procedure; each imputed dataset was analyzed with adjusted ANOVA model, p-value calculated using the re-randomization test; the results across imputed datasets were pooled.
[e] Adjusted linear regression model with incorporated non-inferiority margin of 1.9 MVSS points for the SOC arm, one-sided p-value calculated using the re-randomization test.
[f] Adjusted logistic regression model, p-value calculated using the re-randomization test.
[g] Estimated in 3 steps: 1. missing values were imputed using multiple imputations procedure; 2. each imputed dataset was analyzed with stratified Wilcoxon test, p-value calculated using the re-randomization test; 3. the results across imputed datasets were pooled.
[h] Adjusted logistic regression model accounting for multiple wounds per patient, p-value calculated using the re-randomization test.
[i] Estimated in 3 steps: Missing values were imputed using multiple imputations procedure; each imputed dataset was analyzed with adjusted linear regression model, p-value calculated using the re-randomization test; the results across imputed datasets were pooled.
[j] Median and 95 % CI estimated using Kaplan Meier method. P value was calculated using Log Rank test.
[k] Median and 95 % CI estimated using Kaplan-Meier method.
[l] Adjusted parametric frailty model with incorporated non-inferiority margin of 7 days for the SOC arm.

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Declaration of Competing Interest

Yaron Shoham is a consultant for MediWound Ltd. (Yavne, Israel) and Vericel Corp. (Cambridge, MA, USA). Lior Rosenberg is a consultant for MediWound Ltd. (Yavne, Israel). The other authors have no conflicts of interest to disclose.

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Author contributions statement

YS and LR conceptualized and designed the study, collected the data, prepared the figures and tables, and critically reviewed and revised the manuscript. AJS contributed to the design, collected the data, drafted the initial manuscript, prepared the figures and contributed to the critical review of the manuscript. RPN, RS, RB, MK, SJM, YW, JM, GML and SL collected the data and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the study.

Patient consent statement

Informed consent for experimentation with human subjects was obtained for all the study participants from parents or legal guardians.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.burns.2025.107417.

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