Safety of enzymatic debridement in extensive burns larger than 15% total body surface area

Hofmaenner, Daniel A ; Steiger, Peter ; Schuepbach, Reto A ; Klinzing, Stephanie ; Waldner, Mathias ; Klein, Holger ; Enthofer, Katharina ; Giovanoli, Pietro ; Mannil, Lijo ; Buehler, Philipp Karl ; Plock, Jan A

Abstract: OBJECTIVES Bromelain-based enzymatic debridement has emerged as an alternative to surgical eschar removal. Indications include partial thickness, mixed pattern, and full-thickness burns. Enzymatic debridement has been approved by the European Medicines Agency for treating burn wounds affecting <15% total body surface area (TBSA). Data and evidence for the treatment of areas >15% TBSA in one session is scarce. The aim of this retrospective study was to retrospectively analyze off-label use of enzymatic debridement in a single burn center for large TBSA burns. METHODS Between 01/2017 and 12/2018, 59 patients with partial- to full-thickness burns underwent enzymatic debridement in a single center study. Patients were categorized into two groups: the regular use group with a treated area less than 15% TBSA and the off-label group (OG) with larger TBSA debrided in one session. Treatment was evaluated for systemic inflammatory reaction, bleeding, hemodynamic instability and electrolyte shifts. RESULTS In total, 49 patients were treated in the regular use group with a median application area of 6% (IQR 2.5-9.5) and 10 patients were treated in the off-label group with a median application area of 18% (IQR 15-19) TBSA. We found no significant differences regarding blood pressure, body temperature or hemodynamic stability during and after enzymatic debridement. No treatment-related serious adverse events were observed in either group. Catecholamine use was similar in both groups. No differences in leukocyte counts, CRP, PCT and lactate prior to application and during the following three days were observed. Sodium, potassium, chloride and phosphate levels did not differ. We found no evidence of an electrolyte shift. Survival was 49 of 49 patients (100%) in the RG and 7 of 10 patients (70%) in the OG ($p = 0.004$). CONCLUSION Enzymatic debridement did not result in any expected or unexpected side effects in the patient groups investigated. These preliminary results indicate the potential safety of bromelain-based enzymatic debridementin the treatment of burns greater than 15% TBSA.

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Safety of enzymatic debridement in extensive burns larger than 15% total body surface area

Daniel A. Hofmaenner [a], *Peter Steiger* [a], *Reto A. Schuepbach* [a], *Stephanie Klinzing* [a], *Mathias Waldner* [b], *Holger Klein* [b], *Katharina Enthofer* [a], *Pietro Giovanoli* [b], *Lijo Mannil* [b], *Philipp Karl Buehler* [a,1,*], *Jan A. Plock* [b,1]

[a] *Institute of Intensive Care, University Hospital Zurich, Zurich, Switzerland*
[b] *Department of Plastic and Hand Surgery, Burn Center, University Hospital Zurich, Zurich, Switzerland*

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ABSTRACT

Objectives: Bromelain-based enzymatic debridement has emerged as an alternative to surgical eschar removal. Indications include partial thickness, mixed pattern, and full-thickness burns. Enzymatic debridement has been approved by the European Medicines Agency for treating burn wounds affecting <15% total body surface area (TBSA). Data and evidence for the treatment of areas >15% TBSA in one session is scarce. The aim of this retrospective study was to retrospectively analyze off-label use of enzymatic debridement in a single burn center for large TBSA burns.

Methods: Between 01/2017 and 12/2018, 59 patients with partial- to full-thickness burns underwent enzymatic debridement in a single center study. Patients were categorized into two groups: the regular use group with a treated area less than 15% TBSA and the off-label group (OG) with larger TBSA debrided in one session. Treatment was evaluated for systemic inflammatory reaction, bleeding, hemodynamic instability and electrolyte shifts.

Results: In total, 49 patients were treated in the regular use group with a median application area of 6% (IQR 2.5–9.5) and 10 patients were treated in the off-label group with a median application area of 18% (IQR 15–19) TBSA. We found no significant differences regarding blood pressure, body temperature or hemodynamic stability during and after enzymatic debridement. No treatment-related serious adverse events were observed in either group. Catecholamine use was similar in both groups. No differences in leukocyte counts, CRP, PCT and lactate prior to application and during the following three days were observed. Sodium, potassium, chloride and phosphate levels did not differ. We found no evidence of an electrolyte shift. Survival was 49 of 49 patients (100%) in the RG and 7 of 10 patients (70%) in the OG ($p = 0.004$).

Conclusion: Enzymatic debridement did not result in any expected or unexpected side effects in the patient groups investigated. These preliminary results indicate the potential safety of bromelain-based enzymatic debridementin the treatment of burns greater than 15% TBSA.

* Corresponding author at: Institute of Intensive Care, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland.
E-mail address: Philipp.buehler@usz.ch (P.K. Buehler).
[1] Contributed equally.

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1. Introduction

At present, severe burn injuries are still associated with high morbidity and mortality rates, despite guideline-based referral and treatment in highly specialized burn centers. In recent years, bromelain-based enzymatic debridement has emerged as a new therapy option for deep partial- to full-thickness burns [1]. Enzymatic debridement is an alternative to standard care therapeutic approaches for eschar removal such as scrubbing, tangential excisions and other topical measures [2–5]. When enzymatic debridement is used within the first 72 h after injury, it is widely accepted that enzymatic eschar removal reduces also bacterial contamination, wound infections, blood loss, the need for autologous skin transplants and the length of hospital stay [3,6]. Principal indications include treatment of extremities and face [6–8].

However, data on large-area applications are limited and enzymatic debridement with NexoBrid® is not approved for large burns with burned areas exceeding 15% TBSA [9]. Moreover, data on potential therapy-specific side effects after enzymatic debridement is lacking. In particular, there is shortage of knowledge regarding inflammatory host response and related hemodynamic effects after application. Hypothetically activation of host immune cells by enzymatic escharolysis with subsequent release of proinflammatory mediators could induce systemic inflammatory effects following a second hit hypothesis. However also anti-inflammatory activity of Bromelain could theoretically effectuate the opposite. Eschar removal exposing a significant wound area may also result in additional fluid or electrolyte shifts, and potential bleeding, respectively.

The aim of this study was to investigate off-label extensive enzymatic debridement more in depth. We intended to analyze large TBSA application in comparison to regular enzymatic debridement treatment regarding systemic inflammatory effects, electrolyte shifting, hemodynamic instability and potential adverse events.

2. Methods

2.1. Study design

This study consisted of a single-center, retrospective data analysis conducted at the Burn Center of the University Hospital Zurich (Zurich, Switzerland). The ethics committee of the Canton Zurich approved the study protocol (Kantonale Ethikkommission Zurich BASEC ID 2017-01681). All patients were informed in depth prior to treatment and possible adverse events were explained thoroughly. All patients agreed to this procedure, in accordance with guidelines of the Swiss Academics for Medical Sciences (Supplementary Appendix). The decision to apply enzymatic debridement was based upon a pre-existing European consensus statement [6].

The patients were categorized into two groups, the regular treatment group with a treated area below 15% TBSA and the off-label treatment group with an area greater than 15% TBSA debrided in one session. The standard operating procedures in the burn center specify that each patient undergoing NexoBrid® treatment is admitted to the intensive care unit (ICU) of the Burn Center to ensure adequate analgesia, monitoring and if necessary sedation. It is an interdisciplinary treatment involving nurses, surgeons and intensivists. All patients had the same pre- and post-soaking dressing regimens before and after enzymatic debridement according to standard operating procedures.

2.2. Inclusion/exclusion criteria

All burn patients admitted to the burn center, irrespective of the total burned surface area, that were treated with enzymatic debridement within the ICU between January 2017 and December 2018 were eligible for the study and statistical analysis. Exclusion criteria were incomplete, erroneous or implausible electronic medical records or laboratory values.

2.3. Data collection

Two in-hospital electronic medical records databases were utilized to collect the data (KISIM Version 5.0, Cistec AG, Zurich, Switzerland and Patient Data Management System PDMS Version 6.1, iMDsoft, Dusseldorf, Germany).

Study-specific parameters included demographic data (age, sex, type of burn injury), relevant comorbidities (diabetes, alcohol abuse, drug abuse, immunosuppression, arterial hypertension, coronary artery disease, peripheral arterial occlusion disease, malignancies), vital signs (blood pressure, heart rate, body temperature), hemodynamic instability (any required hemodynamic support with catecholamines and/or other vasopressors), sedating medication (dosage of opioids, and anesthetics) and blood test results (sodium, potassium, chloride, magnesium, phosphate, calcium, leukocyte/neutrophil/lymphocyte count, C-reactive protein (CRP), procalcitonin (PCT), lactate, central venous oxygen saturation). Furthermore, treatment-related side-effects (clinically evident allergic reaction to applied agent, e.g. skin rash, respiratory compromise etc.) and serious adverse events (death, anaphylactic reactions, bleeding events) were analyzed. Bleeding was defined as an acute drop in hemoglobin level (greater than 1 g/dl) combined with other clinical signs of blood loss (change in baseline heart rate/blood pressure/etc.) according to the physician in charge. Non-demographic parameters were analyzed at four different timepoints with regard to the ED (−24 h, +24 h, +24–48 h, +48–72 h).

2.4. Statistical analysis

For continuous variables, results are expressed as median and interquartile range, whereas categorical variables are shown as numbers and percentages. Mann–Whitney *U* test, Wilcoxon signed-rank test or repeated-measures ANOVA were used to compare different groups. Post hoc tests with pairwise comparisons of either selected means of interest or all possible combinations of means were performed. Post hoc Sidak's multiple comparison correction was applied to account for multiple testing of comparisons between groups. All tests were two tailed; $p < .05$ was considered significant.

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Table 1 – Demographic data and characteristics.

	Overall (n = 59)	Regular treatment (n = 49)	Off-label treatment (n = 10)
Demographic data			
Male	43 (72.9%)	36 (73.5%)	7 (70.0%)
Age (y)	42 [31–59]	40 [32–59]	47.5 [31–58]
Height (m)	1.72 [1.65–1.80]	1.70 [1.65–1.79]	1.78 [1.70–1.80]
Weight (kg)	80 [68–90]	80 [66–90]	80 [80–90]
BMI (kg/m^2)	26.23 [23.41–30.06]	26.23 [23.15–30.07]	25.95 [24.69–27.78]
Alcohol level (‰)	0 [0–0.25]	0 [0–0]	0.15 [0–1.98]
Comorbidities			
Arterial hypertension	12 (20.3%)	10 (20.4%)	2 (20.0%)
Peripheral arterial occlusive disease	1 (1.7%)	1 (2.0%)	0 (0.0%)
Coronary arterial disease	6 (10.2%)	4 (8.2%)	2 (20.0%)
Diabetes mellitus	4 (6.8%)	2 (4.1%)	2 (20.0%)
Steroid medication	2 (3.4%)	2 (4.1%)	0 (0.0%)
Alcohol abuse	6 (10.2%)	5 (10.2%)	1 (10.0%)
Drug abuse	8 (13.6%)	8 (16.3%)	0 (0.0%)
Immunosuppression	1 (1.7%)	1 (2.0%)	0 (0%)
MTX medication	1 (1.7%)	1 (2.0%)	0 (0%)
Preexisting malignancy	0 (0%)	0 (0%)	0 (0%)
Renal function			
Creatinine (μmol/l) at admission	72 [60–93]	71 [59–93]	78 [68–89]
eGFR (ml/min) at admission	111.37 [86.14–131]	110 [82.88–132.36]	112.41 [104.53–123.25]
Creatinine (μmol/l) day2	81.5 [66–104]	80 [60–98.5]	87.5 [75–114]
eGFR (ml/min) day2	97.11 [78.64–121.16]	99.11 [79.42–129.34]	93.98 [73.71–110.5]
Characteristics burn injury			
Cause of accident			
Scalding	9 (15.3%)	8 (16.3%)	1 (10.0%)
Flame (deflagration)	34 (57.6%)	27 (55.1%)	7 (70.0%)
Fat/Oil burns	6 (10.2%)	5 (10.2%)	1 (10.0%)
Contact burn	2 (3.4%)	2 (4%)	0 (0%)
Electrical burn	1 (1.7%)	1 (2%)	0 (0%)
Electric arc	2 (3.4%)	2 (4.1%)	0 (0%)
Explosion	5 (8.5%)	4 (8.2%)	1 (10%)
TBSA (%)	13 [6–26]	11.5 [5–16]	42.75 [24–65]
ABSI Score	5 [4–7]	5 [4–7]	8.5 [7–11]
Baux Score	61.5 [43.5–84.5]	54 [40.5–76]	105.75 [86.5–112]
Inhalation trauma	5 (8.5%)	2 (4.1%)	3 (30%)
Prehospital Cooling	32 (60.4%)	24 (54.5%)	8 (88.9%)
Distribution of burn depth			
superficial	0 (0%)	0 (0%)	0 (0%)
superficial dermal	30 (50.8%)	26 (53.1%)	4 (40%)
deep dermal	29 (49.2%)	23 (46.9%)	6 (60%)
full-thickness	0 (0%)	0 (0%)	0 (0%)
Others			
Temperature [°C] at admission	36.5 [36.0–36.8]	36.55 [36.2–36.8]	35.65 [34.15–36.15]
Hypothermia at admission (<36.0 °C)	12 (23.5%)	6 (14%)	6 (75%)
Duration between accident and admission [h]	2.32 [1.25–5.58]	2.63 [1.49–6.28]	1.02 [0.73–2.78]
Length of hospital stay [d]	19 [10–32]	16 [9–27]	40.5 [19–55]
Prehospital intravenous infusions [ml]	750 [300–1200]	825 [275–1275]	700 [500–1000]
SAPS II Score	26 [19–36]	25 [19–33]	38.5 [28–45]

Demographic and injury characteristics of patients requiring enzymatic debridement of a limb, the trunk or multiple locations, from January 2017 to December 2018. Data expressed as number (%) or median, [Interquartile Range].

Abbreviations: eGFR estimated glomerular filtration rate, MTX methotrexate, TBSA Total body surface area, ABSI Abbreviated Burn Severity Index, SAPS II Simplified Acute Physiology Score.

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Table 2 – Intervention data.

	Overall (n = 59)	Regular treatment (n = 49)	Off-label treatment (n = 10)
Anesthesia			
Analgosedation	1 (1.7%)	1 (2%)	0 (0%)
Regional anesthesia (axillary plexus block)	5 (8.5%)	5 (10.2%)	0 (0%)
Regional anesthesia (femoral block)	2 (3.4%)	2 (4.1%)	0 (0%)
General anesthesia	51 (86.4%)	41 (83.7%)	10 (100%)
Time (minutes)	445 [330–540]	435 [300–540]	495 [430–630]
Cum. dose of propofol during intervention [mg]	200 [120–250]	167.5 [100–237.5]	200 [200–266]
Max. rate of remifentanil during intervention [mcg/h]	300 [250–300]	300 [225–350]	250 [250–250]
Cum. dose of fentanyl during intervention [mg]	0.4 [0.2–0.5]	0.4 [0.2–0.5]	0.5 [0.45–0.6]
Cum. dose of ketamine during intervention [mg]	60 [35–160]	50 [20–70]	250 [250–250]
Enzymatic debridement			
Time to surgically cover wounds with NexoBrid intraoperatively [min]	40 [30–60]	30 [30–60]	65 [45–80]
Body surface area [%] treated with NexoBrid	7 [2.5–12]	6 [2.5–9.5]	18 [15–19]
Time to apply NexoBrid after injury [d]	1 [1–3]	1 [1–2]	2.5 [0–4]

Surgical and anesthesiologic intervention data of the enzymatic debridement. Data expressed as number (%) or median, [Interquartile Range].

Table 3 – Outcome parameters.

	Regular treatment	Off-label treatment	Difference between predicted means	95 CI of the difference	p value	Adjusted p value (Regular vs. Off-label treatment)			
						Day -1	Day 1	Day 2	Day 3
Inflammation values									
CRP [mg/l]	135.7	228.7	−92.94	−132.8 to -53.11	0.5362	**0.0016**	0.2913	0.3701	0.0848
Leucocytes [G/l]	10.25	9.608	0.6446	−1.080 to 2.370	0.6306	0.9841	0.8157	0.7505	>0.9999
PCT [mcg/l]	3.691	2.713	0.9783	−1.839 to 3.796	0.6327	0.9995	0.6973	0.8812	0.9898
Patient characteristics									
Heart rate [bpm]	87.79	104	−16.24	−22.50 to −9.983	0.5315	0.566	**0.0048**	**0.0283**	**0.0157**
Systolic blood pressure [mmHg]	111.4	100.5	10.9	1.323 to 20.47	0.9971	0.5199	0.6918	0.7158	0.8201
Volume during intervention [ml]	475	700	225	0.000 to 780.0	**0.0393**				
Noradrenalin during intervention [mcg/min]	10	10.5	0.5	−7.000 to 12.00	0.7764				
Noradrenaline max [mcg/min]	13.12	16.98	−3.862	−9.841 to 2.116	0.2799	0.9987	0.2777	0.2489	0.9162
Lactate Level [mg/l]	1.733	2.249	−0.516	−0.9848 to −0.04721	0.5505	0.8969	0.0822	0.7463	0.998
ScVO2 max [%]	74.93	76.27	−1.34	−4.820 to 2.141	0.2003	0.5935	0.2735	0.9339	0.9823
ScVO2 min [%]	72.57	72.66	−0.09234	−3.628 to 3.443	0.3479	0.6187	0.6513	0.998	0.974
Electrolytes									
Natrium max [mmol/l]	139.2	142.2	−3.044	−4.649 to −1.438	0.8143	0.6924	0.1182	0.2523	0.0839
Natrium min [mmol/l]	137.9	140.3	−2.381	−3.891 to −0.8705	0.5606	0.8709	0.8298	0.2002	0.0577
Potassium max [mmol/l]	4.302	4.573	−0.2709	−0.4722 to −0.06951	0.1525	0.3476	**0.0081**	0.9768	>0.9999
Potassium min [mmol/l]	3.745	3.817	−0.07207	−0.2218 to 0.07762	0.2557	0.0968	>0.9999	>0.9999	0.9997
Calcium ionized max [mmol/l]	1.199	1.173	0.02602	0.004665 to 0.04737	0.294	0.9968	0.9961	0.4199	0.0553
Calcium ionized min [mmol/l]	1.119	1.082	0.03677	0.009694 to 0.06385	0.777	0.9593	0.4182	0.6052	0.2129
Calcium total max [mmol/l]	2.024	1.968	0.05613	−0.03825 to 0.1505	0.3326	0.9563	0.979	>0.9999	0.2085
Calcium total min [mmol/l]	2.023	1.955	0.06792	−0.02661 to 0.1624	0.4728	0.9721	>0.9999	>0.9999	0.2098

Inflammation parameters, other laboratory parameters and vital signs. Data are presented as means, difference between predicted means, 95 CI of the difference and p value overall and adjusted p value at various time points. The significance level is $p < 0.05$ (*).

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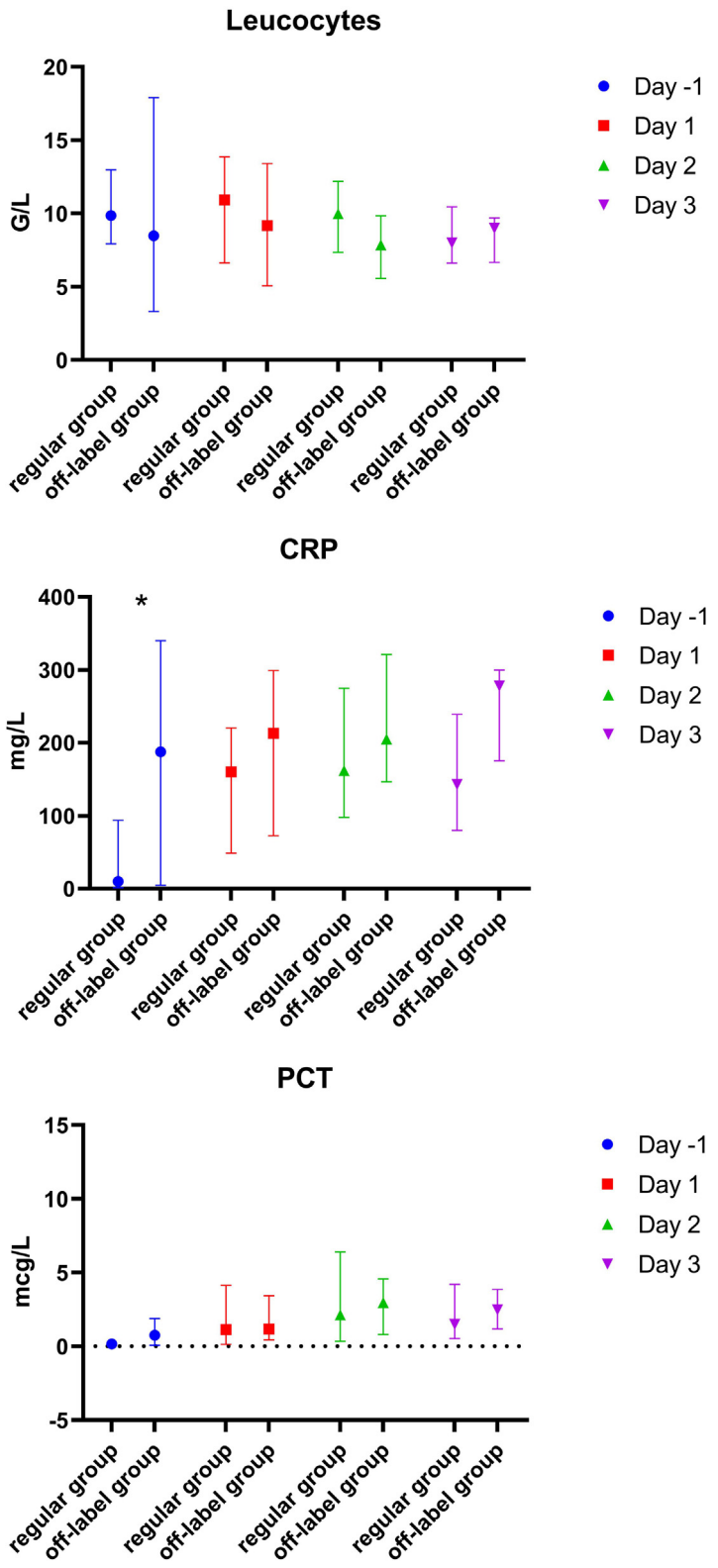

Fig. 1 – Inflammatory parameters.
Inflammatory parameters in standard laboratory analysis before and after enzymatic debridement with NexoBrid® in the regular treatment (<15% TBSA) and off-label treatment group (>15% TBSA). Data are presented as median and interquartile range. The significance level is $p < 0.05$ (*).

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Statistical analysis was performed using SPSS Version 23 (SPSS Science, Chicago, IL, USA), Graphpad prism 8 (San Diego, CA, USA), and Microsoft Excel (Microsoft Office Professional Plus 2013; Microsoft Corporation, Redmond, WA, USA).

3. Results

In total 59 patients were included in the data analysis. No patients were excluded according to exclusion criteria. In total, 49 patients were treated in the regular use group with an application area of 6% (IQR 2.5–9.5) and 10 patients were treated in the off-label group with an application area of 18% (IQR 15–19).

The demographic and injury characteristics, baseline and patient characteristics are summarized in Table 1. We found no differences in baseline and patient characteristics between the two groups.

Data directly related to the specific interventions are shown in Table 2. We found no differences in the timing of the procedure (i.e. time from admission to hospital until application, 2.5 [0–4] vs. 1 [1–2] days, p = 0.295), which means patients in the off-label group did not undergo ED later than patients in the regular use group.

Time needed to surgically cover the wounds (65 [45–80] vs. 30 [30–60], p = 0.024) was longer in the OG (Table 2).

Table 3 shows further details in terms of inflammation parameters, vital signs, other laboratory values and electrolytes at different time points. We found differences in heart rate for post-operative day 1–3 and fluid substitution during the intervention between the groups. All other potential side effect parameters showed no differences during the period investigated. No adverse or serious adverse events (death, anaphylactic reactions, bleeding events) occurred during this period. We found no difference in blood transfusions during enzymatic debridement procedure between the groups.

Fig. 1 shows different laboratory routine parameters for the inflammatory response on the day before the application of enzymatic debridement and the three subsequent days. The baseline CRP showed a difference between the two groups in the 24 h before debridement, with lower levels in the group with smaller burn and treatment areas.

Fig. 2 shows the vital parameters of the patients. We utilized these as monitoring parameters of hemodynamic instability. Only differences in heart rate on days 1–3 were detectable. We found no differences in catecholamine therapy during the intervention and over the following three days.

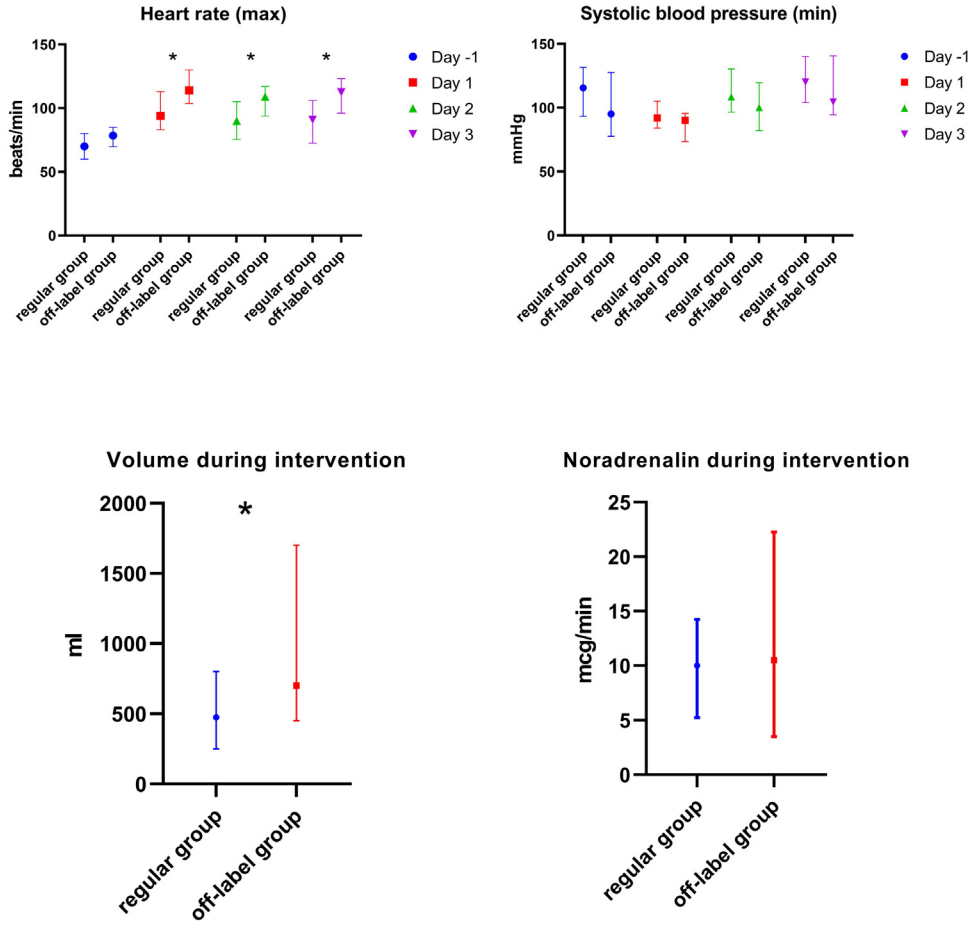

Fig. 2 – Vital signs and treatment.
Vital signs before and after enzymatic debridement with Nexobrid® in the regular treatment (<15% TBSA) and off-label treatment group (>15% TBSA). Hemodynamic treatment during intervention. Data are presented as median and interquartile range. The significance level is p < 0.05 (*).

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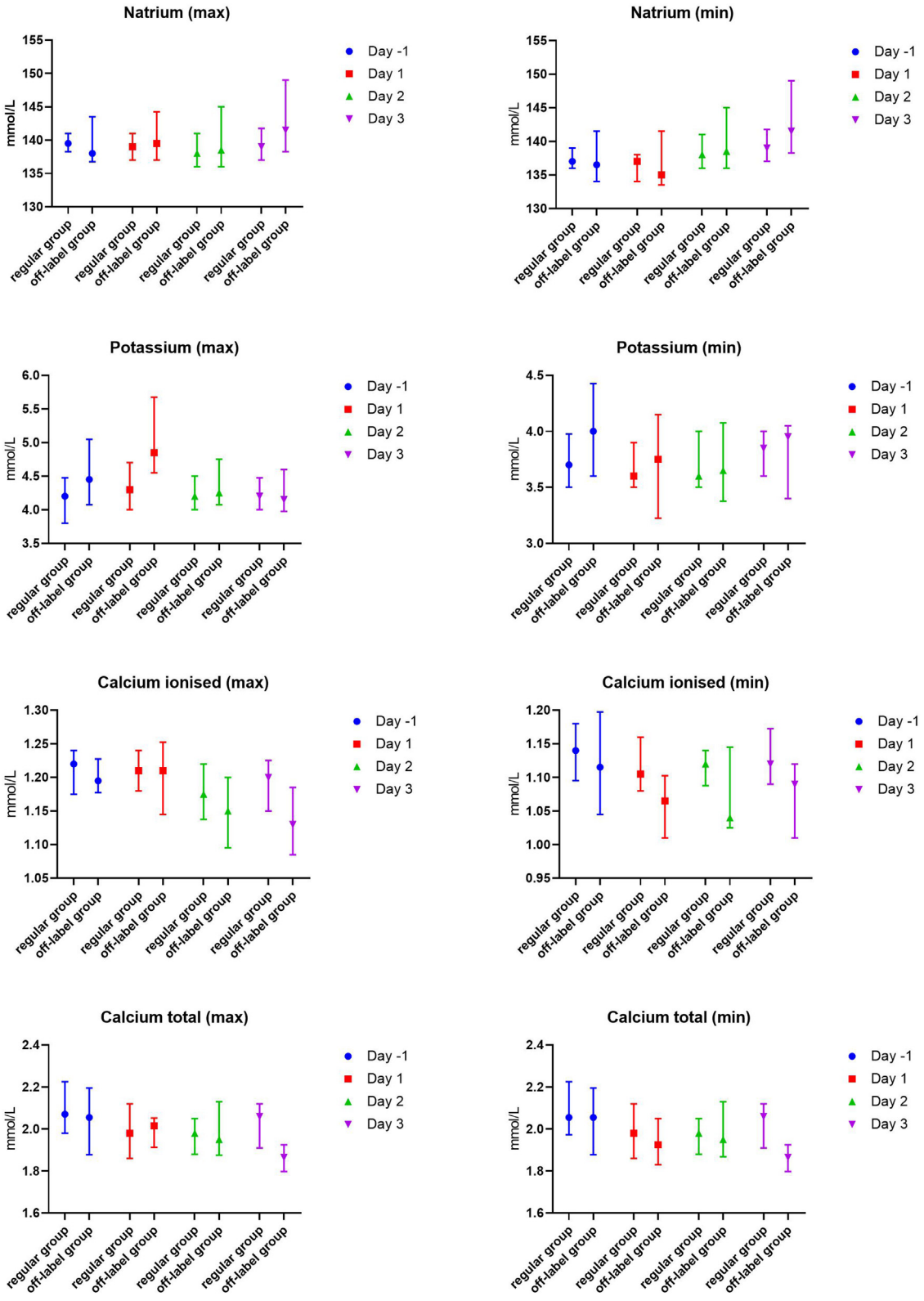

Fig. 3 – Electrolytes.
Electrolytes before and after enzymatic debridement with Nexobrid® in the regular treatment (<15% TBSA) and off-label treatment group (>15% TBSA). Data are presented as median and interquartile range. The significance level is $p < 0.05$ (*).

During the intervention, fluid delivered was higher in the off-label group.

In the course of treatment, no differences in electrolyte values could be observed. (Fig. 3)

In the regular use group, 30 of 49 patients (61.2%) underwent skin grafting, in the off-label group 5 of 10 patients (50%) ($p = 0.510$). In the regular use group, TBSA was 11.5 vs. 42.75% in the off-label group ($p < 0.0001$). ABSI was lower in the regular use group (5 vs. 8.5, $p = 0.0002$), Baux Score was lower in the regular use group (54 vs. 105.75, $p < 0.0001$). Survival was 49 of 49 patients (100%) in the regular use group and 7 of 10 patients (70%) in the off-label group ($p = 0.004$). In the regular use group, wound infections occurred in 6 of 43 patients (12.2%) and in 4 of 10 patients (40%) in the off-label group ($p = 0.06$).

4. Discussion

The present study aimed to investigate the safety and potential side effects of extensive (>15% TBSA), off-label use of enzymatic debridement compared to its regular use (<15% TBSA).

The main results show that off-label use of bromelain-based enzymatic debridement (burn injury >15% TBSA) was not associated with relevant hemodynamic or inflammatory effects in comparison to regular use (<15% TBSA). No adverse events were detected.

The observed difference regarding fluid requirements was most probably associated with the larger burn wound area debrided. In this regard, also elevated heart rates in the off-label group were not clinically relevant and mostly due to the hypermetabolic state of the patients. They were not considered clinically out of proportion, as no significant change was found in blood pressure and patients did not receive extra vasoactive support.

Interestingly, despite larger burn areas in the off-label group no systemic inflammatory response could be observed. Our laboratory routine data and systemic monitoring without evidence for a “second hit” are somewhat contradicting to previous reports on fever occurring after bromelain-based debridement [10]. It remains speculative without more scientific evidence, if anti-inflammatory effects of bromelain, which are described in other reports, may have contributed to these observations in our cohort [11–13].

Although other side effects apart from fever after application of enzymatic debridement have been reported in a single case report [14] the present study did not reveal any relevant adverse events after application, irrespective of the burn area.

In a rat model, higher concentrations of bromelain were shown to prolong prothrombin time and activated partial thromboplastin time [15,16]. This might hypothetically lead to more bleeding events in the off-label group. Interestingly, no such events were noted in the off-label group in the present study. This finding is in accordance with a previously published study showing no changes in blood coagulation parameters in humans after giving bromelain [17].

Enzymatic debridement was shown to be also safe in patients with arterial hypertension, coronary artery disease and peripheral arterial occlusion disease, supporting previous evidence of benefits of bromelain in cardiovascular pathologies [18–21].

To our knowledge, this is the first study addressing clinical off-label use of bromelain-based enzymatic debridement in more excessive burns, which is approved for regular use for burn injuries with TBSA <15% in Europe by the European Medicines Agency.

Our findings imply that enzymatic debridement can be performed safely in critical care patients with deep partial to full-thickness burns without significant hemodynamic impairment, electrolyte abnormalities or increased inflammation. We thus suggest that burn specialists also consider enzymatic debridement in patients exceeding 15% TBSA currently under off-label informed consent. In our opinion, the higher mortality in the off-label group was not related to enzymatic debridement but rather to the severity of the burn injury (%TBSA, ABSI, Baux).

Our study has several limitations. Data were collected retrospectively in a single-center, which may represent selection bias. The relatively small number of patients may have resulted in a lack of power and thus erroneously have missed differences. Furthermore, in clinical reality, the massive burn-associated inflammatory response might mask effects caused by the enzymatic debridement. Nevertheless, this report about systemic effects of enzymatic debridement exhibits the innovative potential of NexoBrid® for large area treatment >15% TBSA.

In conclusion, bromelain-based enzymatic debridement can be carried out safely in specialized burn centers without relevant side effects in large-area burns. The availability of a reliable and complication-free enzymatic debridement without significant systemic effects could open new horizons in the treatment of severe burns.

Author's contributions

Conception and design: PKB, JAP
Ethics Approval: PKB
Acquisition of data: DAH, PKB, KE
Analysis and interpretation of data: DAH, PKB
Writing up of the first draft of the manuscript: DAH, PKB
Revising the manuscript: DAH, PS, RAS, SK, MW, HK, KE, PG, LM, PKB, JAP
Drafting the final version of the manuscript: PKB, DAH

All authors have made substantial contributions to all of the following: the conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.

The manuscript, including related data, figures and tables has not been previously published and that the manuscript is not under consideration elsewhere.

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Conflict of interest

JAP is a consultant for Mediwound Germany.

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All other authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.burns.2020.10.012.

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