

A NEW BROMELAIN-ENRICHED PROTEOLYTIC ENZYMES CONCENTRATE TREATMENT IN PATIENTS WITH EXTENSIVE BURNS: ROMANIAN CONSENSUS

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Abstract

In the light of the recent studies, enzymatic debridement is associated with an increased safety profile, an enriched capacity for selective debridement of burn injuries, a significant reduction of blood loss during therapy and a marked decrease of the classical surgical excisions needs. In order to evaluate the results, to establish and extend the indications of enzymatic debridement (ED), a national meeting was organized, with experts who have gained significant experience regarding the use of enzymatic debridement during the therapeutic protocol of burned patients. The main objective of the meeting was to establish a national consensus regarding the enzymatic debridement based on the experience gained during the treatment of 342 patients within 7 Romanian health units. The consensus panel included Romanian experts with an extended experience in treating burns. The following parameters were analysed: optimal time for application, the used technique, pain management, and recommended behaviour after debridement, relationship between enzymatic debridement and grafting, analysis of haematological parameters, learning curve and learning technique. This consensus paperwork may attend as initial testimonial for the employment of enzymatic debridement with user-oriented references until forward proof and formal guiding principle are available.

Rezumat

În ceea ce privește debridarea enzimatică, studiile recente arată că aceasta se asociază cu un profil crescut de siguranță, o capacitate crescută de debridare selectivă a leziunilor de arsură, o reducere semnificativă a pierderilor sanguine asociate actului terapeutic, precum și o scădere marcată a necesității efectuării exciziilor chirurgicale clasice. Pentru evaluarea rezultatelor, stabilirea și extinderea indicațiilor debridării enzimatice a fost organizată la nivel național o întâlnire cu experți care au acumulat o experiență semnificativă în ceea ce privește utilizarea debridării enzimatice în protocolul terapeutic al pacienților cu arsuri. Obiectivul principal a fost elaborarea unui consens național, pe baza experienței acumulate în timpul efectuării debridării enzimatice în cazul a 342 de pacienți care au beneficiat de tratament în cadrul a 7 unități sanitare din România. În vederea stabilirii conduitei optime în ceea ce privește debridarea enzimatică au fost analizați următorii parametri: timpul optim de aplicare, tehnica utilizată, managementul durerii, conduita recomandată după debridare, relația dintre debridarea enzimatică și greșare, analizarea parametrilor hematologici, curba și tehnica de învățare. Acest consens poate fi considerat un ghid preliminar pentru utilizarea debridării enzimatice cu recomandări orientate către pacient până când sunt disponibile dovezi suplimentare și ghiduri sistematice.

Keywords: enzymatic debridement, burn treatment, concentrate of proteolytic enzymes enriched in bromelain

Introduction

Nowadays, for the eschar obliteration in burn patients, surgical debridement is reviewed as the gold standard. Performed within early 48 h, this procedure may enhance the follow-up of the burn wound treatment,

in regard with a considerable blood and heat loss improvement, and it encounters a lose selectivity, that is both operational and necrotic tissue may be carved [1-3]. Throughout time, various alternative techniques have been expanding in the attempt to beat these limitations, including hydro-surgery and enzymatic

debridement [2-5]. Not any of these can be appointed at the moment as standard of care.

The worldwide interest in the field of burns is increasing, innovation being the key to developing new medical techniques [6, 7]. The proposal related to the new concept of enzymatic debridement was based on the attempt to discover the therapeutic alternatives, which would increase the safety profile while reducing the overall treatment costs [8-9].

Starting from the principle regarding the selective debridement of devitalized tissues as the main factor related to the reduction of the healing period and having in the foreground the goal of obtaining minimal scarring, this new therapeutic approach was introduced, which involves performing the non-surgical enzymatic debridement of the burn lesions [10-12].

The literature shows that the main advantages of enzymatic debridement are: accelerating the healing period, increasing the safety profile of the treatment, obtaining high quality results in terms of scarring, improved functional recovery, reduced blood loss associated during the medical intervention, as well as a higher cost/benefit ratio compared to the classical surgical treatment.

Currently, worldwide intense research is being conducted towards the phenomenon of enzymatic debridement. In Romania, 342 patients have been treated using enzymatic debridement in 7 health care units, evenly distributed throughout the country. We concede that European and Italian consensus have newly been brought out [13, 14]. In their light, we acknowledge the relevance of the international recommendations as the ground and the beginning point for characterizing furthermore nation-specific consensus and proposals, like in our case, to preferably seize patterns and fluctuations in operating procedures that are frequently national and region-specific. Only one Romanian centre was engaged in the European consensus. Accordingly, it did not fully express the range and acquaintance of burn surveillance with enzymatic debridement in Romania. Mainly, the joined centres in the Romanian consensus tableau yielded a complex experience of a large number of patients treated using this technique.

In order to determine the position and the benefits of bromelain enzymatic debridement across the overview existing literature and in the light of the users' experience, gained during the treatment, a national consensus session was announced to afford statements for practice.

Materials and Methods

Endorsed by RSAS (Romanian Society of Aesthetic Surgery), on performing enzymatic debridement, with the purpose of removing the eschars in burn treatment, the Romanian proposals were characterized succeeding a process to assess the level of accordance (a measure of consensus) between choiced experts, representing

the Romanian burn centres, involving the enzymatic debridement's clinical issues. Systematic consensus accounts (e.g., Delphi method) were not performed, due to the scarce size of publications and innovations of the enzymatic debridement treatment modality in burns, and a changed consensus procedure was strengthened. The research results were centralized and statistically analysed, using the exact Fisher test, to test which variables differentiate according to the degree of satisfaction of experts in relation with the statements. The main objective was to obtain a national consensus, which could be the basis for improving the treatment of patients with extensive burns.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Declaration of Helsinki from 1975, as revised in 2008, as well as the national law. Informed consent was obtained from all the patients included in the study.

Panelists

The expert panellists were selected taking into account the clinical experience and former publication on enzymatic debridement involving the concentrate of bromelain-based proteolytic enzymes, general knowledge and renown in the burn treatment. Each assisting centre was asked to display one vote *per* statement, impassive the multitude of attendant participants from each centre.

Process

All panellists were given an online questionnaire with 34 manageable, pre-formulated consensus statements on enzymatic debridement for eschar removal in burns based on the peer-reviewed studies and the clinical significance, as well as the invited panellists' selected subjects. The following issues were covered by the statements: indications, large surface indication, preparation and application, the perfect time of application related with the multiple indications, pain management and anaesthesia, post-interventional wound management, skin grafting, follow-up and scar revision intendency, patient's perspective, logistical aspect and training outcomes. The major part consisted of approving all 34 pre-formulated statements. The panellists were required to note the endorsement or divergence with each consensus statement and, at the end, to reflect the consensus statements list. Therefore, a series of questions were developed, to which the participants were invited to answer according to the experience gained during the treatment of the patients admitted in their clinical departments.

Consensus agreement

Regarding the enzymatic debridement from this study, consensus was achieved when at least 80 percent accordance to every statement was expressed. Tables I - VII present the results, with the first column listing each statement's number (1 - 34), the second column submitting the statement, the third column displaying the number and percentage of "yes/no" votes and the

4th column indicating the synopsis whether the statement achieved consensus based of the aforementioned criteria.

Standard of care

All over the consensus process, surgical removal with tangential knives and/or hydro surgery were considered as surgical standard of care (SoC) and put on the wall if congruent with enzymatic debridement. Everything that isn't specifically required for enzymatic debridement will be followed for SOC for burn eschar removal, according to the panellist.

Results and Discussion

The following themes and consensus statements are grounded following the compacted experience of

treating 342 patients and in agreement with the existing literature data.

Regarding the topics related to the optimal time for application and the used technique, the participants were asked about the experience gained regarding the interval between the traumatic event and the enzymatic debridement, as well as details specific to the technique of application. Enzymatic debridement should be performed within 72 hours of the injury. If the wounds are not infected, anti-infective agents can be without delay employed after scar cleansing; however, anti-infective agents are not high ranked when talking about flushing and soaking, put in balance with saline in these wounds.

Table I

Consensus statements and agreement on optimal time for application and the used technique

No	Consensus agreement	Yes	No	Consensus
1	The enzyme treatment can be applied under optimal conditions within the first 24 hours after the trauma	7/7 (100%)	0/7 (0%)	Yes*
2	The treatment can be applied 3 days after the trauma on condition that the patient is prepared in an efficient manner	7/7 (100%)	0/7 (0%)	Yes*
3	The preparation of the treated area through rigorous primary surgical hygiene (enzymatic debridement of blisters) and hydration of the lesions in order to improve the penetration of the product is needed	7/7 (100%)	0/7 (0%)	Yes*
4	The optimal duration for the maintenance of the product on the lesion is 4 hours	6/7 (85.71%)	1/7 (14.28%)	Yes*
5	There is enough experience with longer duration for the maintenance of the product on the lesion compared to the interval recommended by the manufacturer	7/7 (100%)	0/7 (0%)	Yes*
6	The circumferential isolation of the lesion during the application of the product contributes to the increased efficiency of the enzymatic debridement	7/7 (100%)	0/7 (0%)	Yes*

*p < 0.001 for all statements (using the exact Fisher test)

Table II

Consensus statements and agreement on indications

No	Consensus agreement	Yes	No	Consensus
7	Enzymatic debridement represents a firm alternative to classical surgical excision related to preserving the remaining viable dermis	7/7 (100%)	0/7 (0%)	Yes*
8	The enzymatic debridement may be used for the treatment of head, hands and feet injuries, for 15% of the body surface area (BSA) in one session	7/7 (100%)	0/7 (0%)	Yes*
9	Suitable surveillance and hemodynamic assistance are requested in case of ED upwards of 15% BSA/session and it is deemed as an off-label indication	7/7 (100%)	0/7 (0%)	Yes*
10	The ED essential indication is the eschar deletion of the in thermal burns (flame, scalds, contact), while chemical and electrical burns are not specified through the indications	7/7 (100%)	0/7 (0%)	Yes*
11	The treatment can be performed in multiple sessions without increasing the risk level associated with the therapy	7/7 (100%)	0/7 (0%)	Yes*
12	In case of circumferential burns, the application of concentrate of proteolytic enzymes enriched in bromelain decreases the need to perform escharotomies	6/7 (85.71%)	1/7 (14.28%)	Yes*
13	The employment of enzymatic debridement for surfaces greater than 15% during the same session is not part of the usual practice	6/7 (85.71%)	1/7 (14.28%)	Yes*
14	ED have relevance in entire depth burns	7/7 (100%)	0/7 (0%)	Yes*
15	ED as a first choice in the early admission might hinder the progress of burn induced compartment disorder in comprehensive trunk burns	7/7 (100%)	0/7 (0%)	Yes*
16	In case of established respiratory compromise, ED cannot be performed replacing surgical treatment for extended trunk burns	7/7 (100%)	0/7 (0%)	Yes*
17	In case of determined compartment syndrome and high voltage, ED is not the election choice in the extremity	7/7 (100%)	0/7 (0%)	Yes*
18	Facial burns are a high rated indication for ED	7/7 (100%)	0/7 (0%)	Yes*
19	In the management of facial burns, before and after ED treatment, ophthalmological exam is appropriate	7/7 (100%)	0/7 (0%)	Yes*
20	ED is the treatment option for genital and perineal burns	7/7 (100%)	0/7 (0%)	Yes*

*p < 0.001 for all statements (using the exact Fisher test)

Table III

Consensus statements and agreement on pain management

No	Consensus agreement	Yes	No	Consensus
21	Pain therapy is essential for the proper development of enzymatic debridement in the intraoperative and postoperative stages	7/7 (100%)	0/7 (0%)	Yes*
22	The use of loco-regional anesthesia is a firm solution for limb burns	6/7 (85.71%)	1/7 (14.28%)	Yes*
23	In minor burns, ED can be accomplished using local anesthesia	7/7 (100%)	0/7 (0%)	Yes*

*p < 0.001 for all statements (using the exact Fisher test)

Table IV

Consensus statements and agreement on post-procedural conduct

No	Consensus agreement	Yes	No	Consensus
24	The enzyme debridement is associated with the decrease of the need for grafting, contributing to the overall decrease of the grafted body surface area	7/7 (100%)	0/7 (0%)	Yes*
25	Enzyme debridement contributes to lowering the risk level related to the treatment of patients with extensive burns by reducing the number of surgeries and decreasing the hospitalization period	6/7 (85.71%)	1/7 (14.28%)	Yes*
26	Long-term post-operative monitoring confirms that functional and aesthetic results are improved compared to the classical surgical treatment consisting of non-selective excision and grafting	7/7 (100%)	0/7 (0%)	Yes*

*p < 0.001 for all statements (using the exact Fisher test)

Table V

Consensus statements and agreement on haematovigilance

No	Consensus agreement	Yes	No	Consensus
27	The use of enzymatic debridement allows an improved control of blood loss compared to the classic surgical treatment, selective debridement being the main argument	7/7 (100%)	0/7 (0%)	Yes*
28	Emergent post-ED injure bed colour, bleeding models and 3D morphology should be evaluated by a practiced burn surgeon	7/7 (100%)	0/7 (0%)	Yes*
29	After ED, concerning farther treatment proceedings, a management plan should be straight drafted and implemented by an practiced burn surgeon	7/7 (100%)	0/7 (0%)	Yes*
30	In the wounds that are awaited to recover without autografting, membrane application and allografts it is possible to be claimed subsequent to the wet-to-dry phase	7/7 (100%)	0/7 (0%)	Yes*
31	The temporarily application of allografts in wounds can be performed for wounds that are not awaited to heal impulsively after ED preceding to autografting	7/7 (100%)	0/7 (0%)	Yes*
32	Indication for antibiotics administration is corresponding to surgical eschar excision	7/7 (100%)	0/7 (0%)	Yes*

*p < 0.001 for all statements (using the exact Fisher test)

Table VI

Consensus statements and agreement on learning curve

No	Consensus agreement	Yes	No	Consensus
33	The protocol recommended by the manufacturer can be easily reproduced by medical specialists, extending the indications requesting additional expertise	7/7 (100%)	0/7 (0%)	Yes*

*p < 0.001 for all statements (using the exact Fisher test)

Table VII

Consensus statements and agreement on cost-efficacy of enzymatic debridement

No	Consensus agreement	Yes	No	Consensus
34	ED maybe an effective tool for reducing the resources outcome (blood items, surgery, OR room capacity, human materials)	7/7 (100%)	0/7 (0%)	Yes*

*p < 0.001 for all statements (using the exact Fisher test)

For applications lasting more than 4 hours, all centres have reported effectiveness and safety. After 4 hours, the enzymes do not inactivate on their own. Clinical evaluation is used to assess burn wound, and no further technical measurements are required. Although

using the concentrate of bromelain-based proteolytic over more than 15% BSA *per* session is marked as an off-label indication, sequential-retarded applications, each implicating up to 15% BSA on different regions, are deemed on-label use. All centres had prior

experience in treating more than 15% BSA areas, applied sequential. Attendant fluids, high-profile surveillance, and pre-treatment threat bedding are required while handling patients on more than 25% BSA. Due to fluid loss and systemic issues, the same patient can be treated in different areas after at least 24 hours from the first application. Re-application in the same area is not advisable.

Bromelain is a combination of sulfhydryl proteolytic enzymes. According to the extraction site, they know each other stem bromelain (SBM) (EC 3.4.22.32) or fruit bromelain (FBM) (EC 3.4.22.33). Bromelain performs its enzymatic function over a wide-ranging spectrum and it is stable over a range of pH (5.5 to 8.0) and temperature (35.5°C to 71°C). Regarding the proteolytic enzymes functions, it is extensively explored, due to its surprising reliance in industries. But, apart from its industrial applications, the main one regards the phyto-medical potential. The literature describes some of bromelain actions: the inhibition of platelet aggregation, anti-oedematous, anti-thrombotic, anti-inflammatory, modulation of cytokines and immunity, skin debridement and fibrinolytic activities [15, 16]. These discoveries present bromelain as a promising candidate for the advancement of future anticancer restorative procedures. Remarkably, although there are several studies dealing with bromelain, the knowledge on the complete anticancer activity of this substance is yet less explored. The focus of Vidhya Rathnavelu *et al.* was to evidence the anticancer effects of bromelain, by studying the direct suppression of cancer cells, along with the evaluation of the anti-inflammatory activity and immune system function modulation of bromelain [17].

It also supports digestion, increases other drugs absorption and is a potential postoperatively agent that improve the wound management and decrease the postsurgical inconvenience and swelling [18].

The biochemical and pharmacological features of bromelain enhance the therapeutic potential of bromelain, as it is known that the main component of the raw bromelain is a proteolytic enzyme labelled glycoprotein, along with protease inhibitors, organic acids, coloured pigments. As yet, eight proteolytically active compounds have been isolated from bromelain [19]. From the total proteins, which cover 2%, proteinases are the most potent fraction. The composition of bromelain differs taking into account the source and the purification method; the protease content is increased in the stem bromelain compared with bromelain determined from the fruit [20]. Bromelain is absorbed into the human intestines and presents a half-life of ~ 6 - 9 h. At only one hour after administration, the highest level of bromelain it is reached [21]. Bromelain raises the bioavailability and diminish the possible side effects that are related with different antibiotics [17].

Regarding the indications, enzymatic debridement (performed with a bromelain-based proteolytic enzymes

concentrate) is the selective method for removing burn eschar, particularly in burn patterns with deep and mixed depths, where is fundamental to preserve the viable dermis and profound stratum, but the defiance resides into obtaining the standard of care. Enzymatic debridement is assessed off label for paediatric patients (age < 18 years). There are fewer centres that used ED on this particular type of patients. The paediatric patients' treatment should be evaluated as a peculiarly tailored clinical resolution taking into account the physician experience until more studies validate this indication.

The chapter dedicated to pain management focused on understanding the participants' experience regarding the necessity of performing the peri-procedural anaesthesia, as well as on the efficiency of the loco-regional blocks in case of limb burns. It should be considered that enzymatic debridement is a painful procedure that is why the analgo-sedation or anaesthesia is demanded, in correlation with the extent and profoundness of the burns. Appropriate pain management is especially important: at least 15 minutes prior to the application of enzymatic debridement, on-demand for the next 4 hours, and after the drug is removed. Depending on the type of analgo-sedation/anaesthesia, interdisciplinary pain management and proper monitoring should be combined.

The analysis of the post-procedural behaviour focused on defining the relationship between enzymatic debridement and the need for grafting, the ability to reduce the total graft surface, reducing the overall risk level, and obtaining improved aesthetic and functional results compared to those obtained by classical surgical treatment. The deeper the dermis is affected, the greater the diameter of the circular bleeding patterns in the dermis is. Exposed fat after treatment is a sign that skin grafting should be done as quickly as possible. After 2 - 18 hours of debridement, the wound should be examined for bleeding patterns. After enzymatic debridement, as bleeding may eventuate straightway, wet dressings may obstruct accurate assessment.

Regarding the blood loss, the expertise of the participants was requested regarding the comparative analysis of this parameter compared to the classical surgical treatment consisting of excision and grafting. Enzymatic debridement, as shown in several literature surveys, meaningfully decreases blood loss when resembled to the standard of care [22-24]. Associated with the anticoagulative therapy or maladies, however, there is a threat of blood loss enhancement. Haemoglobin monitoring should be done on a regular basis.

The analysis of the learning curve was focused on establishing the difficulty level related to acquiring the knowledge necessary to perform the standard protocol, as well as of extending it in order to obtain additional results. Enzymatic debridement may be performed by a qualified surgeon at the time of admission, but it does not necessitate the use of an

operating room or surgical staff. According to the European encounter of a mass burn casualty occurrence in Bucharest [13], 39 seriously burned patients were fortunately healed at two different hospitals in the first 48 hours. Lack of training and the bromelain enriched concentrate stock availability are two potential drawbacks of using rapid enzymatic debridement. The existence of a national/international mass disasters burn network, as well as the ability to forward both bromelain concentrate and qualified experienced professionals to the disaster site to watch and lead the processes, help to defeat the above constraints in these emergency situations.

Regarding the decrease of the need to perform grafting, as well as the risks associated with the surgical act, the use of enzymatic debridement is proving to be a very useful technique [25], as it appears from the completion of the questionnaire by the participants. Another aspect emphasized by the experts refers to the hydration of the lesions, namely the fact that maintaining the hydration of the remaining viable dermis after the enzymatic debridement is fundamental for successfully avoiding secondary grafting.

Enzymatic debridement has aroused the interest of the international scientific community, a multitude of scientific materials being dedicated to the understanding of the mechanisms and long-term effects on the healing quality of patients who have suffered burns. According to Schulz *et al.*, most studies have shown that enzymatic debridement is more appropriate and thus can conserve viable tissue with excellent outcome results [6]. In the same paper, the authors show that the enzymatic debridement proved to be an effective method in 90% of cases, complete healing (with less than 5% remaining defect) being achieved in approximately 28 days.

Regarding the versatility of enzymatic debridement with bromelain-enhanced products, Shoham *et al.* shows encouraging results in the treatment of chronic wounds, all wounds achieving an average of $68 \pm 30\%$ debridement in an average of 3.5 ± 2.8 enzymatic debridement 4-hour sessions [26]. The authors also present preliminary results that indicate the effectiveness of enzymatic debridement with bromelain-enhanced products in the treatment of chronic lesions, while maintaining a high safety profile.

Enzymatic debridement using bromelain-enhanced products expands the plastic surgeons' arsenal, while providing good long-term results, according to the article published by Osinga *et al.* [27]. The results of the study conducted at the University Hospital of Zurich showed that the average length of hospitalization was 38 (1 - 92) days, the patients included in the study being aged between 19 - 78 years (average 51) and presenting body surface area affected by burns between 1% and 67%. On average, the burned body surface treated by enzymatic debridement was 11%, the interval between trauma and debridement being 7 days (1 -

19). The conclusions of the study supported the effectiveness of the enzymatic debridement for the treatment of burns, as well as the reduced need to perform surgical treatment in these patients.

The experience gained by Romanian plastic surgeons with respect to the employment of ED in the treatment of severe burns created the premises for a study dedicated to understanding their opinion on the principles of enzymatic debridement and the ability to implement this system nationwide.

Enzymatic debridement is a fruitful therapeutic option for the treatment of patients with moderate and severe burns. The literature shows [2, 23, 24, 28-30] and the experience of the participants to the consensus confirms the efficiency of the enzymatic debridement in the patients with compartment syndrome. Regarding the long-term post-procedural prognosis, from a functional point of view the selective preservation of viable structures represents an extremely important factor that contributes to the improvement of the quality of the scars and, consequently, to the increase of the potential related to functional recovery [24], regarding this aspect being also a strong consensus among study participants.

Conclusions

The enzymatic debridement represents a firm alternative to the classic surgical treatment, in strict compliance with the manufacturer's indications, also having encouraging results regarding the extension of these indications, the treatment being performed by experienced surgical teams.

Regarding the national consensus, this initiative aims to achieve uniformity related to the treatment performed by specialized professionals.

The research has a significant importance given the fact that so far in Romania no such approach has been made. The present study aims to establish the foundation for further research, the results contributing to the development of the existing knowledge in order to obtain the best treatment for the patients affected by extensive burns.

Conflict of interest

The authors declare no conflict of interest.

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