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Combination of enzymatic debridement with Nexobrid and surgical debridement under intensive care in a patient with massive burn injury: A case report

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Abstract：A 73-year-old man, critically injured in a burn incident resulting from cooking gas explosion, was transferred by helicopter ambulance to Shimane Prefectural central hospital. Upon arrival, the patient was intubated. The Total Burn Surface Area（TBSA）was 84%, mainly with Deep Burns（DB）, and the Prognostic Burn Index（PBI）was 150. We performed enzymatic debridement on the maximum insurance coverage of 30% Burn Surface Area（BSA）in total with topical agent Nexobrid（Kaken Pharmaceutical Co., Ltd.）, a concentrate of proteolytic enzymes extracted from pineapple stem, launched in Japan in August, 2023. Nexobrid only removes nonviable necrotic tissue or eschar in Deep Dermal Burns（DDB）and DB even in the early period after trauma, when accurate evaluation of burn depth is often challenging. Early accurate debridement raises the possibility of dermal preservation, which is important for spontaneous epithelization, and wound bed preparation if skin graft is needed. While the patient died of circulatory failure 4 days after trauma, our experience suggests that Nexobrid is an early, accurate, and less-invasive alternative in debridement, and may assist treatment for burns that affected larger area with surgical debridement combination. However, additional experiences and follow-ups are required to susbtantiate its benefit.

Key words：burns, enzymatic debridement, Nexobrid

外科手術と壊死組織除去剤ネキソブリッドを併用して デブリドマンを施行した全身熱傷の一例

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概　　要：症例は73歳男性，ガスコンロへの引火により全身熱傷（Ⅲ度熱傷，熱傷面積（Total Burn Surface Area: TBSA）84％程度，熱傷予後指数（Prognostic Burn Index: PBI）150程度）を受傷した一例に対して，2023年８月より日本国内で販売開始となった壊死組織除去剤ネキソブリッドを使用してTBSA 30％の範囲にデブリドマンを施行した．ネキソブリッドは蛋白分解酵素を有するパイナップル茎搾汁精製物を有効成分とする薬剤である．皮膚の壊死部と正常部の境界が不明瞭な受傷後超早期（12時間以内）または早期（12-72時間以内）であっても本剤の熱傷部への塗布により熱傷で生じた壊死組織のみを除去することが可能であり，深達性Ⅱ度熱傷，Ⅲ度熱傷への適応が推奨されている．デブリドマンの高い選択性によって真皮が温存される可能性が高まり，自然な上皮化の促進や植皮の必要面積の縮小などにつながる．本症例の患者は循環不全により死亡したものの，適切な部位に使用し，外科的壊死組織除去と組み合わせることで，将来的により効率の良い熱傷治療を提供できる可能性が示唆された．今後さらなる経験例を増やし，経過を見ていく必要がある．

索引用語：熱傷，化学的デブリドマン，ネキソブリッド

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【Introduction】

Nexobrid（Kaken Pharmaceutical Co., Ltd.）, launched in Japan in August 2023, is a concentrate of proteolytic enzymes extracted from pineapple stem and is designed to remove nonviable necrotic tissue or eschar in deep dermal burns（DDB）and deep burns（DB）[1]. Initial assessment of burn depth is often inaccurate[2,3] as it is difficult to visually distinguish vital from necrotic tissue at early period after trauma, which may result in unnecessary surgery or damage to the vital dermis. In contrast, a high selectivity of debridement at early hours after trauma using Nexobrid may potentially facilitate dermal preservation and an early accurate burn depth evaluation may help determine the appropriate treatment[2,4-6]. Following its recent approval in Japan, only few domestic reports on Nexobrid exist, and report about its application on massively burned patient with severe systemic state remains scarce. Herein, we report a case of severe-burn patient treated with Nexobrid, along with a literature review.

【Case Presentation】

A 73-year-old man with critically-ill burn was transferred through a helicopter ambulance to Shimane Prefectural Central Hospital. The patient was involved in cooking gas explosion at 5:00 am on that day. Although the patient was initially transported to another hospital, the hospital could not deal with the case and the patient was transferred to our hospital. On arrival at 11:03, the patient was mechanically ventilated with mild spontaneous breathing, and was receiving midazolam infusion for sedation. The Glasgow Coma Scale（GCS）was E1VTM1. The vital signs were as follows: low blood pressure and heart rate, which were not able to be measured, and SpO_2 by pulse oximetry 99%（FiO_2 0.6, mechanically ventilated. The Total Burn Surface Area（TBSA）was 84%, with most part of DB and partial DDB combination affecting the entire body **(Figure 1a–c)**. The burn index（BI）was 77 %, and the prognostic BI（PBI）was 150. The patient has a history of rheumatoid arthritis and cerebral infarction with left-sided hemiparesis. Daily medication included methotrexate, folate, and biaspirin. The patient was living alone and maintained autonomy in activities of daily living（ADL）.

Initial burn assessment: Burn Surface Area (BSA) % and burn depth

Face and neck	4 + 5 %（DDB + DB）
Chest and abdomen	3 + 15 %（DDB + DB）
Back and buttocks	1 + 5 %（DDB + DB）
Right side of the upper limb	8 %（DB）
Left side of the upper limb	9 %（DB）
Right side of the lower limb	4 + 12 %（DDB + DB）
Left side of the lower limb	2 + 16 %（DDB + DB）

After admission, immediate skin-incision on the lower abdomen and bilaterally in the lower limb for decompression **(Figure 1a, c)** was made at the emergency room to prevent compartment syndrome. A life-saving emergency burn surgery for 3 h over around 20% Burn Surface Area（BSA）was scheduled. Surgical debridement and skin graft under general anesthesia were performed 11 hours after trauma. The patient was first placed in the left lateral position, and split-thickness skin grafts（STSG）were harvested from the right lateral back using a mechanical dermatome set to 0.2 mm thickness. The patient was subsequently placed in the supine position, and a debridement using electrocautery on the neck, chest, abdomen and the anterior surface of bilateral thigh was performed mainly over DB. Full-thickness debridement was performed in the sequential excision manner down to bleeding, visually vital fat tissue **(Figure 2a)**. Part of the harvested STSG were placed into a skin graft mesher and expanded to a ratio of 1:6. We applied the unmeshed STSG（sheet grafts）on the neck, and the meshed grafts on the chest and abdomen **(Figure 2b)**. Staples were used to fix the STSG to the wound bed, and tie-over dressing was applied to secure its immobilization. As the surface area that needs to be covered was larger than the available donor sites, we applied dermal substitute matrix（PELNAC® Bilayer Wound Matrix, Gunze Co., Ltd.）to the anterior surface of bilateral thigh for dermal wound bed preparation. Delayed sequential skin grafting

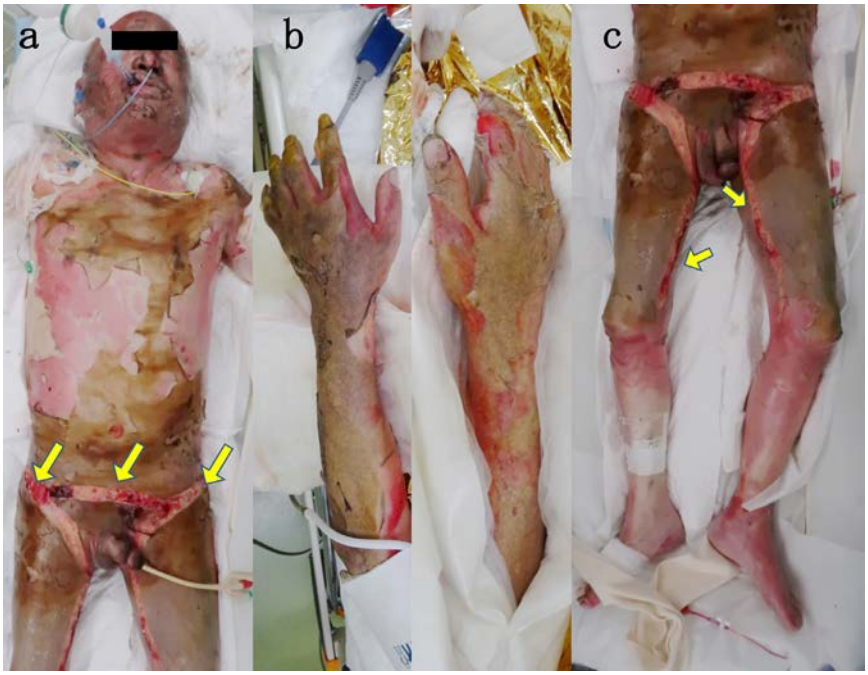

Figure 1. Patient with burn caused by cooking gas explosion（before the initial surgery）. Upon arrival, immediate skin-incision for decompression on the lower abdomen and the lower limb bilaterally was performed（arrows）.（a）Partial Deep Dermal Burns（DDB）and Deep Burns（DB）on most part of the chest and abdomen.（b）DB on the bilateral forearms.（c）DDB and DB on the bilateral lower limb.

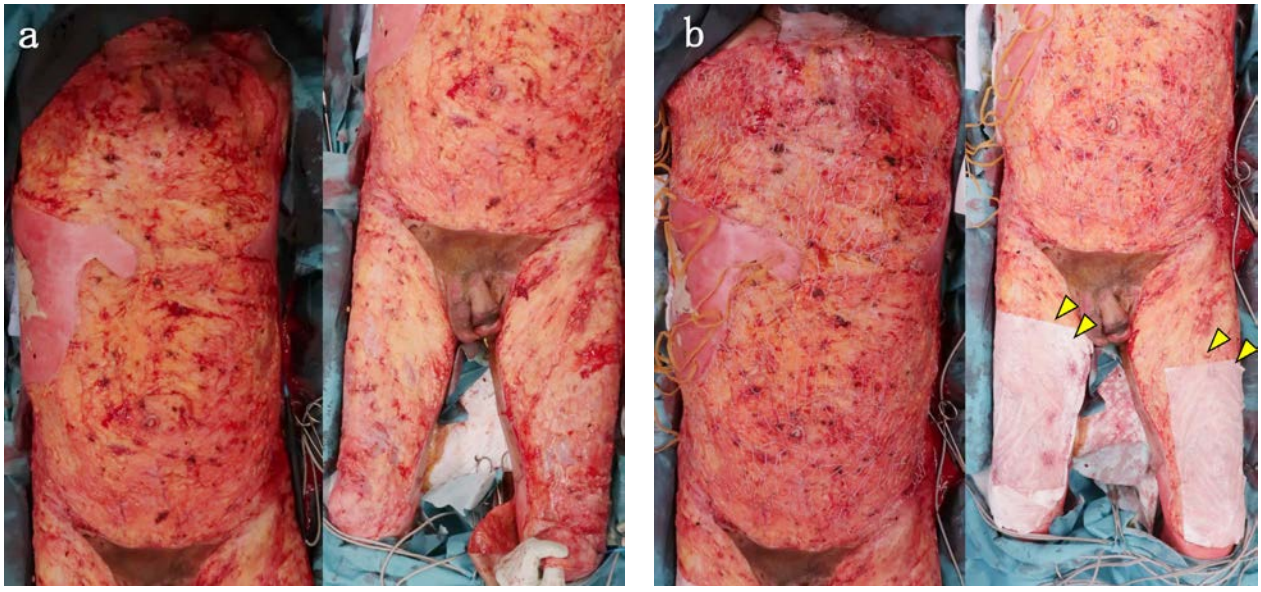

Figure 2. After surgical debridement and split-thickness skin graft.（a）Full-thickness debridement was done in the sequential excision manner down to bleeding, visually vital fat tissue.（b）Part of the harvested STSGs expanded to a ratio of 1:6 was applied on the chest and abdomen. Unmeshed STSGs（sheet grafts）were applied on the neck. Staples were used to fix the STSG to the wound bed. Due to the shortage of STSGs, we applied dermal substitute matrix（PELNAC® Bilayer Wound Matrix, Gunze Co., Ltd.）to the anterior surface of bilateral thigh for dermal wound bed preparation（arrow heads）.

using cultured epidermal autograft（JACE®, Japan Tissue Engineering Co., Ltd.）, was planned. Prior to surgery, a small part of healthy skin tissue was harvested from the patient on day 2 for culturing epidermal cells. The patient maintained a low blood pressure that lasted after the initial surgery, which required careful monitoring and blood pressure management with continuous norepinephrine infusion. Further decrease in blood pressure was observed even at postural changes during daily wound care at the bedside. Under this critically-ill state with unstable hemodynamics, we decided not to conduct another debridement surgery for the remaining affected surface area, and perform enzymatic debridement using Nexobrid instead. Enzymatic debridement was performed on the maximum insurance coverage of 30% BSA in two different sessions with 15% BSA each. On day 2, Nexobrid（15% BSA in total）was applied to the right and left side of the upper limb, at 32 h and 27 h after trauma, respectively **(Figure 3a-c)**. On day 3, 60 h after trauma, Nexobrid was applied to the bilateral lower limbs in a same manner, which corresponds to another 15 % BSA **(Figure 3d, e)**.

Following the instruction and adding some arrangements, Nexobrid was applied in three consecutive steps including preparation, application and removal[1)].

■ Preparation

The wound was thoroughly cleaned with normal saline to remove blisters（keratin layer of the epidermis）and other unnecessary tissues, followed by 2 h occlusion of the burned area with gauze soaked with normal saline.

■ Application

The surrounding skin area around the targeted wound surface was covered with semipermeable waterproof film（Multi Fix-Roll®, ALCARE Co., Ltd）to avoid Nexobrid leakage. Nexobrid was applied to the targeted wound surface and was covered with a gauze, which is also sealed with Multi Fix-Roll® at the side of contact with the wound. The wound was left in place for hours after it was dressed with loose, thick, and fluffy gauze with bandage.

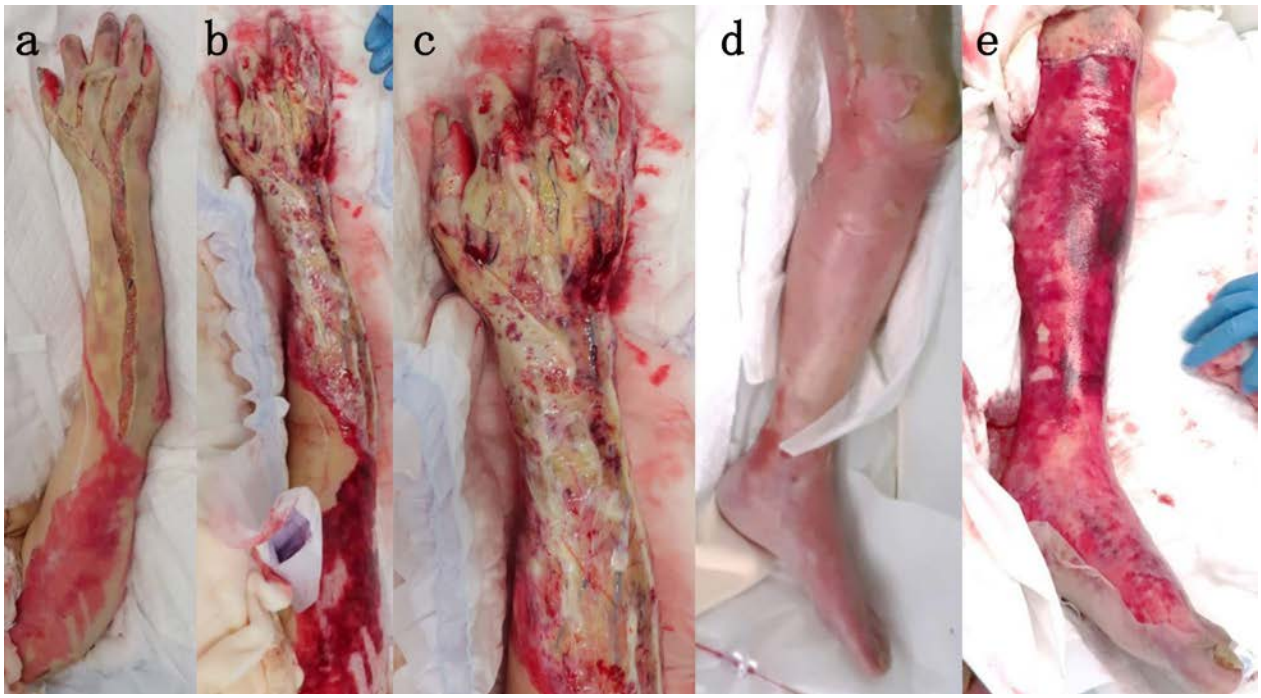

Figure 3. Enzymatic debridement with Nexobrid®（Note that left upper and lower limbs are not shown above）.（a）Right upper limb before the treatment（32 h after trauma）.（b）After the removal of Nexobrid® on the right side of the upper limb, 4 h after its application.（c）Enlarged view of the image（b）.（d）Left lower limb before the treatment（60 h after trauma）.（e）After the removal of Nexobrid® on the left side of the lower limb, 4 h after its application.

■ Removal

The dressing was released, and the treated area was rubbed by a gauze soaked with saline to remove the Nexobrid and other remnants of necrotic tissue. The area was wiped until the clear dermis or subcutaneous tissue appears.

An ointment（Bucladesine Sodium + Sucrose, Povidone-Iodine mixed）was applied to the treated area and wrapped with gauze and bandage.

Debridement quality of eschar and other necrotic tissue appeared to be prominent than we had expected. Some areas appeared to be intact immediately after the debridement, which was easily dissolved with rubbing. However, debridement of the areas where the epidermis remained before the application of Nexobrid were insufficient.

Although most part of the wound appeared to be DB at the initial assessment, dermis was preserved in some areas, which raises the possibility to epithelize spontaneously, or may at least reduce surface area that needs skin graft. In other areas, fat tissues were exposed. The wound was then dressed with gauze soaked with ZALKONIN® SOLUTION 0.025（Benzalkonium Chloride, Kenei Pharmaceutical Co., Ltd.,）. Daily wound care was done with conservative treatment with ointment（Bucladesine Sodium + Sucrose, Povidone-Iodine mixed）to the area where dermis was preserved. Applying STSG in the scheduled surgery for anterior thigh was planned for the area where fat tissue was expose. Due to the worsening of circulatory failure, the patient died 4 days after admission.

【Discussion】

Enzymatic debridement with Nexobrid is indicated for patients with DB and DDB[1)]. Contraindications are described for patients with a known hypersensitivity to bromelain, pineapples, papayas, and papain[1)]. It can be applied even at markedly early（within 12 h）to early（between 12-72 h）timing after trauma.[4)]

Over the last few years, enzymatic debridement with Nexobrid has become popular in countries outside Japan. In previous studies, advantages of debridement with Nexobrid include high preservability of dermis owing to its distinguished selectivity in debridement[2,4-6)], reduction in procedural blood loss[5,6)] and shortening the duration of debridement[5)]. Kreiger et al. found that only 28.6% of the area thought to be DB at the initial assessment were indeed burned to this depth[3)]. This indicates the difficulty in distinguishing vital from necrotic tissue on inspection at early period after trauma, which can result in further excision surgery with damage on preservable dermis[2)]. As the dermis is important for epithelization, dermal preservation with Nexobrid after debridement enables an increase in surface area that can spontaneously epithelize, and therefore decreases the surface area that needs skin grafts[2,5,6)]. A study has shown that Nexobrid reduces the number of surgical excisions needed up to one third, and the surface area that needs surgical excision up to one quarter[5)].

As the number of blood transfusion has been reported to be associated with mortality and infectious episodes in major burn patients[7)], reduction in procedural blood loss prevents needless blood transfusion. According to a study, the average time for complete debridement utilizing Neobrid is 2.2 days, which is far below 8.7 days in surgical debridement[5)].

In terms of insurance coverage, the use of Nexobrid is possible with up to 15% BSA per session and must not exceed 30% BSA in total under sequential use[8)]. There is a lack of appropriate evidence on the effectiveness or safety of Nexobrid applying to the BSA larger than 30%; however, the use of Nexobrid over 30% BSA has been reported in other countries[6,9)]. There were two case reports about a partial Nexobrid use over 80% TBSA patient, similar to the presented case[6,9)]. In one case, the patient died due to systemic failure after successful enzymatic debridement[9)], and in another case, the patient was resuscitated with successful skin graft after surgical and enzymatic debridement combination[6)]. Although the latter case showed successful result, a major part of the patient was DDB[6)], which cannot be directly compared with or applied to our case. In case the wound area needed for

debridement is larger than 30% BSA, a combination of enzymatic and surgical debridement would be necessary[6]. At this point, we should consider which part of the wound Nexobrid should be applied. Previous studies demonstrated that facial and hand burns can be good indications[2-4,10,11]. Due to its morphologically ununiform surface, surgical debridement is often challenging in face, and even a small loss of tissue has a large impact on change in appearance[2]. Thus, dermal preservation that promotes less scaring is necessary[2]. Schulz et al. reported 77% of facial burn wounds treated enzymatically appeared more superficially burned than initially assessed[2]. Hand burns, as another good indication, have shown good outcomes both in function and appearance[3,4,10,11]. Hands are markedly vulnerable with its complex anatomical structures packed in limited space[10]. Intricate components such as nerves, vessels, and tendons are prone to be easily damaged by surgical debridement[11], which directly associates with functional loss. Early and highly selective debridement with Nexobrid is therefore beneficial, with skin-grafted areas reduced by 37% compared to the initial assessment in a study[11].

Conversely, according to the European consensus guidelines, debridement with Nexobrid is not recommended in the truncus and extremity with established compartment syndrome[4]. Under such state, immediate decompression is essential, which is only achievable by surgical debridement. Similar to the presented case, for decompression, we performed immediately upon arrival a skin-incision on the lower abdomen and the lower limb bilaterally, which appeared to be ischemic.

Decision on whether the wound needs skin grafts or other procedures after the enzymatic debridement with Nexorid is challenging and remains controversial[4]. The European consensus guidelines suggest skin graft should be considered after 21 days if there is no significant process in epithelization[4], whereas Bowers et al. suggested to wait at least 14 days before decision[6]. The presence of adequate dermis in the wound, is assessed as indicative of a potential to heal spontaneously[6]. However, if subdermal fat is exposed, it is regarded as full-thickness tissue loss, which can highly be an indication for skin graft[6]. Regarding the timing of skin graft, at least two days after enzymatic debridement is recommended by the European consensus guidelines[4], and five days by Bowers et al[6].

Pain management is another important factor in debridement with Nexobrid[4,6,8]. In the domestic clinical trial, opioids, analgesics, and nonsteroidal anti-inflammatory drugs were used[8]. Additionally, use of local anesthesia and regional blocks has been reported in previous literature[6]. A combination of ReCell® (Avita medical, inc.) spray (cultured autologous cell product) and xenograft or allograft is also recommended to reduce pain during dressing changes[6]. In the presented case, the patient was continuously administered with intravenous sedative agent under critically-ill state, which excluded the need for additional pain control. However, strong pain is induced immediately after the application of Nexobrid, and during its removal[8]. Preparation of pain medication is needed when patients are awake.

While our observation period with this patient was remarkably short to conclusively demonstrate the effectiveness of Nexobrid, we advocate for its use in burn patients. This aligns with the recommendation of Bowers et al. who propose that facilities initiating enzymatic debridement should commence with a small area and progressively gain experience in managing extensively burned patients[6].

【Conclusion】

Our experience suggests that Nexobrid can be an early, accurate, and less-invasive alternative in debridement. The potential for treating larger areas affected by burns may be enhanced if enzymatic debridement with Nexobrid is combined with surgical debridement. However, additional experiences and longer follow ups are needed to substantiate the benefit of this approach.

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