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Article

Nexobrid Use in the Elderly

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Abstract

Background: Nexobrid (NXB) is a pineapple-derived enzymatic debridement product approved for patients aged 18 to 65. This study evaluated its off-label use in an elderly population with severe burns. **Methods:** This was a case-series study involving 43 patients aged 66-94 years who had deep-partial and full-thickness burns treated with NXB. We assessed patient demographics, burn characteristics, treatment outcomes, and complications. **Results:** The most common cause of burns was flame. The median total burned surface area (TBSA) was 11%, and the median NXB-treated area was 7.41%. Most patients (76.74%) required surgery following debridement. The median hospital stay was 26.5 days, and the median time to healing was 63 days. The rates for mortality, infections, and transfusion requirements were 25.58% each. Nine patients developed hypertrophic scarring. **Conclusions:** NXB is a useful tool for debriding burns on the hands, face, and limbs in the elderly, offering a less aggressive alternative to surgical debridement. However, a significant proportion of these patients still need surgery to close their wounds and may develop hypertrophic scars. Therefore, a careful risk-benefit assessment is necessary before its application in this patient group.

Keywords: Nexobrid; elderly; experience

1. Introduction

Nexobrid (NXB) is a pineapple-derived product (bromelain) used for the debridement of deep-partial and full-thickness burns. NXB has been approved for patients of all ages [1]. It has been proved to reduce the need for surgery and transfusion [2]. EMA states that the experience using NXB in patients >65 y.o. is limited and requires assessment of risks and benefits [3]. Our Burns center in Vall d'Hebron Hospital has years of experience using this product on elderly patients and regularly participates in consensus documents about its general use [4]. A prior comprehensive analysis from our institution on 300 adult patients (median age 41 years) established that enzymatic debridement (ED) is a reliable method for rapid eschar removal, accurate burn depth evaluation, and often helps avoid unnecessary surgeries, particularly in functional areas like the upper limbs. That study demonstrated NXB's effectiveness across various burn etiologies and its association with outcomes like healing time and scar formation in a general population. However, the specific risks, benefits, and outcomes in the fragile elderly demographic have not been separately analyzed [5]. Given that the experience using NXB in patients >65 y.o. is limited [3], this study aims to shed light on the off-label use of NXB in this specific group, building upon our center's foundational experience."

Based on the available literature, the use of Nexobrid is expected to minimize transfusion requirements and reduce infections, which may lead to a reduction in complications and hospital stays. We expect a higher mortality than in the younger population, attributable to the fragility of the patients and the severity of the injuries rather than to the use of Nexobrid.

Knowledge from this study could contribute to the use of Nexobrid in advanced training, providing preliminary information on its effectiveness, which further needs to be investigated to confirm its safety and effectiveness.

Using a retrospective observational approach, we aim to shed light on the off-label use of NXB on the elderly, particularly on the ideal conditions of its use, its risks, and how to optimize care in burned elderly patients.

2. Materials and Methods

The study was carried out taking into account the principles of the Declaration of Helsinki and with the approval of the Vall d'Hebron Ethics Committee (Protocol number: EOM(AG)027/2023(6136)). All patients signed their consent on admission for the procedure and the collection of their data.

All patients were treated at "Vall d'Hebron Hospital" Burns Center (Barcelona). At the time of admission, a plastic surgeon evaluated the percentage of Total burned body surface area (TBSA) and a critical care doctor assessed the need for intubation. The patients received fluid resuscitation according to the Parkland formula, devitalized skin was removed, and an appropriate dressing was used.

NXB was used in deep 2nd degree and 3rd degree burns up to 4 days after suffering the burns. In the meantime, wet dressings with Microdacyn or Prontosan were applied. Superficial burns were managed with conservative dressings. The procedure was carried out under sedation and regional nerve blocks (when performed on limbs) or under general anesthesia and intubation (when performed on the face). After layering NXB in an occlusive manner and applying vaseline on the edges to avoid spilling, it was left to debride for 4h and then removed in a sterile manner. Finally, a post-NXB burns depth evaluation was carried out up to 2h after removal, with the application of a follow-up dressing over the area.

We collected data from clinical history about age, sex, etiology, TBSA, inhalation injury, need for intubation, surface area treated with NXB, time until NXB application, post-NXB dressing used, hospital stay, mortality, revised Baux score, cause of death, infection, time-to-healing, need for surgery, escharotomy of NXB treated surfaces, need for transfusion (platelets, fresh frozen plasma transfusion (FFP) or red blood cell concentrate (RBC) used up until the first surgery), scar hypertrophy, pressotherapy use.

The results are summarized in a descriptive manner, applying relative frequencies for categorical variables, whereas means and medians were used for numerical ones.

3. Results

Forty-three consecutive patients sixty-five years or older treated with NXB from November 2015 to August 2023 were included on a case-series basis. Their mean age was 74.48 years (Standard Deviation (SD)= 7.56, Range 66-94). There were thirteen women and thirty men. The most frequent burn etiology was flame (83%), followed by scalding (14%) and contact (3%) burns. Four patients suffered inhalation injuries, while seven were intubated (either at the ER or during transfer to our center). Median burned TBSA was 11%, ranging from 0.75% to 78%. Mean time until NXB treatment was 1.16 days (SD=1.13, Range 0-4). The mean percentage of NXB TBSA debrided was 7.41% (SD=6.17, Range 0.75-32).

The median TBSA of the patients that died was 34%, while the median TBSA of the patients that survived and were discharged was 7%. A median of 8% of TBSA was treated with NXB in the patients that died, as opposed to 5.5% in those discharged. The median revised Baux score was 90 overall, being of 109 in the group that died, and 84 in the group that survived.

The following areas were treated with NXB: one face, nine full right upper limbs, seven full left upper limbs, one arm, three forearms, eighteen hands, one breast/thorax, ten complete right lower limbs, twelve complete left lower limbs, one left thigh, three legs and five feet.

The following post-NXB dressings and treatments were applied: Twenty-two Suprathel with Urgotul, thirteen Furacin with Mepitel, six silver sulfadiazine, three MepilexAg, two wet-dressings,

two Linitul and Furacin dressings, and one of direct Furacin, Flaminal, Honey and direct skin graft respectively.

Of the 43 patients included, eleven (25.58%) required blood or blood derivatives transfusion. Ten patients were treated with RBC, with a median of three RBC per patient. Four patients had FFP, with a median of 2,5 per patient. Three patients received platelet transfusion, with a median of 1 bag per patient.

Eleven out of Forty-three patients (25.58%) had an infection before discharge that affected at least the NXB treated burn site. The most frequent bacteria isolated was of the Pseudomonas family (Table 1)

Table 1. Number of burns with clinical infection.

Nº	Microorganism
6	<i>Pseudomonas</i>
3	<i>Staph aureus</i>
2	<i>Enterococcus faecium</i>
2	<i>Enterobacter cloacae</i>
1	<i>Enterococcus faecalis</i>
1	<i>Enterococcus avium</i>
1	<i>E. coli</i>
1	<i>Proteus mirabillis</i>
1	<i>Klebsiella pneumoniae</i>
1	<i>Klebsiella Oxytoca</i>
1	<i>Corynebacterium tuberculo</i> stearicum
1	<i>Morganella morganii</i>
1	<i>Mucor</i>
1	<i>Candida</i>

Thirty-three out of Forty-three patients (76.74%) required surgical coverage after NXB, while zero patients needed escharotomy.

The hospital stay ranged from 2 to 101 days, with a median of 26.5 days. We found a median time to healing of 63 days (Range= 21-207)

Twelve patients ended up needing pressotherapy, and nine developed hypertrophy in NXB debrided and healed areas.

Eleven patients of the total of forty-three died prior to discharge, resulting in a mortality rate of 25.58%. The causes of death are summarized in Table 2.

Table 2. Causes of death.

Nº	Causes
3	Multiple Organ Dysfunction
2	Septic Shock
2	Respiratory Insufficiency due to hyperhydration
2	Bronchoaspiration
1	Tension Pneumothorax
1	Massive Intestinal ischemia

4. Discussion

Burns in this age group occurred more frequently in men and were due to flame. It has been previously described that the incidence of burns in the elderly is somewhat equal in men and women, as opposed to their younger counterparts, where males are more frequently burned [6]. Although only four patients received inhalation injuries, seven had been intubated either on admission, or

before arrival. This discrepancy might be explained with the fact that some patients are intubated on the spot due to circumstances other than the inhalation injuries (pain, trauma...).

A median TBSA of 11% indicates that, NXB was used in our unit mostly in non-severely burned elderly patients, while NXB debrided TBSA of 7.41% could indicate that its use was deemed useful in specific areas of the body, rather than being used in all the TBSA. This premise is supported by the fact that the most frequently enzymatically debrided surfaces were the hands, and areas in lower limbs and upper limbs. 76.74% of patients underwent surgery for coverage, but none received escharotomies. In our unit, NXB use in the elderly allows us to completely avoid compartment syndrome in limbs but mostly does not avoid further surgical coverage of the burns that initially required it. We attribute this to the slower healing of our elderly patients.

Using NXB on the limbs of the elderly, and especially in hands, might ease healing and future surgical debridement, if necessary, allowing for the selective preservation of important structures that might otherwise be damaged during conventional surgical debridement. This in turn might result in less blood loss and better functional recovery for these elderly patients. Future studies are needed to shed light on the blood loss during surgery and later recovery, in areas like hands, face and feet, comparing those treated with and without Nexobrid.

The most frequently used dressing post-NXB was Suprathel with Urgotul (in twenty-two instances) and mostly applied to distal limbs. Many post-NXB burns were reassessed as less deep than initially thought, allowing us to try a more conservative approach with Suprathel to improve the wound's potential for spontaneous healing. This resulted in smaller areas that sometimes-avoided surgery. Mepitel and Furacin (in thirteen burns), silver sulfadiazine (in six cases) and Mepilex AG (in three cases) were used less frequently, and sometimes in preparation for coverage surgery.

One patient with deep burns on the face arrived intubated and was deemed suitable for treatment of the face with NXB in the following 24h, after which honey was used as a dressing. The intubation in this clinical situation provided an advantage that was used to treat an otherwise complicated surface to debride, and intubation would have been needed just to perform this procedure [3]. In our experience also with other patients, honey seems like a good option as a post-NXB dressing on the face and allows for better spontaneous healing and less dressing changes than with other options.

The mean time-to-NXB was 1.16 days, which is consistent with the recommendation of its use within the first 72h [4]. However, in three instances the treatment was administered on the fourth day, which could be due to the clinical condition of the patients in the first days of admission and the risk of applying NXB outweighing the benefits, until the patients had become stable. It would be interesting to see in future studies if the time to NXB is delayed in the elderly due to their usually fragile condition, compared to a younger population debrided with NXB.

The need for transfusion until the first surgery of 25.58% could be due to elevated % of burned TBSA on an older population with aggravating pre-existing conditions. RBC was the most frequent blood component administered, which could be due to preexisting anemia (common in the elderly, and increasing with age) [7], their deteriorating clinical condition, post-NXB bleeding or dilutional anemia due to the initial rehydration. However, we think that the RBC requirements are mostly caused by the patients' clinical condition, rather than other factors. Despite previous concerns about coagulopathy after NXB use [8], only 3 patients required platelets, and four required FFP, with a median of 1 bag of platelets and 2.5 FFP, which is in line with a more recent study showing no clear association between enzymatic debridement and coagulation abnormalities [9].

A fourth of our patients (25.58%) had an infection that affected at least the NXB debrided area at some point before being discharged. This is somewhat expected from elderly patients with an elevated median burned TBSA (11%), an advanced age and preexisting health conditions which could affect the immune system. The appearance in cultures of mostly *Pseudomonas* and *Staph aureus* is consistent with the literature of the most frequently isolated bacteria in burned patients [10]. The

appearance of *Mucor*, *Candida*, *Morganella* and *Corynebacterium* in cultures might hint at immunocompromised elderly patients predisposed to infection.

In our study, a fourth of the patients died during their stay in the hospital (25.58%). These patients had a median TBSA of almost five times their counterparts that did survive (34% VS 7%). The median percentage of NXB debrided surfaces was not much different in one group and the other (8% in the dead group VS 5.5% in survivors). The mortality of burned patients over 65 years of age described in the literature is 4.7% [7], but this includes patients with superficial burns, and patients that don't need admission for their care; these patients are not included in our study, because they were not treated with NXB.

Applying the revised Baux score yielded a median of 90 for overall predicted mortality, which is 20 points away from the cut-off point of 110 for unsurvivability, but still presents our population as one with a high predicted mortality [11][12]. The actual mortality in our sample was 25.58%, hinting that NXB may be safe to use in patients with an initially high predicted mortality. It appears that the most important predictors of death in these patients are still the TBSA, the age and inhalation injuries of the revised Baux score, as the group of patients that died had a median revised Baux score of 109. To understand the real effect of NXB on survival, further studies with a control group is needed.

MOF, Septic Shock and respiratory Insufficiency were the most frequent overall causes of death. They should be the first complications to look for after treating elderly patients with NXB. However, the other 3 causes of death merit attention as well:

A Tension Pneumothorax in a patient with 35% burned TBSA resulted in cardiorespiratory failure and death immediately after skin coverage surgery. Only one upper left limb was debrided with NXB previously. We believe that this was a complication from the anesthetic axillary nerve block that allowed the surgery. NXB needs pain management prior to its administration, and might need sedation, nerve block or even intubation. The risk and benefits of each procedure should be balanced in each patient before deciding if NXB and its associated procedures are worth the risk.

Another patient with 34% burned TBSA died due to massive intestinal ischemia, which we believe was related to a hidden pre-existing condition which worsened due to the burns. Health conditions in elderly burned patients should be carefully searched for, as they can influence the outcome of the burns in the most severe way, conditioning the application of enzymatic debridement.

During a median hospital stay of 26.5 days we stabilize the patient, apply NXB, perform covering surgery (if necessary) and let the patient recover until discharge is possible. Afterwards, patients come to our unit once or twice per week to change dressings and monitor the burns evolution until healing is completed (median of 63 days since the burn). Burned elderly patients usually require adequate support at home that allows them to complete the rest of the treatment at home after discharge. The at-home-support should be determined before discharge and, if not present, should not discourage the physician against keeping the patient in the hospital, as complications can be better monitored and dressing changes can be secured during the patients' hospital stay.

Twelve patients of the surviving thirty-two used pressotherapy, and only nine developed hypertrophy. This leads us to believe that although hypertrophy is less expected to appear in elderly people [13], it is still possible in this population and could be due to the long time it sometimes takes to heal the remaining wounds.

We did not control for preexisting conditions such as diabetes, heart failure, dementia or kidney disease, which could be related to worse outcomes or to a higher burned TBSA on admission (general median of 11% TBSA in contrast to a median of 34% TBSA in the patients that died).

5. Conclusions

We conclude that NXB is a useful treatment for careful debriding of distal limbs and face in the elderly population and that its use should not be withheld when correctly indicated. However, due to the possible pre-existing health conditions and especially in severely burned patients, risk and benefits should be assessed before indicating NXB and the pain-management procedures required

for its use. The mortality of our sample was in line with the predicted mortality of the revised Baux score in the literature, hinting at the safety of NXB. Further studies with a control group are still needed to properly assess survival. Initially hypertrophic scarring was not expected to be present, but it appeared in 9 patients of our group, sometimes despite pressotherapy use. We believe that this is due to the longer time it takes for them to fully heal.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

NXB	Nexobrid
TBSA	Total burned Surface Area
FFP	Fresh Frozen Plasma Transfusion
RBC	Red Blood cell Concentrate

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