

# To bleed or not to bleed? Case series and discussion of haemorrhage risk with enzymatic debridement in burn injuries

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## Abstract

**Introduction:** Surgical burn excision (along with skin grafting) carries the risk of blood loss. The use of enzymatic debridement agents such as Nexobrid® has gained increased popularity as an alternative to surgical debridement in the management of burns with its reported benefits of selective burn debridement, minimising blood loss and potentially reducing the need for skin grafting. However, there is limited evidence regarding its effects on bleeding. Currently, the manufacturer declares there is no evidence for increased risk of localised bleeding and its systemic effects upon coagulation are less clear.

**Methods:** We present two clinical cases demonstrating the possible effects of Nexobrid® on coagulation and bleeding at the debridement site. Comparisons are drawn with the manufacturers' guidance as well as evaluating the current recommendations of its use.

**Discussion:** Nexobrid® is a novel therapy and there are few adverse effects reported in the literature. The basis of its appeal is the reduced blood loss at the debridement site and the selectivity it possesses in preserving healthy dermis. However, our cases have demonstrated that haemorrhage can occur and that those using Nexobrid® should be mindful of the potential bleeding risk from varicosities within the burn wound. We have also illustrated that Nexobrid® can be used in patients with pre-existing clotting disorders without requiring the use of blood products. However, we emphasise the importance of haematological support for its safe administration.

## Keywords

Nexobrid®, enzymatic, debridement, bleeding, burns, coagulopathy, dysfibrinogenaemia, varicosities

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## Lay Summary

Nexobrid®, a debriding agent that contains enzymes, has been developed as an alternative to surgery which for most surgeons is the traditional method of removing dead tissue following a burn injury. The active agent is bromelain and this is derived from the stems of pineapples. This novel treatment is increasingly being used in the management of middle to deep skin thickness burns and it seems to have a number of benefits such as reducing blood loss, reducing the need for skin grafting as well as being able to treat burns in certain areas of the body that would be technically challenging to remove in the standard fashion. It simply targets the dead tissue leaving viable remnants of the skin that would hopefully allow healing to occur without the need for surgical intervention. Being a relatively new concept, current evidence regarding the safety and value of Nexobrid® continues to develop. In 2020, an agreement guideline outlining best practice with the use of Nexobrid® was published. In this statement, it was advised that caution should be taken when using Nexobrid® in patients who have blood clotting disturbances as this could increase the likelihood of bleeding. However, they did not mention that excessive bleeding can potentially occur with this treatment.

We present two clinical cases demonstrating the possible effects of Nexobrid® on the clotting system and bleeding at the application site. Comparisons are drawn with the manufacturers' guidance as well as assessing the current recommendations of its use. We illustrate that Nexobrid® can be safely used in patients with pre-existing clotting disturbances if the correct procedures are performed. We also highlight the potential complication of excessive bleeding if Nexobrid® is used in patients who have co-existing enlarged surface veins along with their burn injury. We feel the guidance should be updated to reflect these findings.

## Introduction

Enzymatic debridement (Nexobrid®, Mediound, Yavne, Israel) has become widely accepted in the treatment of mixed-depth and full-thickness burns, burn wounds involving technically challenging specialised anatomical regions, or because the patient's general clinical condition prevents traditional surgical debridement.<sup>1</sup> While effective, surgical tangential debridement and skin grafting will involve a degree of non-selective tissue removal and may cause problematic bleeding.<sup>2,3</sup> Enzymatic debridement may reduce or eliminate the need for surgical excision, reduce blood loss and potentially avoid the need for skin grafting by preserving more viable dermis and epithelial remnants.<sup>4,5,6</sup> Reduced rates of burn wound infection and length of hospital stay have also been observed.<sup>7</sup>

Evidence regarding the safety and efficacy of enzymatic debridement continues to evolve. Hirche et al.<sup>8</sup> published an updated consensus guideline best practice with the use of enzymatic debridement, covering a number of topics including indications, preparation and application, anaesthesia and outcomes. These guidelines advised caution in the presence of clotting disorders and concluded that any existing coagulopathy should be treated prior to application. This has relevance, as enzymatic debridement is expected to cause some bleeding in every case. Additionally, 40% of patients with major burns will have a degree of coagulopathy on hospital

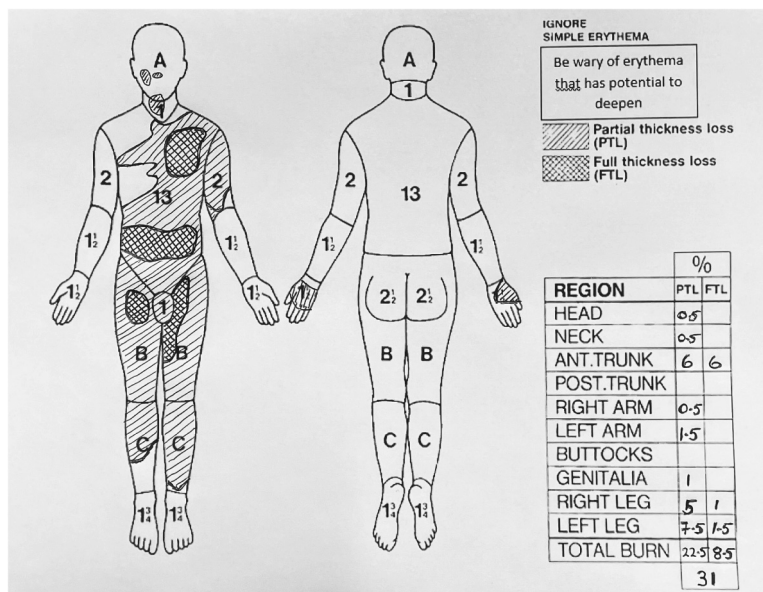
admission.<sup>9</sup> The effects of enzymatic debridement upon coagulation are less clear. Martin et al.<sup>10</sup> documented a case of marginally raised clotting times (prothrombin and activated partial thromboplastin ratio), 24 hours after application of Nexobrid® (6% total body surface area (TBSA) treated). There were no signs of active bleeding at that time and the significance of this finding is uncertain, as no other comparable cases have been reported.

No specific guidance on haemorrhagic risk is available and no evidence on haemorrhage risk or cases of haemorrhage were published at the time of writing. Anecdotally, the Summary of Product Characteristics for Nexobrid® states that during product development, there was no indication of increased risk of bleeding at the site of debridement.<sup>11</sup>

We present two clinical cases of burn injury, treated with Nexobrid® enzymatic burn debridement. First, in a patient with a large burn and pre-existing coagulopathy. The second case involved a patient who suffered significant bleeding following enzymatic debridement. These cases highlight the need for careful patient selection and optimisation and highlight a new relative contraindication for enzymatic debridement.

### Case 1

A 43-year-old female was admitted with a 31% TBSA mixed-depth flame burn to her left breast,



**Figure 1:** Case 1, Lund & Browder Chart documenting extent of burn injury.

abdomen and bilateral thighs (Figure 1). The patient had a prior history of depressive illness and dysfibrinogenaemia. This is an autosomal dominant condition, resulting in creation of defective fibrinogen, with impaired clotting function and a predisposition to bleeding. Tranexamic acid (TXA) is usually required when symptomatic, or as prophylaxis for some procedures, e.g. dental extraction.

Following presentation to the emergency department, intravenous fluid resuscitation was administered, using electrolyte and colloid fluids, according to a local hospital protocol. The burn was assessed and deemed suitable for enzymatic debridement. A pre-treatment plan was formulated, under guidance from haematology consultant colleagues. This included TXA pre-procedure (1 g, three times daily), continued until 48 hours post-application. If excessive bleeding was to occur, then human fibrinogen concentrate (RiaSTAP®, CSL Behring, King of Prussia, PA, USA) would be required. Enzymatic debridement was performed on 25% TBSA in a single session, in an intensive care setting.

At 24 hours post-injury, the patient had an application of Nexobrid® (40 grams total) to all mid-dermal and deep-dermal burns. During the entire Nexobrid® treatment, cardiovascular monitoring was carried out. The clotting profile was recorded pre-treatment and post-treatment (Table 1). No adverse bleeding complications occurred and the clotting profile remained within the local normal range. No human fibrinogen concentrate or blood products were required at any point. The patient required split skin grafting

(8% TBSA) to deeper areas overlying the abdomen, left upper chest and bilateral inner thighs. This took place without complication.

### Case 2

A 61-year-old male sustained a 1.75% TBSA mixed-depth flame burn to the left lower calf. He had a past medical history of chronic lower leg ulceration, due to chronic venous hypertension and recurrent deep vein thromboses, for which he took rivaroxaban. He also suffered from a depressive illness and excessive alcohol intake.

The patient attended the emergency department approximately 12 hours post-injury. On examination, the burn was assessed to be deep-dermal in depth and suitable for Nexobrid®. The last dose of rivaroxaban had been taken 32 hours prior to treatment and it was felt safe to proceed with enzymatic debridement. Blood clotting times on admission were normal.

A popliteal sciatic nerve block was performed in theatre and Nexobrid® (2 grams) was applied to the burn. Approximately 30 minutes following his return to the ward, the patient suffered a peri-arrest event, with obvious haemorrhage at the site of debridement. The blood pressure (measured non-invasively) fell to 50/40 mmHg and the heart rate was 110 beats per minute (BPM). Cardiovascular stabilisation was achieved quickly, with administration of intravenous fluids, 2 units of packed red cells and TXA (1 gram). The Nexobrid® was completely removed, the limb was elevated and calcium alginate and a compressive crepe dressing were

**Table 1.** Coagulation tests throughout admission.

Days	PT (s)	APTT (s)	TT (s)	Hb (g/L)	Haematocrit
On Admission	14.0	22.6	28.9	116	0.476
*Day 1 Pre-Nexobrid®	20.4	34.8	22.2	127	0.397
*Day 1 Post-Nexobrid®	20.7	35.7	22.3	119	0.367
Day 8	11.9	27.7	22.1	-	-
Day 55	13.3	25.5	26.3	-	-
Day 65	13.1	25.0	26.0	-	-

\*coagulation on the day of Nexobrid® treatment. (PT, Prothombin Time; APTT, Activated Partial Thromboplastin time; TT, Thrombin Time; Hb, Haemoglobin)

**Figure 2:** Case 2, Right PCA infarct on CT head.

applied. Estimated blood loss was up to two litres. No bleeding point could be determined at the time of emergency management.

Following initial stabilisation, the patient suffered a second major haemorrhage from the site and a cardiac arrest occurred, which was corrected following two cycles of cardiopulmonary resuscitation (CPR) and intravenous adrenaline. Once stabilised and when it was clear that no further bleeding was taking place, a careful visual wound inspection was carried out. A single discrete breach of a venous varicosity within the Nexobrid®-treated area was observed. The remaining vein tissue appeared normal. Ligation of the vessel was undertaken prior to transfer to intensive care for post-arrest ventilatory support and invasive monitoring.

It was noted during his admission to intensive care that the patient had developed a new left-sided hemiparesis. Computed tomography (CT) scanning demonstrated a posterior cerebral artery (PCA) infarct (Figure 2).

## Discussion

Increasing numbers of burn care providers use enzymatic debridement as an alternative to surgical debridement in the management of deep-dermal burns,<sup>12</sup> mainly due to its ability to selectively remove burn eschar and retain viable tissue. However, careful consideration must be taken with Nexobrid® in patients with known coagulopathy, or in burns which overlie varicosities or large blood vessels.

In major burns, bleeding may arise either from burn-induced coagulopathy (BIC), or from bleeding at the site of debridement. The coagulopathic changes that occur in burns are influenced by many intrinsic and extrinsic factors and may potentiate clotting or bleeding.<sup>13</sup> This is demonstrated in 40% of patients with major burns.<sup>9</sup> The haemorrhagic risk with Nexobrid® is thought to be low and this appears to be the first reported case of haemorrhage following Nexobrid® use.

*Nexobrid® and coagulopathy.* The manufacturer advises caution with regard to clotting when using Nexobrid®.<sup>11</sup> This guidance arose from *in vitro* and animal studies, in which orally administered bromelain was found to reduce platelet aggregation and plasma fibrinogen concentration and to increase prothrombin and partial thromboplastin



times.<sup>10</sup> However, it remains unclear whether topical application has similar effects.

Martin et al.<sup>10</sup> published a case of coagulopathy that occurred shortly after Nexobrid® use, with no reported bleeding. In this case, a 15% TBSA flame burn had Nexobrid® treated on the deeper areas, totalling 6% TBSA. At 24 hours post-treatment, decreased coagulation activity was noted, with increased prothrombin time (PT) and activated partial thromboplastin time (APTT) and reductions in both platelet count and haemoglobin. Following treatment with intravenous Vitamin K, coagulation parameters returned to normal over the subsequent 24 hours. No other intrinsic or extrinsic causes were identified for this coagulopathy.

Case 1 in this report demonstrates the safety of enzymatic debridement in the presence of a coagulopathy, with prophylactic TXA treatment before use. The perceived risk of bleeding was high, given the wound size treated and the patient's underlying dysfibrinogenaemia. As a result, the procedure was carried out in intensive care, allowing invasive monitoring and analgesia. Enzymatic debridement was carried out on 25% TBSA. TXA was administered in three separate doses. No bleeding was encountered and no fibrin products were required. The authors believe this to be the first case documenting the safe use of Nexobrid® in a patient with a pre-existing clotting disorder.

*Nexobrid® and haemorrhagic risk.* Following removal of Nexobrid® from a debrided wound, punctate bleeding is seen within areas of white, viable dermis, or yellow subdermal fat. This bleeding demonstrates debridement to healthy tissue and is simply controlled with appropriate dressings following treatment. Rosenberg et al.<sup>14</sup> in a review of seven clinical studies, reported a phase three randomised study comparing 156 patients treated with enzymatic debridement (n = 75) or surgical debridement (n = 81). Treatment included deep-dermal and full-thickness burns, from 5-30% TBSA. The authors reported blood loss and reduced haemoglobin and haematocrit in both groups, although this was less marked in the enzymatic debridement group than in the surgically debrided group (haemoglobin: 0.52 +/-0.96 g/L enzymatic vs. 1.04+/-1.03 g/L surgical). No cases required treatment to correct haemoglobin or haematocrit. In addition, the manufacturer does not list haemorrhage as a complication of Nexobrid® use, in its Summary of Product Characteristics.<sup>11</sup> In a PUBMED search of published articles involving enzymatic

debridement of burns, no documented cases of haemorrhage complications were found.

Case 2 demonstrates that significant haemorrhage can occur at the site of enzymatic debridement, if the region of burn eschar involves a large blood vessel, or varicosity. The authors suggest that this situation should now be regarded as a relative contra-indication for the use of enzymatic debridement, due to the risk of haemorrhage.

*Nexobrid® and selective debridement.* The selectivity of enzymatic debridement cannot be achieved with surgical tangential burn excision. This selectivity was demonstrated using porcine animal models; Singer et al.<sup>15</sup> demonstrated this finding histologically. Rosenberg et al.<sup>16</sup> reported similar findings, with effective removal of burn eschar from deep-partial and full-thickness burns and no adverse effects on normal skin. Taking these findings into account, it may be hypothesised that in Case 2 in this series, the enzymatic debridement resulted in removal of a patch of superficial varicose vein tissue which had been burned.

*Learning outcomes.* Enzymatic debridement has few adverse effects reported in the peer-reviewed literature. The basis of its appeal is its selectivity in preservation of healthy dermis. Nevertheless, haemorrhage may occur and burn care professionals should be mindful of potential bleeding risks from varicosities within burn wounds. In addition, enzymatic debridement may be used safely in patients with pre-existing dysfibrinogenaemia, without requiring the use of blood products. However, the authors emphasise the importance of senior haematologist involvement at the stage of pre-treatment planning.

## Declaration of conflicting interests


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