ARAV
THE OFFICIAL PUBLICATION OF THE ASSOCIATION OF REPTILE AND AMPHIBIAN VETERINARIANS

BRIEF COMMUNICATION

The Journal of Herpetological Medicine and Surgery, Volume 33, No. 3, 2023 pp. 146–154
DOI: 10.5818/JHMS-D-22-00018

Wound Management, Including the Use of an Extracellular Matrix Powder, in a Blue-Tongued Skink (*Tiliqua scincoides*)

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Abstract

A 10 year old intact male, blue-tongued skink (*Tiliqua scincoides*) presented with large dorsal wounds penetrating deep into the coelomic cavity. After initial debridement, decontamination, and bandaging, a powdered form of porcine extracellular matrix (ECM) was applied to the wound and covered with a non-adhesive bandage. Three days following application, a thin crust formed over the wound bed. Within 7 days of application, reduced wound depth and granulation tissue were present, at which point the crust was removed and a second application of ECM powder was made. Eleven days after initial application, approximately 50% of the wound was covered by thin epithelial tissue extending from the wound margins. Fifteen days after the first application, 100% of the wound appeared to be covered with thin epithelial tissue with marginal crusting. The patient was discharged 24 days post presentation (15 days post initial ECM application) with no further treatment. The owner was instructed to remove the bandage 7 days post discharge. Twenty-four days after the initial application, the owner reported a full shed with complete epithelization and no further crusting. The patient was followed up 31 days after the initial presentation and was assessed as recovered from the initial wounds. To the author's knowledge, this is the first reported use of an ECM powder, or a xenogeneic material, used to treat a traumatic wound in a *Tiliqua*.

Key Words: Blue-tongued skink, extracellular matrix, lizard, *Tiliqua scincoides*, wound management, xenogeneic

Introduction

The Centers for Disease Control established a wound classification system for humans which enables clinicians to make decisions for managing the wound (Onyekwelu *et al.*, 2017). Wound classification is divided into four classes: clean, uninfected wounds of Class 1; clean-contaminated wounds of Class 2; contaminated fresh wounds of Class 3; and dirty, infected wounds of Class 4 (Onyekwelu *et al.*, 2017). Proper identification of wound class allows the clinician to institute an effective management plan to optimize comfort and healing times (Jenkins *et al.*, 2019; Jiao *et al.*, 2019; Subrata *et al.*, 2019). The same principles apply to a veterinary patient with alterations based on species-specific requirements (Mickelson *et al.*, 2016).

Reptile skin is similar to that of higher vertebrates in that it contains an epidermal and dermal layer (Mitchell and Diaz-Figueroa, 2004). The response to injury varies across different reptile species, with lizards producing less of an inflammatory response than do snakes (Maderson and Roth, 1972). However, wound healing follows the same 3–5 phases; inflammation and contraction, proliferation, and maturation with subsequent remodeling (Mickelson *et al.*, 2016; Mitchell and Diaz-Figueroa, 2004). The phases have considerable overlap with progression through the stages required to complete healing; failure to progress results in the wound becoming chronic or non-healing (Öztürk and Ermertcan, 2011; Portou *et al.*, 2015). Each phase has components that contribute to the subsequent phases. During the coagulation phase, the release of pro-inflammatory cytokines results in a fibrin clot supporting the progression to the inflammatory phase (Öztürk and Ermertcan, 2011; Portou *et al.*, 2015). Multiple factors influence the speed and degree of healing in ectothermic species, including temperature, stress, pain, infection, and pre-existing conditions (Smith *et al.*, 1988; French *et al.*, 2006; Mickelson *et al.*, 2016).

During the inflammatory and debridement phase, the wound will show signs of redness, swelling, and heat caused by increased permeability of capillaries, and there is movement of neutrophils, macrophages, and lymphocytes into the wound bed (Öztürk and Ermertcan, 2011; Portou *et al.*, 2015). The monocytes differentiate into tissue macrophages releasing pro-inflammatory cytokines that result in further inflammation and stimulate collagen synthesis and angiogenesis (Pazyar *et al.,* 2014; Portou *et al*., 2015). Further into this phase, lymphocytes are present in higher levels, and although their specific role in wound healing is unknown there are increases in growth factors, interleukin, and tumor necrosis factors (Pazyar *et al.,* 2014; Portou *et al*., 2015).

During the proliferative (repair) phase, the fibroblasts recruited in the inflammatory/debridement phase are required for the production of the extracellular matrix (ECM) (Öztürk and Ermertcan, 2011); angiogenesis also occurs during this time. Macrophages produce angiogenic factors and vascular endothelial growth factor, resulting in dermal endothelial cells migrating into the ECM and forming granulation tissue. From here, epithelial tissue can migrate over the granulation tissue. If possible, the wound will contract during this phase until either tension is too high, there are not enough myofibroblasts, or the wound has completely closed (Öztürk and Ermertcan, 2011; Portou *et al*., 2015). Following collagen deposition, remodeling occurs over the following weeks to months and the remodeled collagen results in strengthening of the new tissue (Öztürk and Ermertcan, 2011; Portou *et al*., 2015).

The ECM is made up of fibrous components including collagens, elastins, laminins, fibrin, vitronectin, and fibrillin and is a critical component of wound healing. It is involved in structure, adhesion, and cell migration. Non-fibrous components or glycoprotein components fill the interstitial space. They include proteoglycans, glycosaminoglycans, fibronectin, and matricellular proteins (Midwood *et al*., 2004; Xue and Jackson, 2015; Mickelson *et al*., 2016; Tracy *et al*., 2016; Mathew-Steiner *et al*., 2021). The ECM and its components are intimately involved in the initial stages of wound healing including hemostasis, inflammation, and proliferation through the interaction with the cellular immune system and pro-inflammatory cytokines. These interactions modulate the migration of fibroblast, epithelial, and endothelial cells while promoting collagen deposition and growth factor sequestration that results in angiogenesis and re-epithelialization (Midwood *et al*., 2004; Mickelson *et al*., 2016; Tracy *et al*., 2016; Mathew-Steiner *et al*., 2021).

The use of ECM materials for wound management has been described in both the human and veterinary literature (Winkler *et al*., 2002; Badylak, 2004; Tracy *et al*., 2016; Edgar *et al*., 2018; Spang and Christman, 2018; El Masry *et al*., 2019). These materials are applied as patches, powders, or hydrogels (Swaim *et al*., 2001; Stashak and Theoret, 2009; Edgar *et al*., 2018; Spang and Christman, 2018). The decellularized products supply many of the proteins and growth factors essential to proliferation, differentiation, and reorganization and can help facilitate the coordination of these steps during the wound healing process (Solarte David *et al*., 2022). This is the first published report of decellularized ECM powder used to treat a traumatic wound in *Tiliqua*.

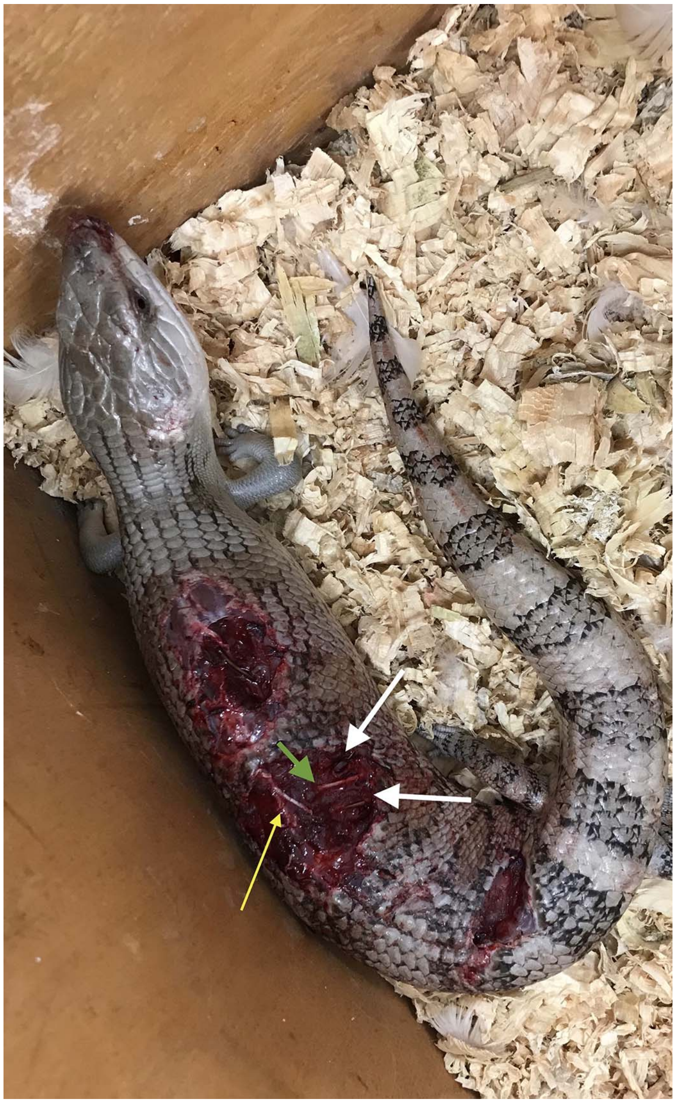

Figure 1. Day 1: A blue-tongued skink (*Tiliqua scincoides*) presented to the hospital with multiple deep wounds to the dorsum from a presumed rodent attack. The green arrow annotates exposed ribs. The yellow arrow is annotating exposed vertebra. The white arrows are annotating the exposed celomic cavity.

Case report

A 10 year old male, captive-bred, blue-tongued skink (*Tiliqua scincoides*), with no known previous issues, was presented for acute injuries to the body suspected to have been sustained by a wild rodent entering the enclosure. Abnormal physical exam findings included tachycardia (90 beats per minute) (reference range 46–70 at 30°C [86°F] (Bartholomew *et al*., 1965) with inspiratory dyspnea and multiple wounds over the trunk. Two wounds penetrated the coelom, noted as bubbles seen at these sites during respiration. There was extensive damage to deeper musculature, with frayed fascia and tendons and exposure of ribs and the vertebral spinous processes (Fig. 1). The patient was ambulating normally, and no neurological deficits were appreciated. An additional wound to the right naris and upper lip was present. Initial diagnostics recommended included blood tests (hematology and biochemistry), imaging (radiographs and computed tomography), and wound culture but were not performed due to the client's financial constraints. Only an estimated white blood cell count was performed and the results were within normal limits for the species (Gibbons *et al.*, 2019).

Initial treatment included active warming of the patient to within the preferred optimal temperature zone for this species (32°C [89.6°F]) (Bartholomew *et al.*, 1965; Dutson and Dutson, 2016), and pain management was provided using methadone at 0.5 mg/kg (Methadone, Jurox Animal Health, New South Wales, Australia) by intramuscular injection in the right triceps muscle. The wound was flushed daily with sterile 0.9% sodium chloride solution delivered through a 35-ml syringe and an 18-gauge BD Vialon catheter (Becton Dickinson Pty Ltd, Franklin Lakes, NJ, USA). The coelomic rents were covered with sterile cotton gauze to prevent fluid entry into the coelom during irrigation. Wound bed culture and sensitivity testing was offered but declined due to financial constraints. A cytological sample was collected with a sterile, cotton-tipped applicator and rolled onto a glass slide for in-house microscopy, which revealed the presence of gram-negative rods, gram-positive rods, and scant gram-positive cocci. The patient was started on oral enrofloxacin at 10 mg/kg every 24 h (Ilium Enrotril Oral, Troy Laboratories Pty Ltd, Glendenning, New South Wales, Australia).

A sterile, porcine-derived gelatin sponge (Gelfoam®, Pfizer Australia, WestRyde New South Wales, Australia) was cut to size and placed over the penetrating wounds. A thin layer of medical-grade manuka honey (Kruuse Manuka G, Jorgen Kruuse A/S, Havreottenm Langeskov, Denmark) was applied and covered with a non-adhesive polyester film bandage (Melolin, Smith & Nephew Pty Ltd, London, UK) and held in place with a polyacrylate adhesive tape (Fixomull® Stretch, BSN Medical (Aust) Pty Ltd, Mount Waverley, Victoria, Australia). The wound was highly exudative and required daily or twice daily bandage replacements until day 3 (Fig. 2). Three days after admission, the primary bandage was changed to a non-adhesive foam dressing (Allevyn™ Non-Adhesive, Smith & Nephew Pty Ltd), reducing the necessary bandage changes to every 2–3 days as required until day 10. The patient appeared comfortable as assessed by the relaxed body position, frequent ambulation, improved breathing pattern, and good appetite; the patient was cooperative and appeared alert during handling for bandage changes. For the remainder of the treatment period, pain management was altered from the previously prescribed methadone to once-daily oral tramadol given at 5 mg/kg (Tramal® Oral Drops, Grunenthal GmbH Germany, supplied by Seqirus Pty Ltd, Parkville Victoria, Australia).

Figure 2. Day 3: The wounds on the blue-tongued skink (*Tiliqua scincoides*) have been debrided of visible devitalized tissue and the coelomic communications appear sealed. The vertebrae are still exposed and the ribs are less visible.

At day 9, the wound was clean, had crusting on the margins, and the remaining tissue appeared viable (Fig. 3). ECM powder, derived from multiple porcine tissue lines (XCelliStem® Wound Powder, Stemsys, Sunrise, FL, USA) was applied to the wound (Fig. 4) and covered with the non-adhesive polyester film bandage and secured in place with a polyacrylate adhesive tape. The wound was left undisturbed for 3 days, at which time a small amount of yellow-green discoloration was observed through the bandage. Beneath the bandage, a yellow-green, thin, firm crust had formed over part of the wound while the remaining portions appeared pink, with a thinner, more translucent crust (Fig. 5). A Gram stain cytology showed no evidence of bacterial infection. Four days later (16 days post presentation and 7 days after the initial application of ECM powder), the wound had appeared to contract further with a similar-appearing crust and reduced discharge (Fig. 6). A healthy bed of red tissue, resembling granulation tissue, covered most of the wound beneath the crust (Fig. 7). A second application of the ECM powder was applied (Fig. 8) and covered with a non-adhesive bandage. Four days later (11 days post initial application and 20 days from presentation), the wound depth was reduced and a thin, epithelial-like tissue covered approximately 50% of the wound bed (Fig. 9), at which time a thin layer of the ECM powder was dusted over the remaining exposed tissue. The wound appeared sufficiently healed at day 24 (15 days after

Figure 3. Day 9: The wounds on the blue-tongued skink (*Tiliqua scincoides*) remain clean and there is evidence of contracture of the most cranial wound; however, the depth of the wound is minimally changed. Vertebrae remain visible and the wounds are moderately exudative.

Figure 4. Day 9: The initial application of a decellularized, extracellular matrix (ECM) powder derived from multiple porcine cell lines on wounds in a blue-tongued skink (*Tiliqua scincoides*).

initial application of ECM) (Fig. 10), and the patient was discharged with a protective, non-adhesive polyester film bandage over the wound site (Melolin, Smith & Nephew Pty Ltd). The client was instructed to monitor for saturation or leakage of exudate through the bandage, abnormal smell, or change to appearance. The client contacted the clinic 4 days later (day 28 from initial presentation), stating the lizard had entered a state of ecdysis and had a smooth thin tissue present under the shed. The patient was re-presented to the clinic 42 days after the initial presentation and 31 days after the initial application of the ECM material, had complete coverage of the wound by epithelial tissue, and was considered to have healed (Fig. 11).

Discussion

This case describes the use of ECM powder dressing derived from multiple types of porcine tissue to treat a large, contaminated, Class 4 wound in a blue-tongued skink (*Tiliqua scincoides*). The choice to allow healing by second intention was made early in treatment, as contaminated wounds are often better managed by second intention healing measures (Swaim and Henderson, 1990; Swaim *et al.*, 2001). Other reasons for managing by second intention healing were species-specific limitations, including poor skin elasticity with osteoderms that would prevent wound closure without excessive tension and devitalization of surrounding tissues. Other options for assisted closure include grafts (xenogeneic or autologous), skin flap reconstruction, laser therapy, negative wound pressure, and hyperbaric oxygen therapy (Sabater González and Mayer, 2019). The use of vacuum-assisted wound closure devices was not considered due to the expected difficulty in keeping such a device in place in this species, and laser therapy and hyperbaric oxygen treatments were not readily available for this case. The large surface area, lack of granulation bed, and poor skin elasticity in *Tiliqua* species precluded the use of grafts or reconstructive surgery in this patient. Large wounds pose specific issues with increased risk for infection, protein and fluid loss, the increased time required for management, and subsequent increased cost of materials, medications, and hospitalization. Our patient continued to consume food readily and gained weight

Figure 5. Day 12: Blue-tongued skink (*Tiliqua scincoides*) 3 days post ECM application, a thin crust covers the wound bed. Heme pigment breakdown is responsible for the green color seen within part of the crust. Contracture of the wound is becoming evident.

Figure 6. Day 16: Blue-tongued skink (*Tiliqua scincoides*) 7 days post ECM application; an intact crust layer is present with scabbing over a proportion of the wound margins. The width of the wound beds are decreased, indicating significant contracture.

during the hospital stay with no additional support required.

The initial choice of enrofloxacin at 10 mg/kg for antibiosis was made due to its effectiveness in reptiles against gram-positive and gram-negative bacteria (Mitchell, 2006). Contamination and infection were considered unlikely to have contributed to the delayed healing as, by day 3, no gross or microscopic evidence of infection was noted. Culture of the wound might have shown otherwise; however, it was not performed due to the owners' financial constraints. Pain, stress, malnutrition, protein loss, and other comorbidities were not considered negative factors in wound healing. The patient was assessed as comfortable with normal ambulation, a good appetite, and continued weight gain and was considered relaxed and comfortable while handled. Diagnostics, including complete blood count, biochemistry, radiographs, and computed tomography, were recommended and would have been beneficial in assessing the patient's general health and post traumatic status but were declined due to cost.

Debridement of damaged tissue is essential for preparing the wound bed for healing (Kirshen *et al.*, 2006). Surgical debridement removed the larger damaged areas, and topically applied manuka honey aided in autolytic debridement and had the added benefit of antibacterial properties, ability to reduce inflammation, and to reduce chronic inflammation while promoting macrophage and fibroblast migration into the wound (Gethin and Cowman, 2009; Minden-Birkenmaier and Bowlin, 2018). Other topical preparations containing silver sulfadiazine were considered; however, these preparations have been linked, in humans, to local toxicity of fibroblasts and keratinocytes (Poon and Burd, 2004), with the possibility of bone marrow suppression and subsequent leukopenia when used in large wounds due to the added propylene glycol (Atiyeh *et al.*, 2007) and thus were not used. Wound coverage with a non-adhesive polyurethane foam bandage material was chosen for its suggested use in highly exudative wounds and because it allows for less-frequent changes and is atraumatic to the wound surface on removal (Sood *et al.*, 2014). This material is also breathable, reduces maceration, prevents bacterial contamination, and conforms well to the surface (Sood *et al.*, 2014). These properties are beneficial when treating wounds in reptilian patients where reduced

Figure 7. Day 16: Blue-tongued skink (*Tiliqua scincoides*). The crust is removed to observe the underlying wound bed. A healthy bed of granulation tissue is present. The vertebrae and ribs are no longer visible, the wound depth has decreased, and the coelomic cavity is sealed.

handling is often advantageous and where there is a need to cover a variably shaped wound with contours.

An ECM needs to be produced to replace damaged tissue (Gurtner *et al.*, 2008; Reinke and Sorg, 2012; Tracy *et al.*, 2016; Rodrigues *et al.*, 2019). This matrix regulates the repair by acquiring and managing several different cell types, which are coordinated during the different stages of healing (Mitchell and Diaz-Figueroa, 2004; Gurtner *et al.*, 2008; Xue and Jackson, 2015; Tracy *et al.*, 2016). Decellularized ECM materials are used to treat various tissue injuries in humans, including soft tissue repair, burns, and ulcers (Brown and Badylak, 2014). These materials are often derived from xenogeneic sources, predominantly porcine tissues. The ECM material is delivered as hydrogels, sheets, or as in the case of this report, a powder (Badylak, 2004; Brown and Badylak, 2014; Edgar *et al.*, 2018; Spang and Christman, 2018). For this case, a sterile porcine ECM powder was used containing a wide variety of components including collagen types I, III, IV, V, laminin, elastin, fibronectin, fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, and hyaluronic acid (XCelliStem®, StemSys, Sunrise, FL, USA), which supports new tissue construction (Frantz *et al.*, 2010; Marçal *et al.*, 2012; Mouw *et al.*, 2014).

Figure 8. Day 16: A second application of the ECM powder was applied to the wound bed of the blue-tongued skink (*Tiliqua scincoides*).

Many reptile patients respond poorly to stress, have variable sized and shaped bodies, and are often poorly compliant when handled, requiring more-frequent anesthetics to facilitate treatments such as debridement and bandaging. The powder form of ECM was beneficial due to its high conforming ability, ease of application, and reduced requirement for bandage changes (Edgar *et al.*, 2018). In this case, the bandage was removed and additional powder was applied on only two occasions. A single debridement was performed 7 days after the initial application of the ECM material to assess the wound healing under the developed crust. In retrospect, this was likely unnecessary and may have prolonged the healing process by disrupting the wound bed when a healthy bed of granulation tissue was already present.

Despite many ECM products on the market, there is still a lack of consensus and complete understanding of their efficacy, safety, and how they interact with the host tissue (Aamodt and Grainger, 2016). For this case, there were initial concerns of foreign body reaction or rejection of the material. Adverse reactions to foreign cellular material include acute inflammation, chronic inflammation, granulation tissue development, and fibrous capsule development (Anderson *et al.*, 2008). Signs of adverse reactions were not detected during or after the treatment period. Although not fully validated, and further investigation into how a host responds to these

Figure 9. Day 20: Blue-tongued skink (*Tiliqua scincoides*) 11 days post initial application of the ECM and 4 days after the second application; a thin crust is present with scabbing of the wound margins extending over a large portion of the wound. Further contracture is evident.

Figure 10. Day 24: Blue-tongued skink (*Tiliqua scincoides*) 15 days after the initial application of the ECM powder; the wounds continued to exhibit further contracture and were covered by the protective crust. The patient was discharged.

ECM biomaterials is required, evidence suggests the process of decellularization leaving behind only the ECM components reduces the risk of foreign body reaction (Aamodt and Grainger, 2016).

The wound healed with thin epithelial tissue without replacing the typical scales. The lack of scales was expected based on previous experiences of wound healing in this species and evidence that epithelial tissue may not regenerate scales as readily on the body compared to the extremities in some lizards (Wu *et al.*, 2014). Whether the progression through the stages of wound healing was altered is challenging to determine, although in the author's opinion, the wound healed more rapidly than previously managed wounds of similar severity. One must interpret the findings in this case with care as there were no control subjects. An option to treat different wound sections using more-traditional bandage materials to observe differences in healing rate and quality was not considered and would have been beneficial in determining if there was added benefit to using ECM products in this case. It is therefore necessary to perform controlled studies to further evaluate the efficacy and safety of ECM products in reptiles.

This case describes the successful management of extensive, contaminated wounds involving skin, muscle, bone, and connective tissues in a blue-tongued skink using an ECM powder derived from multiple porcine cell lines. To the author's knowledge, this report is the first to describe the use of this form of wound management in this species. The positive outcome, in this case, suggests the use of ECM products can be considered an option when managing similar wounds in *Tiliqua*, and potentially other species of reptile, without adverse reaction. Further work is required to understand the use and benefits of ECM materials in reptiles and other exotics.

Figure 11. Day 42: Blue-tongued skink (*Tiliqua scincoides*) 31 days after the initial ECM powder application; the skink presented post ecdysis with a thin, purple tissue covering the wound sites.

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