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Research Article

The Use of Borate-based Biological Glass for the Treatment of Full-thickness Wounds in Six Dogs

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Keywords
• Dog; Wounds; Biological glass; Granulation

Abstract

Objective: To evaluate the clinical outcome after the use of borate-based biological glass for the treatment of full-thickness wounds.

Study design: Retrospective case series.

Animals: Six dogs with full-thickness wounds.

Methods: The medical records of dogs with full-thickness wounds treated during June 2012- January 2016 using borate-based biological glass were evaluated. Data included signalment, wound cause and location, type and duration of previous wound management, time to granulation tissue formation, time to complete wound healing, subsequent procedures if applicable, outcome, and complications associated with treatment.

Results: Six wounds (one per dog) were evaluated. After biological glass application varying degrees of granulation tissue developed at all wounds sites. The mean number of days to achieve complete granulation coverage after bioglass application was 4.8 (range, 3-7 days). This corresponded to a mean number of two biological glass applications per wound. There were no complications noted.

Conclusion: Borate-based biological glass appears to promote granulation tissue formation and may be effective in the management of full-thickness wounds.

Clinical relevance: Borate-based biological glass may be safely used for the treatment of full-thickness wounds. Studies to further define clinical indications and efficacy are warranted.

INTRODUCTION

Full thickness skin wounding is common in veterinary medicine. Causes for these wounds include bite wounds, lacerations, vehicular trauma, decubital ulcers, and post-surgical excision of tumors. Open wound management often consists of debridement, copious lavage, and application of dressings and/or bandages until the formation of viable granulation tissue. Under favorable conditions, sufficient granulation tissue is expected to be present within a full-thickness wound 5 days after wounding, allowing for epithelization to occur [1]. However time to complete healing can be protracted, during which owners often become frustrated and bandage-related morbidity can occur. The desire to expedite this process and to improve wound healing has provided the impetus for research into novel wound care products. To date, various topical agents, impregnated dressings, and hydrogels have been described [2,3]. More recently the application of negative pressure wound therapy has been reported to improve wound healing and decrease length of hospitalization [4-6].

Biological glass or bioglass has been investigated extensively and used in human medicine. Biological glass is used to provide a scaffold for which cellular proliferation, cellular differentiation, and tissue infiltration can occur [7]. The ability of biological glass to promote angiogenesis and activate gene expression during the proliferative phase of wound healing has been documented, specifically the ability to expedite granulation tissue formation [7-11]. The use of biological glass has been described for hard and soft tissue regeneration such as the repair of orthopedic defects, the replacement of ear bones, teeth, vertebrae, and for cutaneous wound therapy [7-11]. Research continues on its potential applications in neuronal repair and drug delivery [12-14].

The mechanism of action of biological glass has been studied extensively in the human literature, primarily the silicate form (45S5) [8-10]. Borate biological glasses have been found to act in a similar fashion [10]. As the glass dissolves in body fluid, calcium and other cations within the glass (Na^+, K^+, Mg^{2+}, and B^+) diffuse out into the solution. The calcium ions react quickly with surrounding phosphate and form an amorphous calcium phosphate. With time this calcium phosphate layer crystallizes to hydrocarbonate apatite (HCA). The bioactivity and tissue adhesion of bioglasses

has been directly attributed to the formation of HCA on the glass to body fluid interface [10].

Calcium is an important factor in wound healing and is suspected to be required for the later stages of wound healing including the migration of epidermal cells. There is also evidence suggesting that the presence of calcium at an open wound bed helps to regulate wound healing processes more effectively [12].

Unlike the silicate glasses, borate-based biological glass forms HCA directly on the surface of the underlying, unreacted glass [10]. Borate-based biological glass has been shown to convert completely to HCA at a rate that is three to four times faster than silicate equivalents [13,15]. This is due to the high solubility of borate in body fluids, and additionally all degraded products can then be excreted in urine [7, 13,15].

Recently, a nanofiber, borate-based biological glass developed specifically for veterinary use has become available (RediHeal®; Avalon Medical, Stillwater, MN). This product is a melt-derived borate-based biological glass nanofiber [16]. A similar formulation has been successfully used in cases of human diabetic ulcers with wound closure rates of 0.3 to 0.8 millimeters per day reported [10-12]. The use of a comparable biological glass product for the healing of feline femoral defects has been reported [17].

The purpose of this study is to report our initial clinical experiences with borate-based biological glass for the treatment of open wounds. To the authors' knowledge, only a single case report outlining the use of borate-based biological glass for wound management exists in veterinary medicine [18]. Based on the human literature, we hypothesize that borate-based biological glass may be a useful addition to current wound management therapies.

MATERIALS AND METHODS

The records of canine patients with open wounds treated with biological glass at two veterinary hospitals between 2012 and 2016 were obtained. Patients were included in the study if information on signalment, wound cause and location, type and duration of previous wound management, and subsequent treatment with biological glass was noted. Only patients with wounds that did not have any macroscopic evidence of granulation tissue after at least five days of treatment with conventional wound management techniques prior to the application of biological glass were included.

Time to granulation tissue formation, time to epithelization (i.e. complete wound healing), subsequent procedures if applicable, outcome, and complications associated with wound therapy was recorded. Dogs with any concurrent abnormalities based on physical examination, hematologic, serum biochemical and/or urinalysis profiles at any time during treatment were excluded.

RESULTS

The records of 14 canine patients treated with borate-based biological glass were retrieved. In all cases the borate-based veterinary formulation was used (RediHeal®). Eight of 14

Table 1: Summary data for canine full-thickness treated using borate-based biological glass.

Patient #	Signalment	Wound Type	Days to Bioglass Application	Wound Size (l x w cm)	Borate-based Bioglass Therapy			Definitive Treatment
					Days to ≤ 50% Granulation Coverage	Days to Complete Defect Coverage	No. of Applications	
1	8y FS Labrador	Chronic decubital ulcer, right hock	5	3.5 x 2.8	2	5	2	2nd intention
2	12 FS Pit Bull	Wound of unknown origin, right antebrachium	5	3.2 x 4.7	2	3	2	2nd intention
3	8mo MI Chihuahua	Degloving after vehicular trauma, left tarsus	7	6.3 x 4.2	3	7	3	2nd intention
4	8y MN Mixed	Bite wound repair with necrosis and dehiscence (+ culture with enterobacter), left lateral neck	5	7.1 x 3.6	2	5	1	Delayed primary closure
5	7mo FS Yorkshire terrier	Escharotomy after open radius/ulna fracture repair	8	3.4 x 2.2	2	4	1	2nd intention
6	10y FS Greyhound	Chronic wound to dorsolateral paw with bone exposure	10	4.2 x 3.7	3	5	2	2nd intention

Abbreviations: FS:Female Spayed; MN: Male Neutered; MI: Male Intact.

patients had biological glass used as the sole treatment for wound management and were excluded. The remaining six patients had wound beds lacking macroscopic evidence of granulation tissue after five days of conventional wound management and were included in the study (Table 1). Breeds included Labrador retriever, pit bull terrier, Chihuahua, Yorkshire terrier, mixed breed, and greyhound. The mean age was 6.5 years (range 7 months to 10 years). Four spayed females, one intact male, and one castrated male were included.

Etiologies of wounding included those of traumatic etiology (n = 3), revised repair of previously treated dog bites (n = 1), chronic non-healing (n = 2). Each dog has a single wound that was treated (Table 1).

Various methods of stabilization and wound management were employed prior to the application of biological glass. Common initial treatments included wound debridement and copious lavage using sterile saline, moisture retention dressings, wet-to-dry or soft padded bandage placement, and/or topical and/or systemic antimicrobial therapy. The use of these initial, conventional treatments did not elicit granulation formation at the sites at or after five days. The mean time between initial wounding and biological glass application was 6.7 days (range, 5-10).

In preparation for biological glass application, all wounds were copiously lavaged using sterile saline and debrided as indicated using standard surgical techniques. The wound bed was then dried using sterile gauze sponges. Using aseptic technique the wound bed was then completely covered using the biological glass. Light dressings using a non-adherent dressing pad (Telfa® or Adaptic®, Medline Inc.) as a contact layer were applied over top to ensure that the biological glass remained in place (Figure 1).

Three of 6 case were receiving antibiotics prior to biological glass application. Aamoxicillin/clavulanate acid (Clavamox; Zoetis US) 14.8mg/kg twice daily prescribed in one case and cephalexin (Virtus Pharmaceuticals) 20-23.2mg/kg twice daily 2 cases. All antibiotic therapy was discontinued once the presence of granulation tissue was noted.

The timing between wound evaluations ranged between 2-5 days depending on the effusiveness of the wounds and the need for dressing changes. Wounds were inspected for the presence of granulation tissue. Biological glass therapy was continued if the granulation tissue was not sufficient to consider either delayed closure of the wound or to allow healing via second intention.

Varying degrees of granulation tissue was present at all of the treated wounds of each dog after the initial biological glass application (Figure 2). In 3/6 wounds evidence of contraction and peripheral epithelialization was present after a single bioglass application. The mean number of days to achieve complete granulation coverage after bioglass application was 4.8 (range, 3-7 days). This corresponded to a mean number of two biological glass applications per wound (range, 1-3) during the time period.

In 2/6 cases a blue-staining identical to the color of the biological glass was noted at the wound bed. This discoloration was no longer apparent post lavaging. One patient underwent delayed primary closure of its wound 5 days post application. The remainders of the wounds were allowed to heal via secondary intention. The mean time to complete epithelialization of the wounds was 12.8 days (range 9 -18 days). There were no complications related to biological glass usage noted.

DISCUSSION

We found that borate-based biological glass induced granulation tissue formation and expedited wound healing in wounds that had no macroscopic evidence of granulation tissue after at least 5 days using conventional therapies.

When comparing to reports regarding traditional wound management techniques using moisture retention or wet-to-dry bandaging, we believe that with biological glass application the rate of granulation tissue formation may be an equivalent, if not superior [3,5]. This earlier clinical evidence also appears to be comparable to results achieved using negative pressure wound closure devices, published both in the human and veterinary literature [4-6,12].

In the case series presented within this paper, borate-based biological glass was used in the treatment of chronic non-healing wounds including decubital ulcers, wounds secondary to vehicular trauma, and ulcerative lick granuloma. These wounds were selected due to evidence of delayed healing despite exposure to conventional wound treatment. This characteristic allowed us to comment on the ability of biological glass to promote granulation tissue formation in a site previously devoid. Given an appropriate environment, it is expected to have healthy granulation tissue within a wound 5 days post injury. We postulate that the borate-based biological glass provided a porous scaffold providing not only structural support, but by mimicking the microstructure of fibrin allowing for cellular migration, proliferation, differentiation, and angiogenesis [7,8,16]. Thus allowing wound healing to proceed.

When compared to other currently available dressings or treatments, borate-based biological glass is relatively inexpensive, easy to apply, and does not require hospitalization. The blue, “cotton-candy” like formulation can be applied to any defect using forceps and/or a gloved finger. It can also be packed into various wound beds, including crevices and interdigital

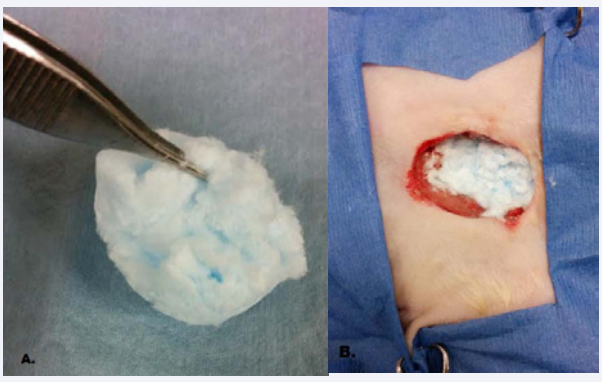

Figure 1 A. Borate-based biological glass nanofiber. B. Patient 11. Open wound on the left lateral thigh. Note the blue bioglass sterilely applied within the wound bed.

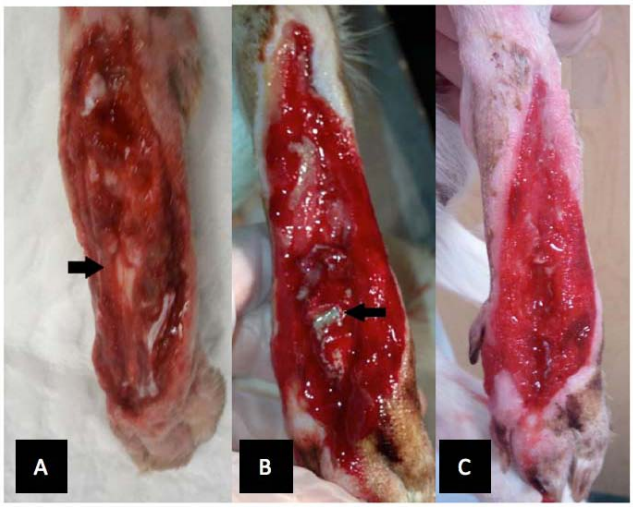

Figure 2 Pictures from patient 3, a degloving wound sustained after vehicular trauma. The wound had been treat for 7 days without evidence of healing prior to bioglass application. A. The wound after first bioglass application (36 hours). There is a central region of exposed bone (arrow) and mild granulation tissue at the wound periphery. B. 72 hours after initial biological glass placement. Healthy, bleeding granulation tissue predominates and the bony defect is covered. Residual bioglass can be seen at the site. C. After completion of biological glass treatment (7 days after initial bioglass application), healthy granulation tissue with evidence of epithelialization and contraction at the wound edges.

spaces where other dressing materials have previously been a challenge. A light protective bandage is applied over top and based on the manufacturers' recommendations and dressing changes can be performed every 2-3 days in instances of effusive wounds or 4-7 days for dry wounds. This dressing can be used as an alternative to negative pressure wound therapy in instances where owner finances or wound size and/or location preclude VAC use and hospitalization.

In this case series, no complications related to borate-based biological glass application were noted. A blue-green staining of the wound bed secondary to the dissolution process was noted in some cases, but was of no apparent clinical significance. Histologic evaluation of the wound bed would be needed to confirm this assumption.

Additionally, no evidence of infection was noted in any of the treated wounds, including those without previous antimicrobial therapy. The use of biological glass in these cases may have directly contributed to this as it the inherent antibacterial properties of biological glasses secondary the pH shifts during dissolution has been reported [10,11]. The proposed antibacterial property of borate-based biological glass is interesting and warrants additional investigation as to its clinical application and significance.

Biological glasses are currently used routinely for orthopedic and dental procedures, with few, minor complications reported (e.g. persistence of pre-existing infection and exuberant callus formation). Applications for biological glass in the field of wound management are still being investigated and human trials are ongoing.

Limitations of this study are correlated to its retrospective design and include low case number, lack of objective measurements, and absence of a standardized treatment protocol. An additional limitation is related to the low number of wounds closed via delayed closure. The majority of these patients had financial constraints and subsequently declined any additional surgical treatments.

Despite these limitations, this retrospective case series highlights the potential clinical applications of borate-based biological glass in veterinary wound therapy and it should be considered an addition to current wound management practices. Borate-based biologic glass application appears to promote granulation tissue formation where it had previously been refractory to healing with other conventional wound therapies. To the authors' knowledge RediHeal® is the only biological glass product marketed for veterinary use and specifically formulated for wound healing.

We are encouraged by these initial and early clinical outcomes and believe this treatment warrants further investigation. A prospective study to directly compare the effects of borate-based biological glass to more conventional wound management (moisture retention dressings and/or negative pressure wound therapy) on the rate of healing of full-thickness wounds in dogs should be considered.

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