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THE EFFICIENCY OF THE NATURAL COLLAGEN COATING IN THE TREATMENT OF EXTENSIVE CHRONIC DEFECTS OF THE SKIN AND SURROUNDING TISSUES IN DOGS

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ABSTRACT

The occurrence of extensive non-healing and chronic skin defects with loss of tissue substance in companion animals are a frequently solved problem. The management of the therapy of large-area defects and absent tissues is a challenge for setting up successful therapeutic management and achieving wound closure, satisfactory cosmetic effect, and restoration of the functionality of the damaged area. In veterinary medicine, we often encounter the failure of wound therapy methods commonly used in closing defects, as a result of which the defect closure time is prolonged. The longer the time required to close the defect, the greater the risk of microbial infection and complications associated with healing in the case of extensive damage to the surrounding soft tissues. Direct influence of the individual phases of healing with supportive alternative therapy appears to be a very suitable solution for the treatment of chronic wounds. To overcome the shortcomings related to partially efficient conventional wound dressings, efforts are oriented toward developing new and effective platforms for wound healing applications. Five patients referred to the Small Animal Clinic of the University Veterinary Hospital were included in this clinical study. Patients were referred to the clinic with extensive long-term non-healing wounds, necrosis and secernation, or ongoing infection, with loss of tissue substance, which showed signs of chronicity. After assessing the patient's state of health and subsequent cleaning of the wound bed from contaminants and damaged tissues, collagen sponge Suprasorb® C was applied to the surface of the cleaned wound bed. The average time for the complete closure of the defect was 24.6 days since the introduction of the primary treatment. In all patients, we observed the complete closure of the defect, restoration of functionality of the damaged tissues, and achievement of a cosmetic effect without complications in the recovery process, which points to the excellent effectiveness of the collagen covering in the wound healing process.

Key words: collagen sponge; conservative management; chronic skin defect; non-healing wound; wound healing

INTRODUCTION

In companion animals, the healing of large skin defects resulting from traumatic accidents can be challenging

to treat since they need a complex management consisting of accurate debridement of the damaged and necrotic tissues, local and/or systemic infection control, protection of the underlying tissues, and induction of cutaneous tissue regeneration. To this aim, surgical tissue reconstruction (i. e., skin graft) and medical treatments are often associated to reach complete anatomical and functional recovery of the damaged area, reducing debilitating side effects, and pain [18, 29].

Wounds have a variety of causes, from surgery, injuries, extrinsic factors (e. g., pressure, burns and cuts), to pathologic conditions such as diabetes or vascular diseases. These types of damage are classified into acute or chronic wounds depending on their underlying causes and consequences [11]. Acute wounds usually proceed through an organized and appropriate repair process, resulting in the sustained restoration of anatomical and functional integrity. On the contrary, chronic wounds are not able to achieve optimal anatomical and functional integrity. Healing is related to, and determined by, both pathological processes nature, degree, and status of host and environment. Systemic factors such as patient age, the presence of vascular, metabolic and autoimmune diseases, as well as ongoing drug therapy, may affect the wound healing process [12]. In the case of chronic lesion, characterized by the failure of normal phases of wound healing in an orderly and timely manner, with a recovery time that usually exceeds eight weeks [10, 14]. An ideally healed wound is an area returned to normal anatomical structure, function and appearance after an injury; a minimally healed wound is characterized by the restoration of anatomical continuity, but without sustained functional results; the wound can recur [12].

The wound management goal is to complete the healing in a rapid manner, with functional and aesthetic outcomes [17]. For many years, wound management was based on covering the wound and the materials used for that had a passive action in encouraging the healing process. However, in recent years, the wound management has been updated due to a greater understanding of the molecular and cellular processes involved in wound healing and preventing the wound from healing. Accordingly, the design and functionality of wound dressings has evolved in the direction of multi-functionality. The critical necessities of modern wound dressings include: biocompatibility, no cytotoxic effect, no antigenic or inflammatory stimulation, a rate of biodegradability directly proportional with the rate of formation of new tissue, a release of incorporated bioactive constituents (drugs), and the control of possible infections [9, 26].

The multidisciplinary association between tissue engineering and regenerative medicine includes aspects from engineering, biology, and material science and ultimately results in the progress of viable alternatives for organs and tissue regeneration/replacement. As an alternative treatment of wounds, tissue engineering has recently suggested a range of solutions, such as the introduction of scaffolds, to manage the treatment process. Scaffolds, 3D structures, not only offer sustenance for tissue formation, but also can shield a wound, becoming an efficient “fence” against external contamination [21]. Biodegradable polymeric materials are ideal carrier systems for biomedical applications. Features like controlled and sustained delivery, improved drug pharmacokinetics, reduced side effects and safe degradation make the use of these materials very attractive in a lot of medical fields [19]. They can be loaded with growth or angiogenic factors to favour tissue regrowth or antimicrobials to avoid wound infection [7, 8].

Collagen is one of the most frequently used materials in protein-based scaffolds for skin wound healing; this is not only because of its sheer abundance in the body, but also because it is the main component of the dermal extracellular matrix (ECM). Specifically, collagen type I constitutes 80–85 % of the dermal ECM, while collagen III constitutes 8–11 % [22]. Collagen sponges are especially useful in wound healing because their wet-strength allows their suturing to soft tissue and provides a template for new tissue growth [4, 13]. Their porosity is controlled by varying the collagen content and freezing rate. These sponges are capable of absorbing large amounts of tissue exudate, adhere smoothly to a wet wound bed, and maintain a moist environment, while shielding against mechanical trauma and bacterial infection [30]. Collagen is part of the ECM and interacts with macromolecules and cells promoting cellular attachment and spreading [2]. It provides directional information for cell attachment, migration, and proliferation through integrins which are expressed on the surface of most cells of the ECM [20, 25] and its breakdown products become integrated into the developing physiological ECM. Although there has been much discussion about the potential immunogenicity and adverse reactions to the application of collagen within biomedical

devices, collagen is considered to contain very weak antigenic components and the incidence of such adverse reactions to the presence of collagen are extremely rare [15, 16]. Indeed, studies have demonstrated that the presence of collagen within biological implants and scaffolds do not elicit immune responses [24]. The treatment of extensive chronic defects of the skin and surrounding tissues in dogs presents challenges in the form of ending the chronic condition, the inflammatory phase and starting the closure of the skin defect. Collagen as a biodegradable external component brings significant progress in the process of closing a skin defect, as well as a carrier of supporting substances that help the process of granulation and epithelization. Therefore, the clinical study was aimed to the monitoring of the effectiveness of wound treatment by straight bovine collagen covering attached on the surface of defect.

MATERIALS AND METHODS

In this clinical study, five patients from the Small Animals Clinic, Section of surgery, orthopaedics, roentgenology and reproduction at the University of Veterinary Medicine and Pharmacy in Košice were included. Patients were with long-term non-healing wounds of various aetiologies with loss of tissue substance that showed signs of chronicity (persistent inflammatory phase of the healing process). The group of patients consisted of five dogs: crossbreed (n = 4) and a Rhodesian Ridgeback (n = 1), with a mean age of patients of 5.6 years. There were three males and two females. The clinical study included wounds of various aetiologies, such as stab wounds (n = 2), wound dehiscence (n = 2) and laceration (n = 1) located on different parts of the body.

After the primary clinical examination of the patient with an assessment of the patient's state of health, the wound was macroscopically evaluated with regard to: the extent and localization of the wound, hyperaemia, oedema, secernation, granulation, necrotization, and contraction of the wound edges. Macroscopic evaluation of the wound changes and the healing process was performed at each wound check, during the entire period of therapy. The regularity of the wound check, the replacement of the wound covering, and the length of the therapy were different for individual patients depending upon the individual stages of healing in which the current injury was located.

The patients were sedated at the initial clinical examination and prepared for surgery and the mechanical removal of contaminants from the surface of the wound bed by an intravenous application of butorphanol (Butomidor, RP Richter Farma, Austria) at a dose of 0.2 $mg.kg^{-1}$ b.w. and medetomidine (Cepetor, CP pharma, Germany) at a dose of 0.020 $mg.kg^{-1}$ b.w. The introduction of the patient into general injection anaesthesia was performed by propofol (Propofol, Fresenius Kabi, Germany) at a dose of 3 $mg.kg^{-1}$ b.w., with intravenous (IV) prolongation of anaesthesia as needed. A combination of amoxicillin and clavulanic acid (Synulox RTU, Zoetis, Czech Republic) at a dose of 15 $mg.kg^{-1}$ b.w. was used as the initial antibiotic therapy administered subcutaneously. In each patient, a sample was taken from the wound using a sterile microbial swab for bacteriological cultivation and determination of the antibiogram in a certified laboratory. The microbial culture indicated the need to use a systematic antibiotic therapy. Based on the results of the microbial culture and antibiogram, it was not necessary to change the set antibiotic therapy in all five patients.

After the primary examination, the wound was flushed with a bacteriostatic and bactericidal lavage solution (Braunol, B. Braun Melsungen AG, Germany) diluted in an isotonic solution (0.9 % NaCl, B Braun Melsugen AG, Germany). The wound bed and edges of the skin defect were refreshed by excochleation, while total removal of the changed structures was not possible based on the state of the surrounding tissues. Enzymatic preparations containing collagenase (Irulox Mono, TJ Smith & Nephew Ltd., United Kingdom) or containing pancreatin, trypsin, chemotrypsin or papain (Pana-Veyxal Salbe, Veyx-Pharma, Germany), were applied in places where it was necessary to gently separate the changed structures, necrotic and damaged tissue without iatrogenic damage. In the case of painful inflammation of the skin, a dermal gel containing ketoprofen (Fastum gel, A. Menarini Industrie Farmaceutiche Riunite Srl, Italy) was applied to the site of inflammation. Collagen sponge (Suprasorb® C, Lohmann & Rauscher, Germany) was applied to the surface of the cleaned wound bed.

In places where the wound exceeded the coverage of the collagen sponge, preparations based on ointment and cream were used – cream containing the silver salt of sulfadiazine and sodium hyaluronate (Ialugen plus, IBSA, Slovakia s.r.o., Slovakia), or ointment containing neomy-

cin and bacitracin (Baneocin, Sandoz GmbH, Austria), or ointment containing iodine (Betadine, EGIS Pharmaceuticals PLC, Hungary).

A three-layer bandage with non-sterile gauze squares (Lohmann&Rauscher, Germany), a secondary layer of Cellona® synthetic cotton wool (Lohmann&Rauscher, Germany), and an elastic CoPoly wrap (CoPoly, Czech Republic) placed circularly on the surface to the site of damage was used as a surface covering.

RESULTS

The average healing time for patients from the primary treatment and application of collagen covering in combination with bactericidal preparations, to closure of the defect was 24.6 days. The shortest duration of therapy from the primary treatment was 13 days. The longest period of therapy from the primary treatment was 45 days. These results pointed out and confirmed the excellent effectiveness of the collagen covering in the wound healing process of extensive non-healing chronic wounds with loss of tissue substance. The expected effect of collagen as a natural material was not to create toxic intermediates and not force the body to react to the material; effectively support the healing process and not causing any complications in the patient's recovery process. During the entire time of the regeneration process, from the beginning of the application of the collagen sponge until the closure of the defect, the point of contact of the collagen with the surrounding soft structures was evaluated using macroscopic indicators of the state of healing, which were: secernation, hyperaemia, oedematization, and necrotization of the defect surface. The progress of the healing process was evaluated by every re-bandaging of the wound. The state of the aforementioned indicators of macroscopic assessment of wound healing was different in each patient at the beginning of the treatment, but after the start of tissue regeneration at the place of application of the collagen coating, they were very similar and almost not observed.

The first patient that was referred to the clinic with the dehiscence of a surgically treated bite wound, localised on the cranial surface of the chest, extending laterally and dorsally along the scapula and neck, irregular in shape (Fig. 1). The closure of the skin defect occurred on the 45th day after the onset of therapy.

The second patient was referred to the clinic with a devastating injury to the right thoracic limb (Fig. 2). The patient had symptoms of grade four lameness with massive swelling in the metacarpal region. After 28 days from the start of the therapy, there was complete healing of the wound with first-degree lameness.

In the third patient with a dehiscence of a surgically treated bite wound with necrosis and secretion on the right side of the abdominal wall, extending from the right flank to the lateral side of the thigh, complete closure of the wound occurred on the 23rd day from the start of the therapy.

In the fourth patient with a puncture wound on the palmar surface of the left thoracic limb with an ongoing infection, the defect was closed on the 13th day from the start of therapy (Fig. 3).

The fifth patient was referred to the clinic with a stab wound of a circular shape on the foot pad of the fifth toe of the left hind limb. The wound was closed after 11 days from the start of the therapy and re-epithelialization of the wound surface occurred on the 14th day from the start of therapy.

All five patients point to the difference in the condition and location of the skin defects and thus the impossibility of a uniform assessment of the wound and individual setting of therapy. In all patients, it was damage to the skin and surrounding structures after the failure of previous therapy of a different provoking aetiology. Swelling, hyperaemia, and secretion of varying extent were noted in all patients after the primary examination. Necrotization around the defect was noted in two patients. The initiation of therapy with the application of enzymatic preparations resulted in a calming of the inflammation around the defect and significant progress in the wound healing process. Detachment of the changed structures and the formation of a granulation bed were recorded as early as three to five days (Fig. 4). The disappearance of swelling and secretion was observed in the following days. The subsequent application of a collagen cover, together with an ointment containing the silver salt of sulfadiazine and sodium hyaluronate, brought progress in the steps of closing the skin defect with new epithelization and tissue remodelling (Fig. 5). The difference in the closure time of the skin defect was directly proportional to its localization with regard to the lateral pull, size and extent of the damaged structures.



Fig. 1. Dehiscence of a surgically treated bite wound, localised on the cranial surface of the chest



Fig. 2. Devastating injury to the right thoracic limb



Fig. 3. Puncture wound on the palmar surface of the thoracic limb with an ongoing infection



Fig. 4. The massive formation of a granulation bed



Fig. 5. Closing the skin defect with new epithelization and tissue remodelling

DISCUSSION

The wound healing process unites several overlapping phases: i. e., homeostasis, inflammation, proliferation/granulation, and remodelling. It involved a cascade of cells, matrix components and other biological factors to act together in order to facilitate the healing and restore the tissue integrity. Still, when the healing course deviates from the normal path, the healing does not advance past the inflammatory phase [28].

During our study, we focused on the treatment of five patients which were referred to the clinic with chronic wounds without progress in the healing process. All patients had a desirable outcome and closure of the defect in the fastest possible time. The results of our work points to the effectiveness of collagen covering in the therapy of

wounds that cannot pass through the inflammatory phase of the healing process and show signs of chronicity.

Collagen offers structural support to the body and regulates cellular functions such as: cell shape, proliferation, differentiation and cell migration [5]. It stimulated cellular and molecular cascades of wound healing and enabled the development of new tissue and wound debridement. An abrupt change could be noticed with the application of the collagen matrix in the wound bed within 10–14 days and an improved wound would be seen with the chronic wounds. When such dressings come into contact with wound exudate, they absorb wound fluid and thereby create a moist environment around the wound. These dressings are semipermeable to water and oxygen. Because of the hydrophilic nature of collagen, the fluid is retained and cells having phagocytosed microorganisms are picked up. It has an important function in the natural wound healing system by inducing clotting and forming matured scar in the area of the wound. In the event of wound healing as collagen combines with dermal cells, growth factors and cytokines derived from the patient, it accelerates the re-epithelization of the skin. The collagen dressings are also designed as vehicles to deliver therapeutic drug on the wound surface [23].

In our case, we observed a significant improvement after the application of the collagen sponge within the first few days. It created a moist environment for closing the wound in the defect site and the beginning of the formation of new granulation tissue occurred on average three days after application. In wounds with massive secernation, a large amount of exudate was absorbed and secernation stopped on average on the fifth day after the application of the collagen. The collagen, which we applied as a natural material to the site of damage, did not create toxic intermediates after application and did not cause an organism's reaction to the material. It protected the wound site from further external mechanical and microbial stress; thanks to the fact that it created a mechanical barrier against the external environment.

B o h l i n g et al. [3] in their study described the course of wound healing in dogs and cats. In secondary wound healing, the wound defect in cats was filled with granulation tissue more slowly than in dogs. The formation of granulation tissue in the wound bed began in dogs at an average of 4.5 days and in cats at 6.3 days. The complete granulation of the tissue occurred in 11.7 days in dogs, and in cats the granulation time was observed to be more than 19 days.

In a study published by A r a v a t h i n et al. [1], the effectiveness of the collagen cover was observed against the control group in a mammalian model for a period of 12 days. On the 6th day after the application of the collagen cover, a layer of granulation tissue was formed and the inflammation decreased. The secretion was present on average until the 6th day. The wounds were filled with compact granulation tissue on day 12 without the presence of exudate. A wound size reduction of 90 % was observed in the collagen-based sponge treated group, whereas it was 75 % in wound control group.

In a study conducted by V e v e s and S h e h a n [27], in human medicine performed on 276 patients of diabetic foot ulcer divided equally into two groups, one group was treated with collagen and the second with other dressing materials. They found no significant difference in the completeness of healing of wounds when old wounds (>six months old) were compared. But the healing was better with the rapid start of granulation tissue formation and wound closure in wounds of less than six months' duration treated with collagen dressings. In addition, patients with collagen covering experienced a reduction in pain and a reduction in bacterial colonization in the wound.

The results of the study by C o l a k et al. [6] demonstrated that collagen dressings are better than conventional dressings with regard to early granulation tissue and shorter hospital stay. The aim of this study was to compare the results of diabetic foot ulcer patients treated with and without collagen. Of the total 64 patients included in the study, 30 were treated with physiological serum (PS) and 34 with collagen. Complete closure was achieved in 17 (56.6%) of the PS group patients after 12 weeks of treatment. The rate was 25 (73.5%) in the collagen group. The mean duration of treatment was 9.2 weeks in the PS group and 8.08 weeks in the collagen group. The recovery time and recovery rates were determined to be better in the collagen group than in the PS group.

In our study of collagen wound therapy in dogs, the wound began to fill with granulation tissue on average on the 3rd day and was filled with compact granulation tissue on average on the 12th day from the start of the therapy. The average time for the complete closure of the defect since the primary treatment was 24.6 days. The shortest duration of therapy from the primary treatment to the closure of the defect was 13 days. The longest period of therapy from the primary treatment to the closure of the defect

was 45 days. The length of therapy in this patient with the dehiscence of a surgically treated bite wound was directly proportional to the large extent of the injury, bacterial contamination, the presence of necrotic tissue and massive secernation from the wound. The application of collagen covering to chronic types of wounds supports the healing process and the closure of the skin defect, depending on the size and location, in the shortest possible time with the restoration of the functionality of the damaged structures.

CONCLUSIONS

A big challenge in therapeutic management has been chronic large-area, deep wounds with a lack of loose skin for their closure. Macroscopic results after the targeted application of a collagen cover in combination with bactericidal and supportive preparations on the surface of wounds of various aetiologies, which remained in the inflammatory phase of healing without progress in the healing process, indicates the success of the chosen therapeutic method. Since the wounds were of different aetiology and extent, the collagen cover is effective for different types of wounds regardless of other factors such as breed predisposition, condition, body weight, age, etc. Collagen cover opens up the possibility of using collagen as a carrier of other therapeutic substances that support the wound healing process, such as growth factors, stem cells, antibiotics, or natural substances such as cinnamon and clove extracts and others that have an anti-inflammatory effect, in the therapy of chronic large-area non-healing defects with loss of tissue substance and impaired function of the damaged area for faster wound closure, restoring the functionality of damaged tissues and achieving the maximum cosmetic effect.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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