Is there an alternative to acellular dermal matrix for wound management? Revisiting the role of a bioactive collagen and hyaluronic acid-based dressing hyaluronic acid

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ABSTRACT

Wound healing is a complex process, which involves a lot of synergistic interactions between several cell lines, cytokines, enzymes, and growth factors. In the last few years several biomaterials and bioactive dressings, which are considered to play an active role in wound healing have been introduced. Both collagen and Hyaluronic Acid (HA) have been largely adopted for wound management and its combined used as bioactive dressing have been studied. We reported our clinical experience with an advanced wound dressing consisting of HA plus heterologous collagen type I applied on acute and chronic wounds of different aetiology in in a retrospective cohort of 30 patients. All patients included have cutaneous open wounds completely healed by only second intention, and all wounds were treated by using Bionect Pad® (BP). If necessary, some cases were managed with combined treatments in order to obtain an adequate wound bed preparation before the application of BP. Thirty patients with an average age of 60,2 years were treated for wounds of different aetiology. Wound types included venous ulcers, posttraumatic wounds, surgical wound complications, pressure sores, burns, peristomal ulcerations and skin ulcerations after radiation therapy. The average healing time was 31 days (range: 21-76 days). Basing on our encouraging results, we believe that such bioactive dressings may be considered as a useful and reliable alternative to other well-known and established treatment methods such as acellular dermal matrices or advanced wound dressings in selected cases.

INTRODUCTION

Hyaluronic Acid (HA), is a glycosaminoglycan which is virtually present in all human tissues where it represents a fundamental constituent of the Extracellular Matrix (ECM).

From a functional perspective, while in the past HA was merely considered as space-filling compound and shock absorbance, it is now evident that depending on its molecular weight and through interactions with its primary receptors, HA's biological functions are far more intricate. Its important biological role in controlling cellular water homeostasis has been well established due to its high grade of hydration. Since highly hydrated matrices facilitate cell migration and proliferation, HA can supervise and regulate cell behaviour and cell-cell interaction, especially in the case of wound healing. These regulating functions and the interactions with other macromolecules depend on the molecular weight and the concentration of HA. Due to its peculiar structural properties, versatility, ubiquitous nature in mammalian systems and biocompatibility, HA represents a safe and reliable alternative in several biomedical applications, such as visco-supplementation, drug delivery, eye surgery, tissue engineering and regenerative medicine. While some applications use HA in its native form, chemical functionalization of the macromolecule is often performed in order to tailor its in vivo residence time and its overall properties, thus overcoming the biological implications of HA degradation.[1-4]

Collagen is the unique, triple helix protein molecule, which forms the major part of the extracellular dermal matrix (ECM) and accounts for 70–80% of the dry weight of the dermis. Mainly produced by fibroblasts, the collagen type I comprises approximately 70% of col-

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lagen in the skin, with type III being 10%, and it acts as a scaffold in connective tissue.[5] Collagen is involved in all 3 phases of the wound healing cascade, both stimulating cellular migration and contributing to new tissue development. In the chronic wound, the deposition of *de novo* collagen is delayed or prevented by numerous factors, such as the elevated levels of enzymes that are involved in the proteolytic degradation of collagen. Basing on the observations on biological and structural properties of collagen, its use in the field of wound management is really attractive.[6]

There are several kinds of collagen dressings, which employ a variety of carriers/combining agents such as gels, pastes, polymers, Oxidized Regenerated Cellulose (ORC) and Ethylen Diamine Tetraacetic Acid (EDTA).

The collagen within these products are usually derived from bovin, porcine, equin or avian sources, which is purified in order to make it nonantigenic. The scaffold structure of the wound dressing serves as a guide for the movement of fibroblasts, macrophages and epithelial cells, and promotes their migration into the wound area.[7-8] In the past two decades, several regenerative products containing hyaluronan and collagen have been developed into the market. These products represent bioresorbable dressings for wound healing, and cell-compatible scaffolds for tissue engineering to enhance the efficacy of regenerative medicine.[9]

Despite collagen and HA are widely applied on wound dressing and scaffolds, some side effects should be considered. For example, hyaluronidase and collagenase degraded the scaffold to produce side products, which induced inflammation and affected wound healing process. The high degradation rate and deficient mechanical property of collagen and HA often fail to meet the requirement of specific application specific application.

For these reasons many attempts to "imitate" the natural extracellular matrix (ECM) have been recently done, and several scaffolds such as collagen–chondroitin sulfate (CS), Collagen–hyaluronic acid (HA), and gelatin–CS–HA have been produced. Despite these scaffolds demonstrated lower degradation rates and higher mechanical strength than collagen alone, their biocompatibility was not fully satisfactory.[10] Basing on these observations, we studied the effects of a new bioactive wound dressing consisting of HA plus heterologous collagen type I (Bionect Pad®, Fidia Farmaceutici S.p.A., Abano Terme - PD, Italy) applied on acute and chronic wounds of different aetiology. The aim of the study was to assess the safety and effectiveness of this new product in wound management, revisiting their role as alternative to acellular dermal matrices in selected and challenging cases. To our knowledge, this is the first report of Bionect Pad® application throughout the medical Literature.

MATERIALS AND METHODS

All patients included in the present study have cutaneous open wounds completely healed by only second intention; all of them were referred to our hospital from April 2018 to April 2019. All wounds were treated by using Bionect Pad® (BP) wound dressing from the date of admission to the date of complete re-epithelialization. The treatment protocol provides for dressing change every 4 days, and an outpatient follow-up visit was performed every 10 days in order to promptly identify any side-effects or delayed wound healing. If necessary, some cases were managed with combined treatments in order to obtain an adequate wound bed preparation before the application of BP. Patients who were treated only temporarily with BP before subsequent surgical reconstruction were excluded. Demographic data or data concerning wound aetiology, type of combined treatment and healing time were recorded.

RESULTS

In the last 12 months we have treated in our hospital a total of 30 patients with wounds of different aetiology by using matrices of BP. The average age of the patients was 60,2 years (range: 23-82 years). The wounds were mainly caused by venous ulcers, followed by trauma, surgical wound complications, pressure sores, burns, peristomal ulcerations and skin ulcerations after radiation therapy. In most patients, combined previuos treatments including negative pressure wound therapy, surgical debridement or other advanced wound dressings were necessary. The average healing time was 31 days (range: 21-76 days). No side-effects leading to treatment suspension were reported. The main features of the treated patients are summarized in Table 1.

CASE N. 2

A 69-years-old man was admitted to our hospital for a posttraumatic wound of the dorsum of the right foot with tendon exposure. After a first surgical debridement, the patient underwent to conservative treatment with negative pressure wound therapy for 3 weeks in order to obtain granulation tissue and partial tendon coverage. Then he was managed conservatively with dressings based on Bionect Pad for 60 days and complete wound healing was obtained (Figure 1).

CASE N. 3

A 43-years-old man reported a history of traumatic rupture of the Achille's tendon. He underwent to surgical

reconstruction of the injuried tendon and the postoperative period was complicated by a wound dehiscence with tendon exposure that was managed conservatively by using negative pressure wound therapy for 6 weeks. Later, once the wound bed was adequately covered by granulation tissue, Bionect Pad was used and a complete wound healing after 76 days was achieved (Figure 2).

CASE N. 5

A 56-years-old man was treated in our hospital for a cement spacer exposure after a periprosthetic joint infection of the left knee. He underwent to surgical removal of the cement spacer, wide bone debridement, placement of a new bone cement loaded with broad spectrum antibiotics and flap coverage by using a local rotation flap. Unfortunately the postoperative outcome was complicated by wound deischence with partial flap necrosis and spacer exposure. After a surgical debridement, a negative pressure wound therapy was applied until a complete coverage of the spacer was obtained. After 30 days, a matrix of BP was used and complete wound healing occurred after 3 weeks (Figure 3).

CASE N. 6

A 36-years-old man reported a history of paraplegia with multiple recurrent pressure sores of the ischium and sacrum. He was visited in outpatient for a further recurrence of the sacral pressure sore. He was previously subjected to several surgical reconstructions of the pressure sores by using local flaps, with consequent multiple surgical scars which precluded a new flap-based reconstruction. Therefore we opted for a conservative management with advanced wound dressings based on collagenase and silver containing hydrofiber which were continued until an adequate wound bed preparation was obtained; after 4 weeks of treatment, a matrix of BP was applied and complete healing of the ulcer occurred after 6 weeks (Figure 4, A-D).

CASE N. 8

A 68-years-old man was treated in our hospital for a Merkel Cell Carcinoma (MCC) of the posterior leg. He underwent to surgical removal of MCC and reconstruction with acellular dermal matrix and subsequent split thick-

Table 1. Main features of the treated patients.

Demographic data	Wound aetiology	Combined treatments	Healing time
Average age: 60,2 yrs (range: 23-82 yrs)	Venous ulcers (tot. 9)	Negative Pressure Wound Therapy (tot. 4)	Average time: 31 days (range: 21-76 days)
	Posttraumatic (tot. 6)	Other advanced wound dressings (tot. 15)	
	Surgical wound complications (tot. 4)	None (tot. 11)	
	Pressure sores (tot. 4)		
	Burns (tot. 4)		
	Peristomal ulceration (tot. 2)		
	Radiation therapy (tot. 1)		
	Tot. 30 patients	**Tot. 30 patients**	

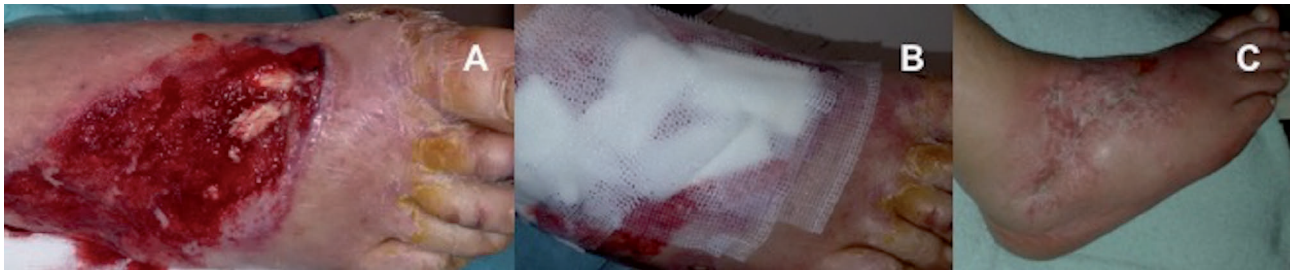

Figure 1. Postraumatic wound of the right foot with tendon exposure after surgical debridement and negative pressure wound therapy (A); Bionect Pad application on the wound bed (B), follow-up visit 45 days (C).

ness skin graft. Postoperative radiation therapy was then administered; after 1 month he developed skin ulcerations and breakdown that were managed conservatively by using BP. A complete wound healing was achieved 3 weeks later.

DISCUSSION

Wound healing is a complex process which involves a lot of synergistic interactions between several cell lines, cytokines, enzymes, and growth factors. Research on wound healing includes identification of those elements that accelerate healing process, materials that work as effective skin substitutes and signals responsible for triggering healing. Bioactive dressings are considered as those that play an active role in wound healing. Examples of bioactive materials that form part of these dressings are collagen, chitosan, hyaluronic acid and pectin.[11]

It is unrealistic to expect a single dressing could have all characteristics that would satisfy all generic needs for wound healing. Therefore, the main goal should be the creation of a versatile dressing which has the capability to positively affect most wound types. This can only be achieved through a multi-dimensional approach which utilizes bioactive additives for a targeted effect.[12]

HA has been widely used as wound dressing and several HA-based biomaterials and bioscaffolds are manufactured in different forms including hydrogels, tubes, sheets and meshes. HA biomaterials and bioscaffolds have a lot of pros, particularly their non-allergic and non-inflammatory nature unlike other materials (e.g. chitosan derivatives). Nevertheless, the resistance of injected HA and HA implants *in vivo* depends on their ability to resist degradation by hyaluronidases and reactive oxygen and nitrogen species (ROS/RNS), thus limiting their efficient usage. To overcome problems with HA degradation, the physicochemical properties of HA including the availability of reactive functional groups on HA have been exploited, thus facilitating chemical modifications on HA and making it a biocompatible material for use in tissue regeneration.[1-4]

Numerous factors which influence wound healing can impair the whole process. In the chronic wound, the deposition of *de novo* collagen is delayed; moreover, recruitment of fibroblasts is retarded and the expression of the collagen gene in fibroblasts is suppressed. Environmental factors also affect the collagen level in the chronic wound bed. Among these factors are 2 classes of enzymes, whose levels are known to be elevated in chronic wounds: the matrix metalloproteinases (MMPs) and elastase. MMPs are implicated in proteolytic degradation of native intact collagen and partially degraded fragments of collagens. The elevated ratio of MMPs to tissue inhibitors of MMPs leads to excessive extracellular matrix degradation. Elastase is also involved in the healing process due to its role in converting pro-MMPs (the natural precursor of MMPs) to active MMPs. Elastase activity is high in the chronic wound, thus heavily contributing to the MMP load in the chronic

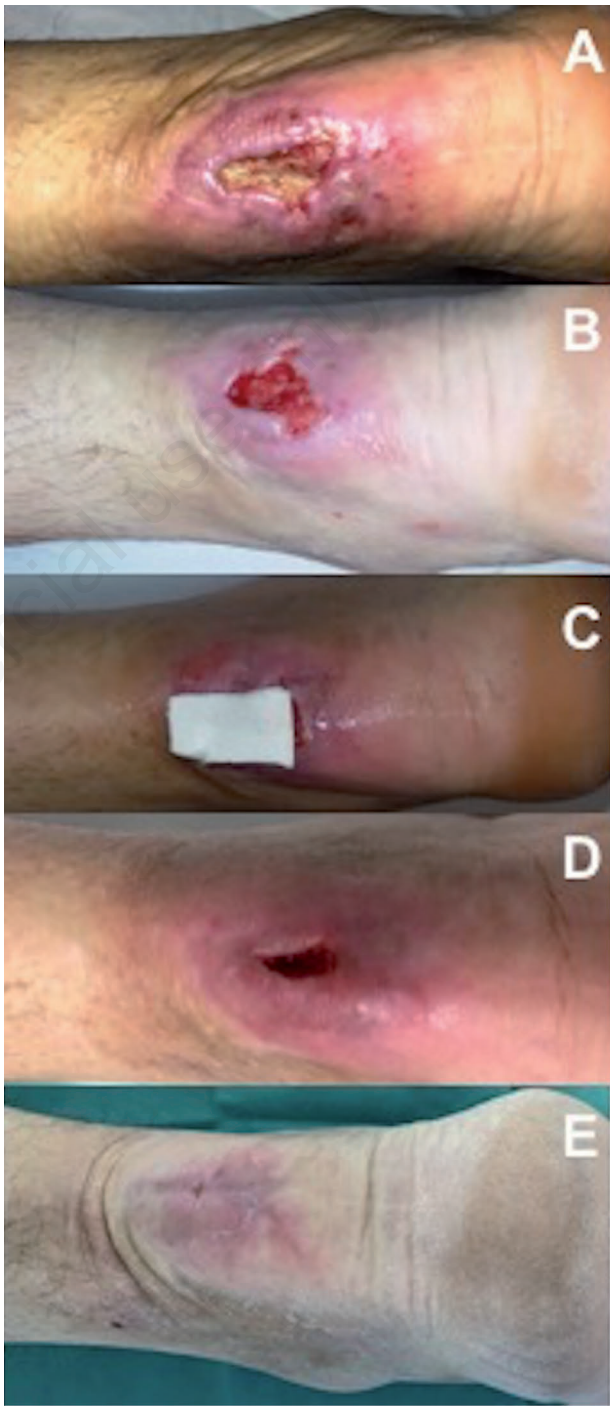

Figure 2. Wound dehiscence with Achille's tendon exposure (A); after adequate wound bed preparation a matrix of Bionect Pad was applied (B-C). Follow-up visit after 50 days (D) and complete wound healing was obtained after 76 days (E).

wound. In summary, the chronic wound is characterized by both decreased collagen deposition and increased collagen breakdown.[6] Therefore the use of collagen dressings in wound management may seem attractive due to the inhibition or deactivation of MMPs, increase fibroblast production and permeation, help for the uptake and bioavailability of fibronectin, preservation of leukocytes, macrophages, fibroblasts, and epithelial cells, and support in the maintenance of the chemical and thermostatic microenvironment of the wound.[5] Collagen dressings which are characterized by a low pH, can lower the pH of the wound fluid, thus decreasing the risk of secondary bacterial colonization Collagen has binding sites for fibroblasts and has a chemotactic effect on these cells. The pore size of the collagen foam is important for cell migration and for the formation of capillaries and scar tissue.[7,8]

The ideal biomaterial should have several features to promote tissue repair or regeneration within chronic wounds: i) attraction of cells that are capable of synthesizing new tissue to the wound site; ii) promotion of cell proliferation; iii) supply of a nonimmunogenic, resorbable scaffold for cellular migration and matrix deposition; iv) organization of new ECM deposition; v) modulation of proteolytic activity; vi) adsorbtion and neutralization of free radicals and/or excess metal ions. It is clear that collagen compounds meet many of these criteria.[13] Several forms of collagen can be used in the clinical practice such as sponges, injectables, films and membranes, dressings, and skin grafts. Collagen sponges are especially useful in wound healing because implanted sponges are infiltrated by amorphous connective tissue containing Glycosaminoglycans (GAGs), fibronectin, and new collagen, followed by various cells, primarily fibroblasts and macrophages. Depending on the degree of cross-linking, the collagen sponge is degraded by collagenases into peptide fragments and amino acids in 3–6 weeks, and the implant is then replaced by native type I collagen produced by fibroblasts.[14]

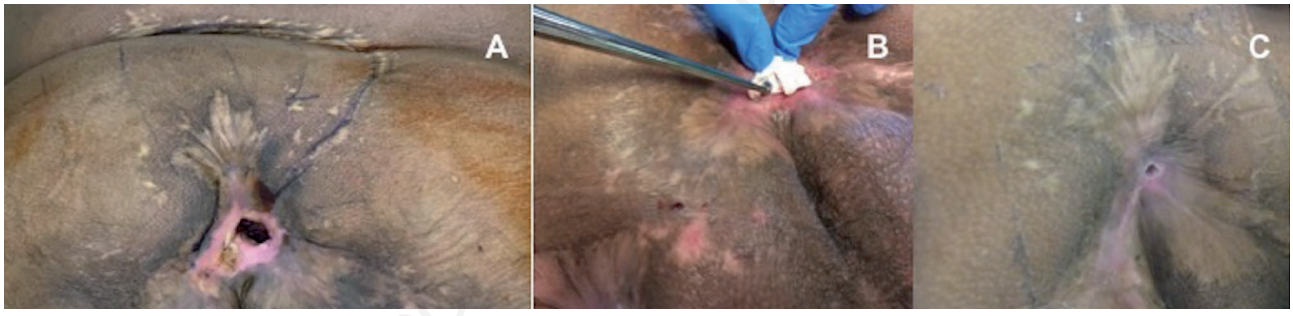

Figure 3. Preoperative picture of a patient with cement spacer exposure after a periprosthetic joint infection of the left knee (A). Postoperative wound dehiscence who underwent negative pressure wound therapy for 28 days (B); bioactive wound dressing application with complete resolution (C-D).

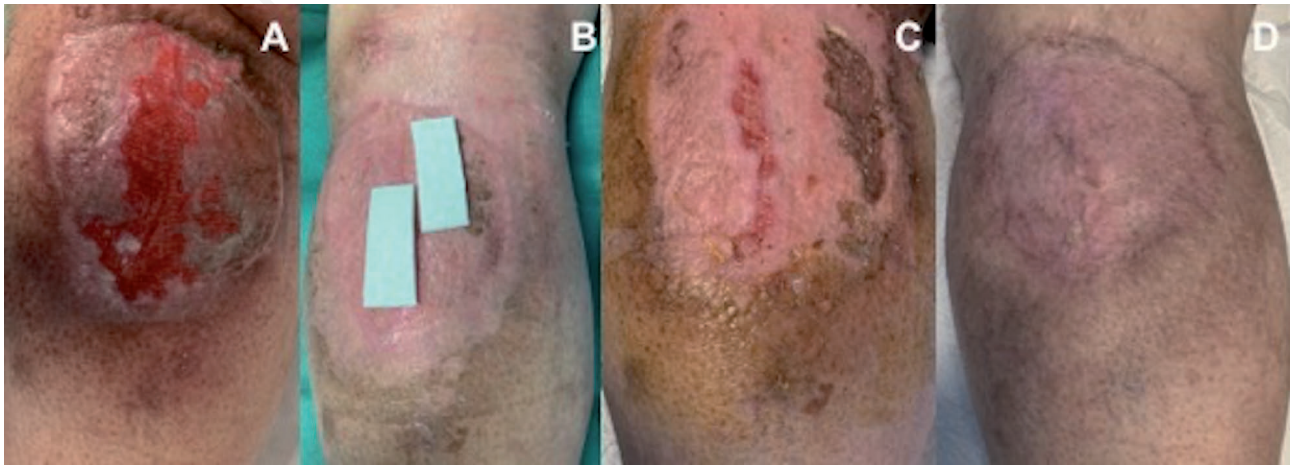

Figure 4. Recurrence of a sacral pressure sore in a paraplegic patient (A); complete wound healing after 6 weeks of treatment with Bionect Pad (B-C).

Since 2003, Kuroyanagi *et al.* (mentioned in Huang *et al.*)[9] conducted a series of experiments on a double-layered spongy matrix consisted of one layer of hyaluronan and the other layer contained collagen and its derived peptides. These two layers of the sponge covalently bonded to form a Culture Dermal Substitute (CDS) were then applied as a wound dressing, and it was observed in the animal model that autologous CDS can provide efficient healing. Two years later the same authors revealed in human patients that fibroblasts in CDS produced several bioactive factors, such as cell growth factors and extracellular matrix components that are important for wound healing, thus improving wound condition, enabling the wound site to adapt to later skin autologous transplantation and shortening time duration for full-thickness skin wound healing.[9]

Composite scaffolds have usually two or more biomaterials combined to improve either their mechanical properties or their functional efficiency or both. The mixing ratio and the degree of cross-linking of the selected polymers are really crucial in determing the biostability, mechanical strenght, and microstructure of composite scaffolds.

Some studies report that scaffolds composed of collagen, HA and CS have beneficial effects when used for skin, bone or cartilage regeneration. In 2012 Kondo *et al.* investigated the effects of a wound dressing composed of Hyaluronic Acid (HA) and Collagen (Col) sponge containing Epidermal Growth Factor (EGF) on various parameters of wound healing in vitro and in vivo and they observed that the combination of HA, Col and EGF promotes wound healing by stimulating fibroblast function.[15] Recently Drobnik et al. investigated whether a collagen tri-copolymer with the addition of HA and CS (Col + HA + CS) can enhance cultures of embryonic nerve cells and wound fibroblasts, thus determining the usefulness of this tri-copolymer for tissue engineering. This study found that cells seeded in tri-copolymer scaffolds demonstrated better metabolic activity than those in scaffolds composed of collagen alone. This reaction was believed to be due to hyaluronic acid modifying the structure of collagen, allowing the formation of interconnections between pores, which supports the migration of cells to internal pores, allows for better communication between cells and improves the nutrition of the seeded cells.[16]

Kirk *et al.* studied the mechanical and biocompatible characterization of a cross-linked collagen-hyaluronic acid wound dressing in 2013. Basing on the observation that non-cross-linked material are much more sensitive to protease degradation compared with carbodiimide EDC cross-linked material, they revealed that stabilization of reconstitued collegan-HA composites by using chemical and/or physical cross-links led to biomaterials with good biocompatibility, higher cellular differentiation potential, increased stability, without cytotoxic or genotoxic effects in the animal model. Furthermore they also demonstrated that the process to generate the EDC cross-linked collagen-HA sponge resulted in the homogenous deposition of the HA throughout the collagen fibers without adverse effects on the collagen structure or pore size, that are fundamental for cell binding, migration and proliferation. In addition, the cross-linking process did not adversely affect the biomechanical strength of the collagen scaffold.[17]

Mathews *et al.* in 2014 studied a biomimetic tripolymer scaffold consisting of chitosan, collagen type 1, and hyaluronic acid that supported the proliferation and differentiation of bone marrow-derived human mesenchymal stem cells (hMSCs) for bone tissue engineering.[18]

Matsiko *et al.* in 2012 revealed that the incorporation of HA in a collagen-based scaffold resulted in a significant stimulation of mesenchymal stem cells (MSCs) infiltration in the scaffold; moreover, these scaffolds showed significant acceleration of early stage gene expression of collagen type II as well as cartilage matrix production.[19]

Some authors also proposed to obtain new composite scaffolds with morphology and physical-chemical properties adequate for controlled drug delivery systems. Vulpe et al. in 2018 studied a cross-linked scaffold based on collagen, hyaluronan and sericin that demonstated to have a porous structure, strength and stability adequate for controlled drug delivery systems with potential use in skin tissue engineering.[20]

Despite studies focused on the single use of collagen or HA have been largely reported throughout the Literature, clinical investigations strictly targeted on bioactive composite wound dressings are still marginals.

Biomaterials are widely used in the field of reconstructive surgery and wound healing, due to their peculiar characteristics of safety, reliability and easy to use. Our long clinical experience with collagen-based Acellular Dermal Matrices (ADM)[21-24] poses some important considerations about their differences with bioactive wound dressings. First, collagen-based ADMs are really useful for neodermis regeneration and act as temporary wound coverage before skin grafting; nevertheless, they usually require at least two surgical steps and hospitalization. Conversely, collagen-based wound dressings could be easly managed in outpatient and may not require a surgical reconstruction with skin grafts. Second, bioactive wound dressings with collagen and HA exploit both the potential of collagen in assembling the scaffold for fibroblasts adhesion and growth, and the potential of HA in controlling tissue hydration, thus ensuring a moist wound bed that is fundamental for a correct reparative process. The combination of these two components leads to a synergical effect with a complete extracellular matrix restoration; furthermore, they produce a stable compound that may exerts a durable effect on the wound bed.

Third, ADMs are usually expensive tools and may be unavailable in some institution; on the contrary bioactive wound dressings may me potentially cost-saving due to their lower number of outpatient visits and dressing change, and an overall out-of-hospital wound management.

Nevertheless, our clinical experience suggests that ADMs still remain the mainstay of treatment in such cases with full-thickness defects and bone exposure as alternative to flap surgery. Indeed, bioactive wound dressings were usually used in our study in those lesions with a well vascularized wound bed and their potential for bone coverage was not yet investigated.

This study is a retrospective cohort study which has inherent selection bias. In addition, no comparison with a standard of care control group such as ADMs or other advanced wound dressings was performed. Further studies are needed to examine potential clinical benefits of this treatment option in large patient cohorts with a standard of care control group.

CONCLUSIONS

The results of the present study show that composed wound dressings could be useful both for acute and chronic lesions of different aetiology; sometimes a combined use with other advanced wound dressings or medical devices such as negative pressure wound therapy may be necessary in order to obtain a well vascularized wound bed.

The good biocompatibility, increased stability, ductility, and the overall biological properties of bioactive composite wound dressings, make them a reliable and useful alternative to other advanced wound-dressings or acellular matrices for regenerative medicine and wound healing. Nevertheless, more studies would be necessary in order to define the appropriate role of these bioactive wound dressing in the field of wound healing.

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