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Short Commentary OMICS International

A Short Commentary about Efficacy of an Flowable Matrix in the Treatment of Diabetic Foot Ulcers

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Abstract

The authors aimed to evaluate the efficacy of an advanced wound matrix (Integra Flowable Wound Matrix, Integra Life Science Corp, Plainsboro, NJ, USA) for treating wounds with irregular geometries versus a wet dressing in sixty patients with diabetic foot ulcers (Grades 3 Wagner ulcer). A randomized clinical trial was conducted in the General Surgery Unit and Geriatric of the Second University of Naples, Italy, in the last 12 months. Forty-seven cases of diabetic foot ulcers were equally and randomly divided into two groups: in a group treated with a wet dressing and expected closure by secondary intention; in another group the lesions were filled with Integra Flowable Wound Matrix and surgical wound edges were either approximated with stitches. The complete healing rate valued at 6 weeks, in the whole study population was 69.56% (Integra Flowable Wound Matrix group, 86.95%, control group, 52.17%; P=0.001). Amputation and re-hospitalization rates were higher in the control group compared to Integra Flowable Wound Matrix group. Therefore, the difference was statistically significant.

This new porous matrix, allows a closure for the first intention of the lesion by reducing healing time and the demolition surgery. An advanced wound matrix is not associated with side effects, is well tolerated. Ease of use, absence of adverse effects, and a minimal invasive approach by primary intention closure of the lesion, make it appropriate in the management diabetic foot ulcers.

Keywords: Diabetic foot ulcers; Tunneling lesions; Biomaterial; Flowable matrix

Short Commentary

Patients with diabetes can develop many different foot complications. Even ordinary injures can get worse and lead to serious complications. Without early and optimal intervention, the wound can rapidly deteriorate, leading to amputation of the affected limb. A diabetic foot ulcer is a critical event in the life of a person with diabetes and is one of the complications of diabetes that can cause life threatening. Diabetic foot ulcers have a major economic impact as well; data have shown diabetic foot ulcers (DFUs) are a major cause of hospitalization for patients with diabetes.

The healing of a skin lesion requires an integration of the complex biological and molecular events in the three phases of wound healing are known as inflammation, proliferation and tissue remodeling. DFUs represent the overthrow of healing processes of non-healing cutaneous inflammation and do not follow an orderly and reliable progression of wound healing. Impaired growth factor (GF) production, vascular neogenesis, macrophage function, collagen accumulation, fibroblast proliferation, and production of extracellular matrix (ECM) components and their remodeling by matrix metalloproteinases are just some of the numerous factors take part in lesion healing deficiencies in these patients [1].

Diseases of the diabetic foot most often happen when there is nerve damage also called neuropathy. This can cause loss of sensation in the foot, so if there is a foot injury the patient may not notice it. Poor blood flow or skin changes or changes in the shape of feet or toes may also cause problems. Neglecting ulcers can result in infections, which in turn can lead to loss of a limb. Even after healing, care must be taken to protect this area and prevent the ulcer from returning.

Therefore, the importance of DFUs treatment is recognized by increasing rates of revascularization, use of compression therapy, removable offloading device, targeted antibiotic therapy and selective debridement technique.

New treatments for diabetic foot ulcers continue to be introduced, but few are subjected to controlled trials [2-6]; consequently, there is a need for new effective therapies to reduce the amputation rates, the major amputations and the healing times preserving the biomechanics of the foot.

Bioengineered skin substitutes have emerged as a new and alternative therapeutic option. Bioengineered skin substitutes were originally used to reduce size of donor site in extensively large burn wounds and have provided better quality of healing in recipient site by producing extracellular matrix. They reduced contraction and scar formation with improvement of extracellular matrix remodeling and elastin regeneration [7,8]. In trials in burned patients was demonstrated significant skin regeneration using the same scaffold [9,10]; a limited numbers of randomized controlled trials that study skin substitutes have been published, but the evidence of studies is encouraging. Among skin substitutes, the dermal substitutes can be manufactured in high quantity with low price, easy to keep and to use.

In patients with acute burns and in patients with chronic skin lesions, following severe injury in skin and peripheral nerves, a dermal substitute highly porous collagen scaffold has induced regeneration displacing the skin autografts in the treatment of skin lesions [11-19].

After severe trauma, in the adult mammal occurs a wound constriction and scar formation. An appropriate control of wound contraction can induce the regeneration of wounded skin [20]. More specifically it has been observed that the regeneration of the highest quality is induced under wound conditions the contraction was inhibited [21].

Collagen scaffolds must prevent the scarring response and therefore the contracture; the scar by nature is populated by myofibroblasts (MFB) and contracted, the matrix serves to prevent this and regenerate a tissue as similar as possible to the original tissue. The peculiar skill to regeneration of collagen-based scaffolds particularly open structure and very large, was related with a decrease in wound contraction. However, collagen-based scaffolds do not all have the same regenerative depending on detailed structural features [12,21]. The level of activity depends on often subtle but distinct structural differences: pore structure, degradation rate and surface chemistry.

The average pore diameter required should remain within a range 20-125μm [12,21]. A pore size of less than 20μm does not allow the cells to come in; at the high end of the pore size range the cells do not come into direct contact with the scaffold surface, but are organized in cell-cell clusters [22].

Wound contraction is further inhibited and dermis regeneration induced when the scaffold degradation rate is about 2-3 weeks in skin. MFB are known to migrate inside the scaffold and adhere on the scaffold surface during this period [23]; in so doing, these cells lose cell-cell contacts that appear to be required for development of large contractile forces. They differed, however, in their cross-link density which is known to control the degradation half-life of the two scaffolds to different levels [22]. In skin lesions treated with a scaffold that degradation rate is about 2-3 weeks a MFB reductions was viewed [13].

Disorganization with loss of alignment in the same plane of MFB, drastic reduction in MFB density was relieved in skin lesion treated with Derma Regeneration Template scaffolds [21]. A change in the phenotype of MFB was directly observed as, dispersion of MFB assemblies and when Derma Regeneration Template (DRT). This change is explained most simply by inhibition of MFB-MFB binding and facilitation instead of MFB-DRT binding, by MFB integrins (α1 β1 and α2 β1) and ligands on the DRT scaffold.

The results of an article show that wound nerves, treated with the collagen scaffold, contained a low concentration of TGFb1, TGFb2 (transforming growth factor), ASMA (alpha smooth muscle actin) and high concentration of TGFb3 [21]. The aSMA is the major marker for contractile MFB, while TGF-b isoforms are either required for or related to MFB differentiation [24].

The high rate of TGF-b and the next excessive ECM deposition has a role in etiology of hypertrophic scarring after deep burn. TGF-b isoforms play distinct roles in wound healing with TGF-b1 and TGF-b2 having predominantly pro-scarring activity and TGF-b3 having anti-scarring effects.

After the injury, the vasoactive amines increase in permeability vascular and accumulation of factors coagulation with the formation of fibrin and release of PDGF and TGF-b aside of the platelets and macrophages activated that call even more neutrophils.

TGF-b has a role in the three phases of lesion healing after injury. In the inflammation phase recalls on the site of lesion histiocytes and neutrophil granulocytes responsible for removing debris cell and release of growth factors; in the proliferation phase promotes angiogenesis, fibroblast proliferation and differentiation into myofibroblasts, and increase the expression ECM components modulating the activity of metalloproteinases and their inhibitors. TGF-b, in maturation phase, induces alignment collagen fibers along tension lines [25]. The cross-linking of collagen and the reorganization keep on for months and represents the phase of remodeling. It follows the contraction of the wound that is facilitated by fibroblasts containing actin.

The observed reduction in MFB density in DRT-treated wounds can be explained most simply by the observed down-regulation in concentration level of TGFb1, the key cytokine required for MFB differentiation [26]. The origin of the observed down-regulation in TGFb1 concentration in the presence of DRT is not clearly understood at present; it could hypothetically result from the great affinity with which TGFb1 has been shown to bind non specifically on the DRT surface and the resulting likelihood of reduction in activity of the bound (relative to the free) cytokine [27]. In another hypothesis, the binding of platelets with DRT would lead to reduced platelet aggregation with reduction in TGFb1 production [28].

The use of sheet biomaterials, providing a scaffold for migration of cell and secretion of vascular growth factors suitable for promoting healing of flat skin lesions [29-32], allows a rapid natural healing of the lesion. It still allows, decreasing major amputations, reducing the risk of surgery and healing time.

The difficulty of use of sheet biomaterials, in cavities and tunnel injuries produced injectable matrices suitable for gel or sliding paste. Integra Flowable Wound Matrix (FWM) consists of a lyophilized product derived from Integra Dermal Regeneration Template, a dermal substitute in sheet form [33]. The FWM, consisting of cross-linked type I collagen, in presence of glycosaminoglycans represented by the chondroitin-6-sulfate, provides resorbable three-dimensional scaffold with a high microporosity which allows a migration of cells in the matrix and its remodeling.

The design and the chemico-physical characteristics of FWM make it suitable for treating lesions of irregular form more easily and with higher success chance, respect the conventional dermal substitutes. The matrix is supplied with a kit containing a syringe of dry collagen particles (3 ml), a luer lock connector and an empty syringe for saline solution. After mixing dry granular collagen with saline solution (3 ml), FWM is ready to be introduced by a flexible injector allows full filling of cavity. It is crucial that, otherwise colonization and vascularization may be inhibited, biomaterials should conform to cavity lesions. A preliminary report, showed excellent results, in terms of healing and side effects, with regard to FWM treatment of post-surgical, post-traumatic and neuropathic ulcers (due to diabetes, spina bifida and congenital neuropathy) [34].

A trial clinic randomized evaluated, in 46 patients with DFUs (Grades 3 Wagner ulcer), the efficacy of FWM compared to wet dressing, for treating tunneling wounds. The patients, admitted to General Surgery Unit and Geriatric of the Second University of Naples, were subjected an adequate preparation of the wound bed by surgical curettage and targeted antibiotic treatment.

Forty-seven cases of diabetic foot ulcers were equally and randomly divided into two groups: in a group treated with a wet dressing and expected closure by secondary intention; in another group the lesions were filled with FWM and surgical wound edges were either approximated with stitches. A significantly elevated rate (86.95%) of

patients in the FWM group, compared to the control group (52.17%), achieved complete healing of the lesion in 6 weeks.

The healing time to was significantly shorter (29.73±9.27 days) in the first group compared to the control the control group.

Safety of the use of biomaterials allowed a low rate compared with the wet dressing, statistically significant, of major amputation and re-hospitalization with more distal amputations in the lower limbs. The advanced wound matrix was well tolerated and in patients (13.04%) with graft failure had no clinical and/or laboratory inflammatory signs was observed [35].

The aim of treatment of chronic skin wounds is to achieve a natural closure of the defects. The main role of traditional surgery, so far, has been represented by the removal of infected tissue, necrotic, until healthy tissue to induce granulation tissue and healing by second intention. The use of biomaterial allows us to reduce healing times by allowing the injury to close the lesion with the primary intention; shorter healing times can be explained as the margins are approximated by points.

Skin substitutes should form a scaffold that guides the differentiation and proliferation of the cells involved in skin healing of lesions [36,37]. The dermal substitutes induce the influx of endogenous fibroblasts, histiocytes, and neutrophils into the wound bed. These cells are responsible for secretion a cytokines and growth factors that induce angiogenesis, extracellular matrix deposition. Within the scaffold, fibroblasts migrate, proliferate and then produce a native collagen. Following, endothelial cells form a vascular network with in neo dermis [38].

However, applying of dermal substitutes conventional sheet-shaped, to irregular shaped wound beds and in particular tunneling wounds have shown significant problems. The treatment tunneled or cavity lesions with sheet-shaped materials are not possible for due to the impossibility of the material to adhere to wound walls [39,40].

FWM is mixed with saline solution and the obtained fluid can be applied in deep lesions and/or irregular geometry. The collagen, after hydration, allows a more intimate contact of the matrix with the wound bed, and a more complete coverage of deep lesions, thus providing a support for cellular invasion and capillary growth. The advanced wound matrix can expand after application, filling the dead space inside the lesion and absorbing tissue fluids, and may be able to stop inflammation because it does not attract platelets and leukocytes, shifting the host response towards regeneration. The advanced wound matrix eliminates inflammation and related consequences [41].

There are multiple experiences of the treatment of DFUs with Integra Dermal Regeneration Template (IDRT): the results of a study showed a reduction the time of wound healing, an increased the rate of wound healing, improved quality of life and less adverse events [42]. Another study that used Integra bilayer wound matrix on diabetic foot ulcers proved to be easy to use, safe and effective [43].

There is not much experience in the literature in the treatment of DFUs with FWN if not a preliminary report already mentioned [34].

Some authors have verified the efficacy and absence of adverse events for the use of a FWN in the projection of the nipple with after a breast reconstruction [44]. Other studies demonstrated improvements functional scores and scar quality with the advantage of minimal invasive injection percutaneous FWM in patients with hand burns [45].

Conclusion

Additional research will shed more light on the promising advantages of this material. Our experience showed the advanced wound matrix can be easily applied, without the need for donor sites or additional risks for the patient. An advanced wound matrix is not associated with side effects, is well tolerated. The absence of unfavorable events, ease of use of the product, and a poorly invasive surgery, can play an important role in care of DFUs. The use of FWM allows rapid healing of the lesion and in particular it can allow us to close the primary intention of the lesion reducing the healing time and surgery demolition.

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