TISSUE ENGINEERING - COLLAGEN SPONGE DRESSING FOR CHRONIC WOUNDS

VLAD DENIS CONSTANTIN^{1,2}, ALEXANDRU CARĂP^{1,2}, SIMONA BOBIC^{1,2}, VLAD BUDU^{1,2}, MĂDĂLINA ALBU KAYA⁵, ȘTEFANIA MARIN^{3,5}, MARIA MINODORA MARIN^{4,5}, BOGDAN SOCEA^{1,2}

¹"Carol Davila" University of Medicine and Pharmacy, Surgery Department, Bucharest, Romania, Corresponding author: Bogdan Socea, constantindenis@yahoo.com

²"Sfântul Pantelimon" Emergency Clinical Hospital, Surgery Department, Bucharest, Romania

³University Politehnica of Bucharest, Center of Surface Science and Nanotechnology, Splaiul Independentei 313, Romania

⁴University Politehnica of Bucharest, Faculty of Applied Chemistry and Materials Science;

⁵INCDP - Division: Leather and Footwear Research Institute, Bucharest 031215, Romania, madalina.albu@icpi.ro

The high number of available wound dressing materials as well as the scientific reports about the topic indicate that the problem of an ideal wound dressing is to be solved. For the last half of century many scientific reports about collagen as wound covering have been published, the benefits of collagen application as a wound dressing being proved. The aim of the present study is to demonstrate the efficiency of the collagen sponge on healing full thickness skin wounds. The study population was divided into two groups: control and experimental. In the control group, the wounds were treated conventionally, using gauze swabs, in the experimental group such wounds being covered with collagen sponge, the results being compared. The wounds from the control group healed in 50 days, covering the wounds with collagen sponge in the case-group shortening the healing process to 27 days. Not only the healing time was shortened but also the quality of the wound repair by dressing the wounds with collagen sponge was enhanced.

Keywords: chronic wounds, collagen sponge, dressing, biomaterial.

INTRODUCTION

There are a number of different collagen dressings commercially available, which employ a variety of carriers/combining agents such as gels, pastes, polymers, oxidized regenerated cellulose (ORC) and ethylene diamine tetraacetic acid (EDTA).

The collagen contained in these products may be derived from bovine, porcine, equine, or avian sources, in a purified form in order to render it nonantigenic. The collagen dressings vary in concentration and type of collagen contained, some of them comprising type I (native) collagen, whereas, other collagen dressings containing denatured collagen. Apart from collagen, these dressings may, also, contain ingredients, such as alginates and cellulose derivatives that can enhance absorbency, flexibility, and comfort, and help maintain a moist wound environment, many collagen dressings containing an antimicrobial agent to control pathogens within the wound. Collagen dressings have a variety of pore sizes and surface areas, as well. All of these attributes are meant to improve the wound management process. Collagen dressings typically require a secondary dressing, such as cotton gauze swabs, as used in the present study.

Recent research has shown that collagen-based dressings produce a significant increase in the fibroblast production, have a hydrophilic property that facilitates fibroblast permeation, enhance the deposition of oriented, organized collagen fibers by attracting fibroblasts and causing a directed migration of cells, promote the uptake and bioavailability of fibronectin, help preserve leukocytes, macrophages, fibroblasts, and epithelial cells, and maintain the chemical and thermostatic microenvironment of the wound.

Collagen dressings act by inhibiting or deactivating excess of matrix metalloproteinases (MMPs), the excess of MMPs determining wound chronicity.

In chronic wounds, which do not heal within six weeks, there is a hyperactivity of the healing process, which is out of phase, non-progressive, and with a persistent, uncoordinated, mixed acute and chronic inflammatory response, the most common cause of the chronicity being infection, from increasing microbial colonization, inevitable in open wounds healing by secondary intention, to increasing contamination and clinically overt infection.

The use of collagen in wound management has not yet been unanimously accepted for widespread clinical use, as the studies on the subject only offer evidence for collagen as a dressing matrix and not as an active agent. Thus, the use of collagen-based products as wound dressings on a large scale still needs to be proved, even though there are many collagen biomaterials available on the market and the use of collagen materials as a scaffold in hernia and abdominal wound repair seems to be clinically and cost-effective.

MATERIAL AND METHOD

The study was conducted in the General Surgery Department "Sfântul Pantelimon" Emergency Hospital from Bucharest, Romania, between January 2015 to April 2017, including 10 patients with chronic postoperative wounds: 4 men and 6 women; age between 18 and 60 years with mean age 39 years and average body mass index 27.6kg/m². The exclusion criteria were diabetes, smoking, and vascular diseases. All the patients had undergone surgical intervention with delayed healing of the postoperative wound. In all the patients, tubular drains were positioned. The suture was performed using Sentasorb or Monofilament. At the end of the procedure, in the operating room, a dressing with sterile cotton gauze and patch was put on the postoperative wound.

From the 10 patients included in the study, for whom the wound-healing process was delayed, due to local infection or seroma, for 5 of the randomly selected cases collagen sponge was applied on the affected wound, for the other 5 cases cotton gauze being used as dressing.

A sponge shaped device, constituted exclusively by lyophilized type I native heterologous equine collagen which transforms in a soft gel that allows contact with the entire wound bed, was used in the present study. The collagen sponge was cut to fit the size of the wound, being applied directly to the wound bed, covering the entire wound, without overlapping the edges of the wound. A secondary cotton dressing was used to cover the collagen sponge. Depending on the amount of exudate, was reapplied daily or at every 48 hours, being absorbed into the wound bed over time.

At each dressing change, surveys with a 10-point scale evaluation were used to assess nontraumatic removal level, ease of application, adhesion, and strength of the 2 treatment methods. All wounds were followed through to full closure.

The number of days necessary for wound healing, the number of infection cases, and wound-related complications, the wound location, the age of wound, co-morbidities and previous treatments were the variables analyzed by the present study. Costs of the medications were also taken into account. At the time of the wound closure patients answered a questionnaire with multiple-choice questions to assess comfort, pain at dressing change, pruritus, adhesion and strength of the dressing, and number of dressing changes.

The study was approved by the ethics committee of our institution and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

Descriptive statistics of quality measures of the 2 dressings are summarized in table 1.

Table 1. Descriptive statistics of Quality Measures of the study paired samples. N represents the sample size of each group; all but the last variable is evaluated by the physician in a 10-point scale

Variable	N	Minimum	Maximum	Mean
Nontraumatic removal level				
Collagen sponge	5	4	9	6,6
Traditional dressing	5	1	5	3
Ease of application (higher-easier)				
Collagen sponge	5	4	9	6,2
Traditional dressing	5	1	5	2,8
Adhesion and strength (higher-better)				
Collagen sponge	5	4	9	6,8
Traditional dressing	5	1	5	2,6
Number of days for wound healing				
Collagen sponge	5	5	7	5,3
Traditional dressing	5	8	16	12

The results revealed significant differences between the two treatment methods for quality measures, the dressing change being about 3 to 4 points less traumatic on average and about 4 points easier on average with collagen sponge than with the control traditional dressing. The collagen sponge remained adherent to the wound in each of the patients in the 24-48 hours, the adhesion and strength being about 4 to 5 points better on average than with traditional dressing.

The number of days for wound healing exhibits a different distribution depending on the type of dressing used, as shown in table I, collagen sponge eliciting a statistically significant median acceleration (about 5–6 days less) for a complete healing compared with the control medication (figure 1, 2).

Figure 1. Postoperative wound seroma (A) with macroscopic aspect after collagen-sponge dressing (B)

Figure 2. Post-surgical excision of inguinal phlegmona wound- evolution under collagen-sponge dressing: day 1 (A), day 2 (B), day 3 (C), day 5 (D)

Statistical analysis revealed no significant differences between the risk of infection and wound-related complications between the 2 treatment methods, with 1 patient from the case-group and 2 subjects from the control-group presenting fever or wound-related complications (dehiscence).

The unitary cost of collagen-sponge dressing is 5 Euros, whereas the unitary cost of a traditional dressing is 30 cents. Collagen-sponge needs to be replaced daily or every 48 hours, while the traditional dressing twice a day or daily. In the present study, all the patients needed at least 3 replacements of collagen-sponge dressings, the total median expenditure with this medication being 15 Euros. Taking into account the time for a complete recovery and the number of required changes of the traditional dressing, a higher variability of costs with this medication was observed (table 2).

Table 2. Statistical description of the cost of a complete treatment with the traditional dressing (in Euros)

Cost	N	Minimum	Maximum	Median
Traditional dressing	5	5,4	11	8,36

A statistically significant median higher cost with Aquacel Surgical (about 6 euros more expensive for a complete medication treatment) compared with the control treatment cost of medication. We analyzed the data gathered from the questionnaires completed by the patients. All patients from the control group reported that the dressing change was painful (maximum scored), one patient from the case-group scoring the pain with the maximum value. All the patients reported more comfort during dressing application, a longer duration, and total atraumaticity during the dressing change with collagen sponge.

DISCUSSION

Adequate dressing material must be used, in accordance with the type of wound. Choosing the best option of wound dressing is determined by its properties, such as the capacity to provide or maintain moist environment, to enhance epidermal migration, to promote angiogenesis and connective tissue synthesis, to allow gas exchange between wounded tissue and environment, its ability to maintain appropriate tissue temperature to improve the blood flow to the wound bed, to provide protection against bacterial infection. The ideal dressing should be non-adherent to the wound and easy to remove after healing, providing debridement and enhancing leucocytes migration. Also, the wound dressing must be sterile, non-toxic and non-allergic.

Skin represents the ideal cover for wounds, a whole range of autologous skin graft techniques being available, from splitthickness skin grafts to complex pedicle or free microvascular myocutaneous flaps, the results being limited in the case of widespread skin loss. Nevertheless, the grafted wounds are at risk of failure or infection of both donor and recipient sites, with considerable subsequent morbidity. Several techniques have been designed to extend the area of split-thickness grafts, such as meshing, or to make harvest simpler and accessible, as in pinch grafting, but they still inflict an injury to healthy, intact skin (Horch, 2005).

Dermal allografts are still used, but they are progressively replaced by new tissue engineering technology, starting with the development of monolayer culture of keratinocytes, up to the use of collagen, hyaluronic acid or synthetic polymers as carriers of live, human-derived fibroblasts and keratinocytes (Horch, 2000)

Even freeze-dried cellular dressings with a carrier matrix have been shown to be effective in healing wounds of diverse origins. Lost functional cells are, thus, replaced by artificial skin substitutes that can control the dysfunctional wound healing process compromised (Cavorsi, 2006).

While it is appreciated that the gold standard of complete healing has to be replaced by surrogates of healing rates using, for example, computerised planimetry, there is often too much emphasis on poor clinical assessments of presence of infection or inflammation, pain, handling of exudate, odour, numbers of dressing changes and dressing acceptability or tolerance, and inadequate ‘add-on’ attempts at cost-effectiveness (Feng, 1999; Fu, 2005; Gault, 1999).

The recently developed wound dressings are produced from biomaterials, derived generally from natural tissues or artificial sources such as collagen, hyaluronic acid, chitosan, alginate and elastin, which play an important role in healing process, their biocompatibility, biodegradability and non-toxic nature being demonstrated, sometimes incorporating growth factors and antimicrobials to enhance wound healing process (Barlett, 1981; Doillon, 1986; Ishihara, 2002).

Collagen, a major structural protein has been discussed by many researchers for their active role in natural healing process. Collagen initiates fibroblast formation and accelerates endothelial migration upon contact with wound tissue (Rao, 1995; Mian, 1992).

There have been several sources of collagen for use as a dermal matrix (table 3).

Table 3. Currently available acellular collagen and dermal matrix products for wound care

Permacol ®	Porcine dermis	Tissue Science Laboratories
Integra ®	Bovine tendon/synthetic polysiloxane	Integra Lifesciences
Fibracol®	Collagen/alginate	Systagenix
Oasis®	Porcine small intestine submucosa	Cook Biotech
Biostep ®	Porcine collagen/alginate/CMC+/-Ag	Smith and Nephew
Catrix ®	Bovine cartilage (powder)	Lescarden
Matriderm®	Collagen/elastin	Suwelak
Decutastar®	Equine collagen	ADL
Septocoll E®	Collagen fleece/gentamicin	Biomet
AlloDerm®	Human cadaver de-epithelialised skin	LifeCell Corp
GraftJacket®	Human cadaver dermal matrix	Wright Medical Technology

The dermal skin substitute Integra® (Integra Life Sciences) is a bi-layer bovine collagen and polysiloxane dressing, used, mainly, for burn wounds. AlloDerm® (Life CellCorp), an acellular dermal matrix derived from cadaveric skin has also been widely used for burn management.

Adequate trials studying the use of collagen as dermal matrix, and other similar dressings, in different wound types other than burns are also awaited. The high costs limits introduction into wide clinical practice, extensive evidence being needed for their application. The application of biomaterials as skin substitutes vary from simple direct application as cell monolayers to polymer, or animal-derived collagen scaffolds.

From the results of our study, it was confirmed that collagen-sponge dressing represents a more comfortable method, easier to manage for the patient, durable, waterproof, and nontraumatic at dressing change, the use of collagen-sponge biomaterials being recommend in all the surgery procedures where the risk of wound dehiscence and maceration is high. There is a plethora of case reports and small patient series, which are supportive for the wide application of the collagen-based biomaterials, but these have a high risk of publication bias.

The limits of the present study are determined by the difficulty with the clinical studies and attempts at randomised controlled trials, being underpowered, with randomisation which is poor or not defined, comparing the dressing with an ineffective traditional therapy such as cotton gauze swabs, evaluations being unblinded and subjective, and therefore biased, high dropout rates often occurring so that assessment even up to 12 weeks represents a challenge for the researcher.

CONCLUSION

Collagen gives the skin its tensile strength contributing to the formation of the natural tissue matrix. Collagen sponge, a biodegradable material, plays an active part in normal physiological wound healing and new tissue formation, representing an attractive choice from a tissue biocompatibility and a toxicological point of view. Collagen sponge was proved to be comfortable and easier to manage for the patient, durable, waterproof, and nontraumatic at dressing change, making it the treatment of choice for the patients with high risk of wound complications. The high costs limits the introduction of collagen-based dressings into wide clinical practice, extensive evidence being needed in order to support their cost-effectiveness. There is no superior product that heals chronic wounds that fail to achieve complete healing, developing a dressing material that addresses the major interfering factors of normal healing process representing the major step in tissue engineering that will help patients and wound care practitioners largely.

REFERENCES

- Barlett, R.H. (1981), "Skin substitutes", *Journal of Trauma*, 21, S731, <https://doi.org/10.1097/00005373-198108001-00041>.
- Cavorsi, J. *et al.* (2006), "Best practice algorithms for the use of a bilayered living cell therapy (Apligraf) in the treatment of lower extremity ulcers", *Wound Repair and Regeneration*, 14, 102–9, <https://doi.org/10.1111/j.1743-6109.2006.00098.x>.
- Doillon, C.J. and Silver, F.H. (1986), "Collagen-based wound dressing: Effect of hyaluronic acid and fibronectin on wound healing", *Biomaterials*, 7, 3-8, [https://doi.org/10.1016/0142-9612\(86\)90080-3](https://doi.org/10.1016/0142-9612(86)90080-3).
- Feng, X. *et al.* (1999), "Fibrin and collagen differentially regulate human dermal microvascular endothelial cell integrins: stabilisation of α v β 3 mRNA Wuk by fibrin", *The Journal of Investigative Dermatology*, 113, 913–19, <https://doi.org/10.1046/j.1523-1747.1999.00786.x>.
- Fu, X. *et al.* (2005), "Engineered growth factors and cutaneous wound healing: Success and possible questions in the past 10 years", *Wound Repair And Regeneration*, 13, 122–30, <https://doi.org/10.1111/j.1067-1927.2005.130202.x>.
- Gault, S. (1999), "Scars and contractures", *Surgery*, 17, 73–5.
- Gelfand, J.M. *et al.* (2002), "Surrogate endpoints for the treatment of venous leg ulcers", *The Journal of Investigative Dermatology*, 119, 1420–5, <https://doi.org/10.1046/j.1523-1747.2002.19629.x>.
- Horch, R.E. *et al.* (2000), "Cultured human keratinocytes on type I collagen membranes to reconstitute the epidermis", *Tissue Engineering*, 6(1), 53–67, <https://doi.org/10.1089/107632700320892>.
- Horch, R.E. *et al.* (2005), "Tissue engineering of cultured skin substitutes", *Journal of Cellular and Molecular Medicine*, 9, 592–608, <https://doi.org/10.1111/j.1582-4934.2005.tb00491.x>.
- Ishihara, M. *et al.* (2002), "Photo crosslinkable chitosan as a dressing for wound occlusion and accelerator in healing process", *Biomaterials*, 23, 833–40, [https://doi.org/10.1016/S0142-9612\(01\)00189-2](https://doi.org/10.1016/S0142-9612(01)00189-2).
- Mian, M. *et al.* (1992), "Collagen as a pharmacological approach in wound healing", *International journal of tissue reactions*, 14, 1-9.
- Rao, K.P. (1995), "Recent developments of collagen based materials for medical applications and drug delivery", *Journal of Biomaterials Science, Polymer Edition*, 7, 623-45.