



Case Report

Use of Fish Skin in the Treatment of Chronic Lower Extremity Wounds: A Case Series Report

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Citation: Outos M, Nussbaumer P (2022) Diffuse Use of Fish Skin in the Treatment of Chronic Lower Extremity Wounds: A Case Series Report. J Surg 7: 1468 DOI: 10.29011/2575-9760.001468

Received Date: 25 January, 2022; Accepted Date: 18 February, 2022; Published Date: 22 February, 2022

Abstract

Background: The treatment and healing of chronic wounds represents an ongoing challenge in surgery and can be a long-term affair causing significant financial burden for health-care systems with the current therapy options. These include many different types of wound dressing, the use of negative pressure wound therapy (NPWT), autolog skin grafts and complicated flap coverings with the associated intra- and postoperative risks and requirements. Fish skin from cod, which is very similar to human skin, offers a new therapy option. We present our first experiences with fish skin in the treatment of chronic wounds. **Material and Method:** This is a series of cases of patients with chronic wounds of the lower extremities, where traditional methods have failed. In our cases, the application of fish skin resulted in complete healing of the wounds. **Conclusion:** Our first clinical experiences show, that the use of fish skin on chronic wounds has clearly therapeutical potential as a treatment alternative. The clinical effectiveness and cost-effectiveness of this therapy option have been proven in numerous clinical

studies. A re-operation is not necessary, the method is safe and no side effects are described.

Keywords: Chronic wounds; Fish skin grafts

Introduction

Wound healing of the lower extremities can be complicated due to accompanying comorbidities, contaminated environment, patient compliance and complex trauma mechanisms. It has been proven that treatment of chronic wounds of lower extremities, in addition to being highly complex, imposes enormous costs on the healthcare system. The application of tissue-based products is increasingly used in therapeutic regimens in wound care management. These products are intended to serve as scaffolds for cellular migration and proliferation [1,2] and come from a variety of sources. These are both biological and synthetic in composition.

A new technology which is increasingly being used is Fragmented Acellular Fish Skin Graft (or FAFSG). This is rich in omega-3 unsaturated fatty acids and has recently been approved

by numerous regulatory agencies. The graft is usually made from Atlantic cod skin, which lives in cold waters of the coast of Iceland and is sustainably harvested in the open sea. This graft is also the only one on the market that is FDA approved in the USA [3]. After the fish skin is placed on the wound, the body's own cells are recruited to assist the body in healing the wound. This occurs as they grow into the pores of the fish skin and become vital tissue [3]. Indications for the use of fish skin are chronic wounds, wound dehiscence, burns and ulceration caused by diabetes or venous ulceration. The advantages of FAFSG are biocompatibility, lack of allergic reactions, increased cell proliferation and vascularization, and no risk of viral disease transmission. The average application is 3-5 times of graft placement, which results in complete wound healing after approximately 5-6 weeks [2]. We have focused on the effectiveness of FAFSG on the lower extremities in patients with trauma-related chronic wounds using the following cases.

Case Report

Case 1: 54-year-old female patient presented to our clinic on 26/06/20 with a chronic wound due to i.m. application of Betaferon

in the context of multiple sclerosis without other comorbidities on the left thigh. The wound extended to the iliotibial tract. Wound debridement with partial wound closure and NPWT was performed on 25/06 and 28/06/2020 with concurrent antibiotic therapy. On 22/07/20, the wound was closed secondarily. After 2 weeks, there was partial wound dehiscence (30%) with visible tractus iliotibialis. The wound was treated with medical honey. However, the wound edges continued to fail to adapt. After another frustrated attempt to refresh the wound edges and secondary suturing on 31/08/20, progressive wound dehiscence with additional necrosis of the iliotibial tract occurred again. This was excised locally, wound edges refreshed, and FAFSG applied for the first time on 25/09/20. Till 22/10/20, FAFSG was applied a total of 7 times. A local inflammatory reaction of the wound edges with the fish skin was treated with cortisone and zinc ointment. After a total of 3.5 months, the wound was completely healed with completed epithelialization.

Case 2: 90-year-old female patient presented on 17/08/20 with an infected hematoma (5x6cm) on the lateral right lower leg after impact trauma 12 days ago, this was evacuated with necrosectomy, debridement and VAC placement. On the first postoperative day, an angiological workup was performed with a new diagnosis of a high -grade stenosis of the superficial femoral artery distally, which was treated by percutaneous transluminal angioplasty. The VAC was changed twice under sterile conditions in the operating room. Additionally, antibiotic therapy was given during the hospitalization. After one week of hospitalization, the VAC dressing was further changed on an outpatient basis. On 15/09/20, the first FAFSG application was made to the wound. A total of 4 applications of fish skin with additional covering of the wound by VAC dressing were performed. After one month, the first islands of epithelialization appeared, so it was decided to apply local dressings with wound gel made of basic ionized seawater, oxychlorite and lithium magnesium sodium silicate. Due to reddened wound margin one month after closure with fish skin, the dressings were changed to cellulose acetate and polyethylene glycol overlays. The wound was completely epithelialized after a total of 4 months.

Discussion

Fragmentary cell-less skin grafts have a complex structure

that provides the optimal environment for a positive tissue response. This positive response manifests itself in the restoration of tissue function and structure [4]. This occurs with the delivery of anti-inflammatory omega 3 fatty acids. These have been shown to act as anti-inflammatory regulators, have an antibacterial effect and also show an antiviral effect, which has already been demonstrated in studies. In addition, a hemostatic effect has been demonstrated when the grafts are placed in the wound bed. In acute wounds, fish skin was found to accelerate wound healing [5]. In a double-blind prospective study, Kirsner et al found that more wounds healed in 28 days when treated with the grafts and that the wounds healed significantly faster than wounds treated with amniotic membranes. This indicates that FAFSG is a superior treatment compared to dHACM, and amniotic membrane dHACM. Not only in terms of healing time, but also in terms of cost effectiveness, as treatment with dHACM had an average 76% higher cost in the study. ($p=2,51*10^{-16}$) [5].

Another study comparing treatments of wounds with fish skin and standard therapy without fish grafts concluded that within 12 weeks, a 67% healing rate is achieved with fish skin and only a 32% healing rate with standard treatment [6]. A retrospective review by Kim et al also concluded that treatment with fish skin accomplishes wound healing more rapidly than traditional wound dressings. Magnusson et al have also shown that omega 3-polyunsaturated fatty acids and anti-inflammatory nature of fish skin grafts have proven beneficial for faster wound healing. Fish skin grafts have been shown to progress chronic wounds past the inflammatory stage to proliferation and remodeling stages of wound healing [7,8].

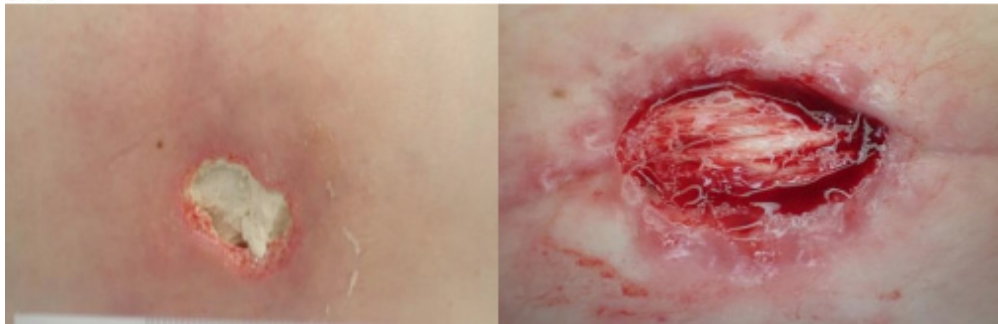
Based on our case studies, we saw that all wounds were completely epithelialized within 4 months after 4-7 applications. Any reaction of the wound edges that occurred was treated with local measures, and no further complications occurred. This case series demonstrates the improved ability of wound healing with the application of FAFSG in the treatment of chronic wounds of the lower extremities, which are classified as high-risk wounds in addition to risk factors such as peripheral artery disease.

The company, which provides the fish skin, offers an outcome-based pricing model applying surrogate markers and endpoints of wound healing for venous leg ulcer (VLU) and

diabetic foot ulcer (DFU) to determine the healing trajectory with standard of care treatment (SOC). The model calculates the chances of complete wound healing in VLU and DFU by week 20 and 24 respectively, after evaluating the initial reduction of the wound area after 4 weeks SOC. Patients who showed >50% reduction in wound area at week 4 were predicted to heal entirely by week 20 continuing using SOC and thus were not eligible for treatment with intact fish skin. Patients with a reduction <50% at week 4 were treated with intact fish skin. The pricing model defined that treatment with intact fish skin should result in a reduction of the wound area >25% in VLUs and DFUs compared to standard of care at week 8. The cost of intact fish skin was only charged to the patient and his health-care insurance if this criterion was met.

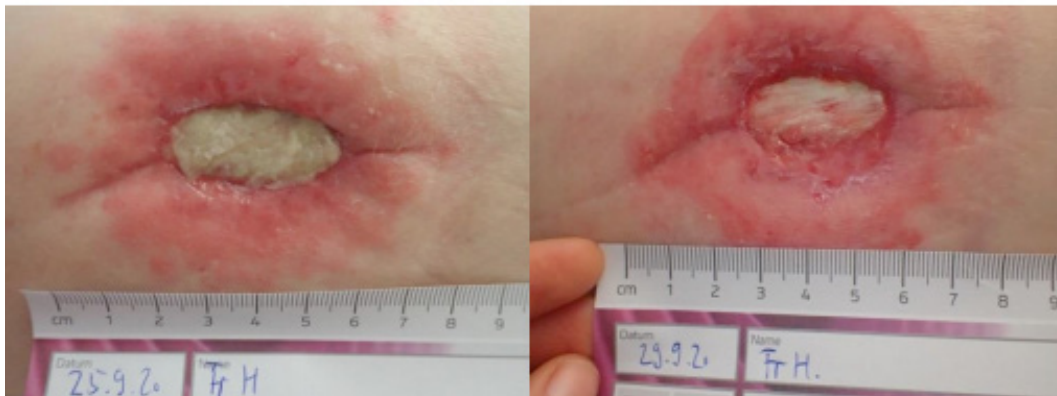
To further determine the clinical effectiveness and efficacy of fish skin wound graft for different types of wounds double-blinded, randomized controlled trials are needed.

Case 1



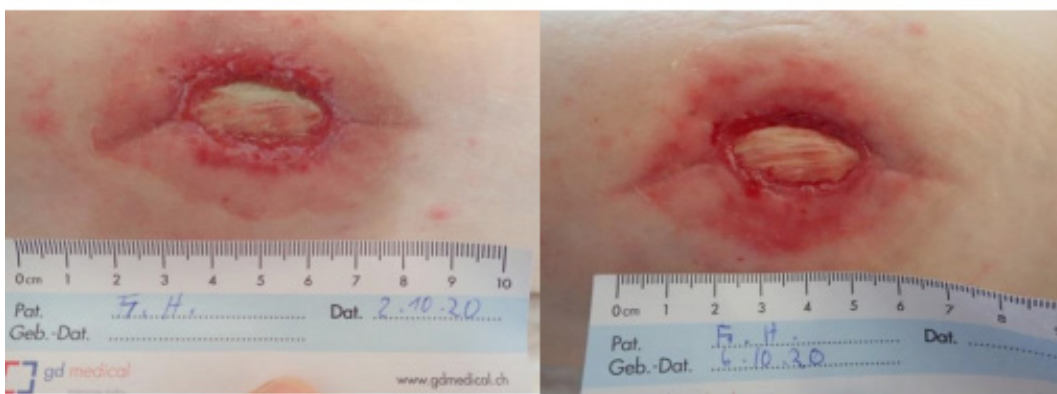
Day of presentation

Before application of FAFSG



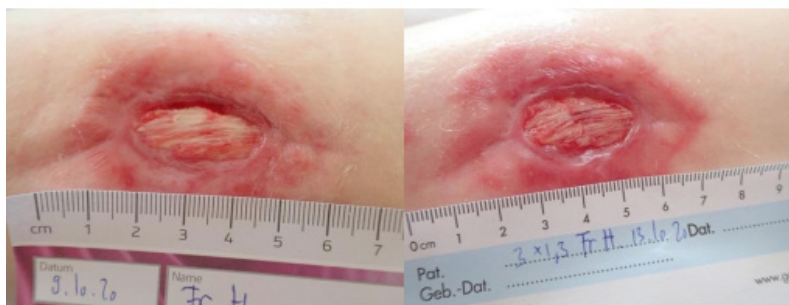
1st application of FAFSG (No1)

2nd application of FAFSG (No2)



3rd application of FAFSG (No3)

4th application of FAFSG (No4)



5th application of FAFSG (No 5)

6th application of FAFSG (No 6)



7th application of FAFSG (No 7)

Two months after first application



Four months after 1st application and completed wound healing



Postoperativ after debridment

1st application of FAFSG (No1)



Figure 1: Day of Presentation to Complete Wound Healing Process.

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