Iran Red Crescent Med J. 2014 December; 16(12): e19500. DOI: 10.5812/ircmj.19500

Published online 2014 December 15. **Case Report**

New Therapy Using Omega-3-Acid Ethyl Esters for Decubitus Ulcers and Stasis Dermatitis: A Case Report

Kazuki Nagai [1,*]; Katsuhiko Matsumaru [1]; Ikuko Hirai [2]; Yujiro Takae [2]; Kazuo Andoh [3]

[1]Department of Internal Medicine, Nagai Clinic, Yokohama, Japan
[2]Department of Dermatology, Saiseikai Yokohama-shi Nanbu Hospital, Yokohama, Japan
[3]Department of Radiology, Saiseikai Yokohama-shi Nanbu Hospital, Yokohama, Japan

*Corresponding Author: Kazuki Nagai, Department of Internal Medicine, Nagai Clinic, P. O. Box: 2350045, Yokohama, Japan. Tel/Fax: +81-458325830, E-mail: k-nagai@mtj.biglobe.ne.jp

Received: April 15, 2014; **Revised:** September 25, 2014; **Accepted:** October 7, 2014

Introduction: In daily practice, it is common to experience difficulty in treating decubitus ulcers (pressure ulcers, also known as decubitus ulcers) and stasis dermatitis of the lower limbs. We hereby report that omega-3-acid ethyl esters were remarkably effective when administered to cases of refractory pressure ulcers and stasis dermatitis for the purpose of improving the blood flow and promoting blood circulation.

Case Presentation: Case 1: A 21-year-old Japanese female with lower-body paralysis. Pressure ulcers appeared on the heel and first toe of her left lower extremity. Although the patient had been treated with various ointments such as dimethyl isopropylazulene and 0.9% iodine-containing ointment, the course showed no improvement, so omega-3-acid ethyl esters was administered orally, completely healing the ulcer of the first toe in 10 weeks. Case 2: A 76-year-old Japanese male. The patient had been treated on an outpatient basis for 15 years due to hypertension, heart failure, type 2 diabetes mellitus, and hyperlipidemia. Two years prior to this presentation, stasis dermatitis occurred in the lower limbs and at the end of last year, erosive ulcers appeared on the front part of the lower-right thigh and shin. Although treatment with various topical ointment and dressings was performed, the course showed no improvement. Oral administration of omega-3-acid ethyl esters was initiated. At 12 weeks, his condition entered the white phase and healed almost completely.

Conclusions: This report is the first to document other treatment possibilities for pressure ulcer and/or stasis dermatitis in cases where the use of topical applied ointments and medications is difficult. This new therapy may therefore help physicians to treat pressure ulcers and stasis dermatitis.

Keywords: Omega-3 Fatty Acids; Ethyl-Eicosapentaenoic Acid; Docosahexaenoic Acid Ethyl Ester; Pressure Ulcers

1. Introduction

In daily practice, it is common to experience difficulty in treating venous stasis dermatitis of the lower limbs and decubitus ulcers (pressure ulcers, also known as decubitus ulcers). For treatment, depending on the condition of the wound, conservative treatment with medicines for external use (1) and dressings (2, 3), as well as surgical procedures are mainly carried out, while decubitus ulcers are refractory depending on their severity.

Recently, Pronova BioPharma ASA (Norway) manufactured Lotriga® granular capsule 2 g (generic name: omega-3-acid ethyl esters 90) with fatty acid having a high level of omega-3 as the active ingredient and containing ethyl icosapentate (EPA-E) and docosahexaenoic acid ethyl (DHA-E) as major ingredients at high concentrations. It contains 930 mg EPA-E and 750 DHA-E per 2g. Pronova and Takeda Pharmaceutical Company Limited ("Takeda") announced that Lotriga is now available for the treatment of hyperlipidemia. It is believed that this EPA-E and DHA-E has an effect of stimulate blood circulation, increase the breakdown of fibrin, a compound involved in clot and scar formation and improving blood flow (4, 5). And more, in peripheral arterial disease, EPA-E and DHA-E induced a marked improvement in endothelial function (6). They have a vasoprotective effect, providing improving elastic properties of the arteries by preventing fibrosis (7). With decubitus, peripheral vascular endothelial function decreases (8), and as a result of blood stagnation, the intercellular adhesion molecule-1 (ICAM-1) and the vascular cell adhesion molecule-1 (VCAM-1) are expressed (9). EPA-E and DHA-E attenuate the expression of inflammatory cytokines such as this VCAM-1 (10, 11). We herein report that omega-3-acid ethyl esters were remarkably effective when administered to two cases of refractory pressure ulcers and stasis dermatitis for the purpose of improving blood flow and promoting blood circulation.

2. Case Presentation

Case 1: A 21-year-old Japanese female. She was struck

with lower-body paralysis of unknown origin at the age of 10, and has lived her daily life in a wheelchair ever since. In September 2012, she wore a new pair of leather shoes when going to work, thus resulting in pressure ulcers suddenly appearing the next day on the heel and first toe of her left lower extremity. Subsequently, the patient visited another hospital and underwent treatment with various topical ointments including dimethyl isopropylazulene and 0.9% iodine-containing ointment; however, the course showed no improvement for approximately 6 months, so she visited our hospital in April 2013. There were pressure ulcers measuring some 5 cm in diameter with an abnormal odor in the heel of the left lower extremity. With insufficient granulation, the ulcers had a defect extending to the subcutaneous tissue. Although the subcutaneous tissue was visible, the bones, tendons, and muscles were not exposed. A brownish-red eschar and a yellowish slough were attached to part of the wound floor, and the depth of the ulcers was partially indeterminable. Full thickness tissue loss had occurred. Subcutaneous fat may be visible but bone, tendon or muscles are not exposed. The case corresponds to National Pressure Ulcer Advisory Panel (NPUAP) Category stage III (Figure 1 A). With the consent of the patient, oral administration of omega-3-acid ethyl esters (2 g once a day) was initiated while applying 0.9% iodine-containing ointment for the purpose of protecting the ulcer surface and the ulcers, which had not changed for 6 months, turned from a brownish-red color to a yellowish color at 2 weeks (Figure 1 B, C), and thereafter entered the yellow phase at 4 weeks, while showing a contractive tendency (Figure 1 D). At 8 weeks, the ulcer surface on the heel was further reduced, with progressed granulation in addition to a tendency for improvement. Moreover, in the ulcer on the first toe, epithelialization occurred around the wound, and the ulcer was reduced and improved entering the white phase (Figure 1 E). At 10 weeks, the ulcer on the first toe healed completely (Figure 1 F). However, diarrhea was caused as a side effect of omega-3-acid ethyl esters, and although continued oral administration was instructed with the aim of complete healing of the ulcer on the heel, it was discontinued in the end of September.

Case 2: A 76-year-old Japanese male. The patient had been treated on an outpatient basis for 15 years due to hypertension, heart failure, type 2 diabetes (T2DM; Diabetes mellitus type 2), and hyperlipidemia. His family history was unremarkable. A physical examination at the time of onset showed the patient to be obese; his height was 156 cm, his weight was 86 kg, and his Body mass index (BMI) was 35.4%. His chest was normal, but his heart rate was irregular, and no abdominal tumor or hepatosplenomegaly were observed. Remarkable swelling was observed due to edema in his legs. His neurologic functions were also normal.

The laboratory data recorded during the visit to our clinic was as follows: hematologic tests were within the normal limits. Serological data included AST was 93 IU/L (normal: 10-40 IU/L), ALT was 105 IU/L (normal: 5-45 IU/L), lactic dehydrogenase (LDH) was 263 IU/L (normal 120-245 IU/L), alkaline phosphatase (ALP) was 310 IU/L (normal 93-271 IU/L), γ-GTP was 263 IU/L (normal: 8-60 IU/L), fasting blood sugar (FBS) was 168 mg/dL (normal: 78-108 mg/dL), hemoglobin was A1c 7.1 % (normal: 4.5-6.0%).

The patient had been unable to sit on the floor (sit on his heels) for 4-5 years because of persistent edema due to anomalous venous drainage in his lower extremities. Two years prior to this presentation, stasis dermatitis occurred in the lower limbs, which was treated with dimethyl isopropylazulene, 0.9% iodine-containing ointment, dressings etc.; however, exudate fluid also appeared together with pigmentation. Moreover, the patient gradually began to experience difficulty walking and was unable to sit on his heels. At the end of 2012, erosive ulcers appeared on the front part of his lower-right thigh and shin. Although treatment with various topical ointments and dressings was carried out, the course showed no improvement (Figure 2 A). Therefore, the oral administration of omega-3-acid ethyl esters was initiated 2g once a day. The course was observed every two weeks. At 4 weeks, the erosive ulcers gradually started granulation (Figure 2 B), and at 8 weeks, the ulcer surface showed a contractive tendency (Figure 2 C). At 12 weeks, the condition entered the white phase and healed almost completely (Figure 2 D). At 14 weeks, the patient had a fall at home, rendering him unable to stand up on his own, and because he kept his lower limbs flexed for 3 hours, cellulitis occurred the next day, leading the patient to be urgently admitted to the Department of Dermatology, Saiseikai Yokohama-shi Nanbu Hospital (Figure 2 E, F). Oral administration of mega-3-acid ethyl esters was continued, a topical ointment was applied, and an antimicrobial agent was administered. The patient was discharged from the hospital with a compression bandage. At 18 weeks, an improvement was seen in his rash symptoms (Figure 2 G, H). Currently, his difficulty in walking has improved and the patient can also sit on his heels.

3. Discussion

Regarding the treatment of pressure ulcers, not only an improvement of the underlying diseases, but also, depending on the condition of wound, conservative treatment with medicines for topical ointments use and dressings, as well as surgical procedures are mainly carried out, while decubitus ulcers are refractory depending on their severity. Moreover, chronic venous insufficiency is appropriately treated by the elevation of the lower limbs and compression stockings, and if stasis dermatitis occurs, then either corticosteroid cream or ointment is applied or it is used in a mixture with zinc oxide paste; however, this condition may still sometimes remain refractory.

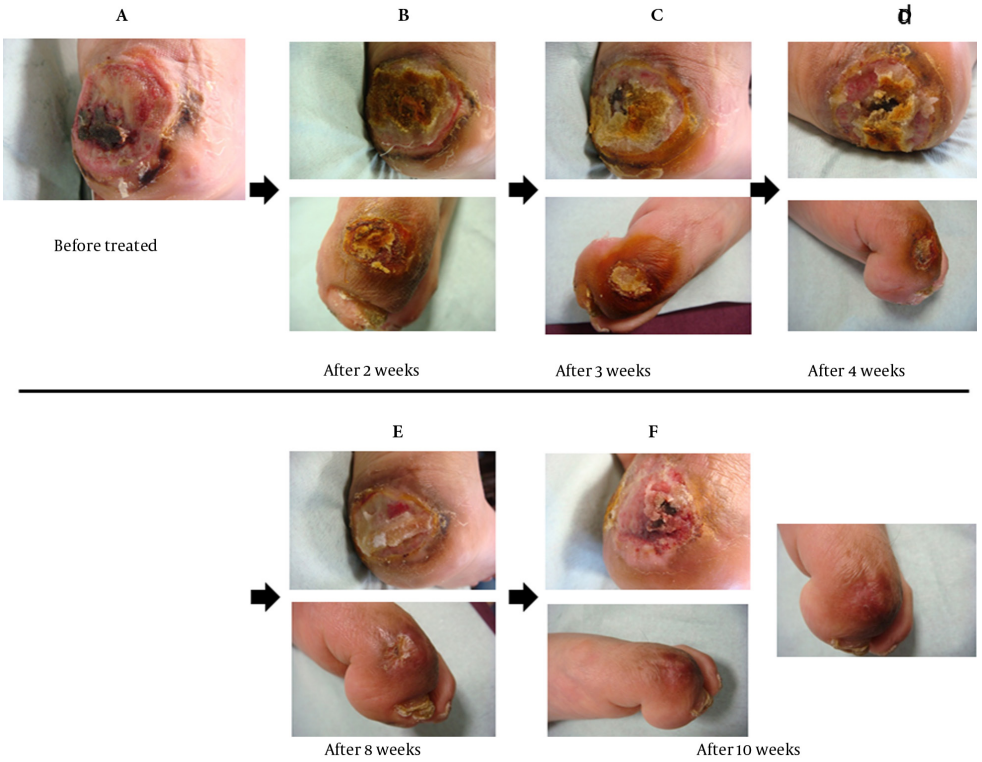

Figure 1. The case corresponds to National Pressure Ulcer Advisory Panel (NPUAP) Category stage III (Figure 1 A). Oral administration of omega-3-acid ethyl esters was initiated, turned from a brownish-red color to a yellowish color at 2 weeks (Figure 1 B, C), and thereafter entered the yellow phase at 4 weeks (Figure 1 D). At 8 weeks, the ulcer surface on the heel was further reduced. Moreover, in the ulcer on the first toe, epithelialization occurred around the wound (Figure 1 E). At 10 weeks, the ulcer on the first toe healed completely (Figure 1 F)

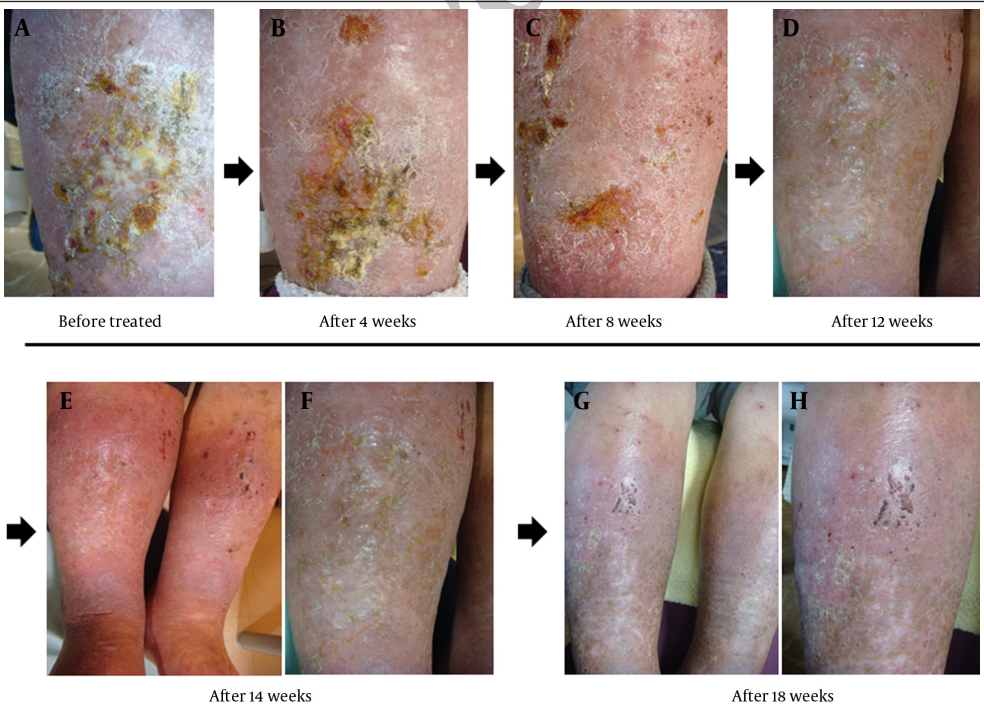

Figure 2. Erosive ulcers appeared on the front part of his lower-right thigh and shin (Figure 2 A). At 4 weeks, the erosive ulcers gradually started granulation (Figure 2 B), and at 8 weeks, the ulcer surface showed a contractive tendency (Figure 2 C). At 12 weeks, the condition entered the white phase and healed almost completely (Figure 2 D). At 14 weeks, the patient had a fall at home, rendering him unable to stand up on his own, and because he kept his lower limbs flexed for 3 hours, cellulitis occurred the next day (Figure 2 E, F). Oral administration of mega-3-acid ethyl esters was continued. At 18 weeks, an improvement was seen in his rash symptoms (Figure 2 G, H)

Recently, a high level of omega-3 fatty acids, containing EPA-E and DHA-E as major ingredients, have been developed and become available for prescription. It contains 930 mg EPA-E and 750 mg DHA-E per 2 g. Usually, for adults; 2 g of Omega-3-acid ethyl esters is orally administered immediately after meals once a day. It is believed that this DHA has an effect of softening the cell membrane of the vessel wall and promoting blood circulation, and it was administered orally to two cases resistant to treatment with ointment under adequate consensus. In Case 1, it is believed that the patient's condition improved by the use of 0.9% iodine-containing ointment because 0.9% iodine-containing ointment was used for the purpose of protecting the ulcer surface; however, the application of that ointment was discontinued at 4 weeks. Moreover, in Case 2, although 0.9% iodine-containing ointment had been applied before oral administering omega-3-acid ethyl esters 90, the course showed no improvement, and it is believed that healing could not be expected after treatment with 0.9% iodine-containing ointment alone. Therefore, it is believed that omega-3-acid ethyl esters improved the treatment effect on the lesions in both cases.

With pressure ulcers, which are local blood flow disturbances, and stasis dermatitis, which is a chronic blood flow disturbance, various inflammatory cytokines have appeared. These omega-3-acid ethyl esters suppress inflammatory cytokines (12, 13) and leucocyte chemotactic factors (14), thus suggesting that wound healing could have been promoted as a result. Although this treatment is not yet fully established, it may be effective not only as a treatment for refractory decubitus ulcers.

This report is the first to document other treatment possibilities for pressure ulcers and/or stasis dermatitis in cases where the topical ointments and medications are difficult. This new therapy may therefore help physicians to effectively treat pressure ulcers and stasis dermatitis.

Acknowledgements

We wish to thank the patients, who gave their written consent for publication and their family members as well.

Authors' Contributions

Kazuki Nagai and Katsuhiko Matsumaru Substantial contributions to conception and design, drafting the article. Critical revision of the article for important intellectual content. Final approval of the version to be published. Ikuko Hirai, Yujiro Takae and Kazuo Andoh Substantial contributions to conception and design. Final approval of the version to be published.

References

1. Piljac A, Stipcevic T, Piljac-Zegarac J, Piljac G. Successful treatment of chronic decubitus ulcer with 0.1% dirhamnolipid ointment. *J Cutan Med Surg.* 2008;**12**(3):142–6.
2. Mauckner P. [The treatment of heel pressure ulcer with V.A.C. therapy using the new V.A.C. GranuFoam "Heel-Dressing"]. *Zentralbl Chir.* 2004;**129 Suppl 1**:S104–7.
3. Bou Torra JE, Soldevilla Agreda JJ, Martinez Cuervo F, Rueda Lopez J. [Collagen powder dressing in the treatment of pressure ulcer. Multicenter comparative study assessing effectiveness and cost]. *Rev Enferm.* 2002;**25**(9):50–7.
4. Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation.* 1993;**88**(2):523–33.
5. Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension.* 1999;**34**(2):253–60.
6. Schiano V, Laurenzano E, Brevetti G, De Maio JI, Lanero S, Scopacasa F, et al. Omega-3 polyunsaturated fatty acid in peripheral arterial disease: effect on lipid pattern, disease severity, inflammation profile, and endothelial function. *Clin Nutr.* 2008;**27**(2):241–7.
7. Koziolova NA, Shilova Ia E, Nikonova Iu N, Agafonov AV, Polianskaia EA. [State of the structure and functions of the arterial wall in patients with chronic heart failure against the background of permanent atrial fibrillation and assessment of vasoprotective effect of omega-3 polyunsaturated fatty acids]. *Kardiologiia.* 2013;**53**(3):15–24.
8. Jiang L, Dai Y, Cui F, Pan Y, Zhang H, Xiao J, et al. Expression of cytokines, growth factors and apoptosis-related signal molecules in chronic pressure ulcer wounds healing. *Spinal Cord.* 2014;**52**(2):145–51.
9. Matic M, Duran V, Ivkov-Simic M, Poljacki M, Gajinov Z, Begenisic M. [Microcirculatory changes in chronic venous insufficiency]. *Med Pregl.* 2000;**53**(11-12):579–83.
10. Yates CM, Calder PC, Ed Rainger G. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacol Ther.* 2014;**141**(3):272–82.
11. Wang TM, Chen CJ, Lee TS, Chao HY, Wu WH, Hsieh SC, et al. Docosahexaenoic acid attenuates VCAM-1 expression and NF-kappaB activation in TNF-alpha-treated human aortic endothelial cells. *J Nutr Biochem.* 2011;**22**(2):187–94.
12. Seljeflot I, Arnesen H, Brude IR, Nenseter MS, Drevon CA, Hjermann I. Effects of omega-3 fatty acids and/or antioxidants on endothelial cell markers. *Eur J Clin Invest.* 1998;**28**(8):629–35.
13. De Caterina R, Cybulsky MI, Clinton SK, Gimbrone MJ, Libby P. The omega-3 fatty acid docosahexaenoate reduces cytokine-induced expression of proatherogenic and proinflammatory proteins in human endothelial cells. *Arterioscler Thromb.* 1994;**14**(11):1829–36.
14. Tull SP, Yates CM, Maskrey BH, O'Donnell VB, Madden J, Grimble RF, et al. Omega-3 Fatty acids and inflammation: novel interactions reveal a new step in neutrophil recruitment. *PLoS Biol.* 2009;**7**(8).