Intact Fish Skin Compared to Human Amnion/Chorion Membrane Allograft: A Double-Blind, Prospective, Randomized, Clinical Trial of Acute Wound Healing

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INTRODUCTION

Most chronic wounds, including diabetic foot ulcers, venous leg ulcers and pressure ulcers, are all full thickness injuries with loss of dermal and epidermal components. While these wounds are not acute, they are routinely debrided back to a more acute state prior to the application of a skin substitute. In full-thickness wounds, dermal regeneration usually fails, resulting in scar formation. The design of this study was established and validated for comparative dermal regeneration in full thickness tissue injury. The study compared the length of time needed for 170 acute full-thickness wounds to heal, which was defined as “full epithelialization”. Fish skin grafts* are skin substitutes naturally containing omega-3 EPA and DHA fatty acids. In this study we compared the efficacy of the fish skin grafts to the most commonly used amnion/chorion membrane allograft (dHACM)# for wound healing.

OBJECTIVE

The primary objective was to determine if healing of acute wounds treated with fish skin is superior in time to heal compared to dHACM.

Figure 1. Proportion of healed wounds at each time point with intact fish skin (orange) and dHACM (blue). P=0.0014.
METHODS
A double-blind, prospective, randomized, comparative clinical trial on 85 participants was undertaken. Each participant had two 4-mm wounds generated on their forearm and were then randomized to receive fish skin on one wound and dHACM on the other. The primary endpoint was time to heal, defined as complete epithelialization by blinded assessment at days 14, 18, 21, 25 and 28. In order to assess the superiority hypothesis, a mixed effects Cox-Proportional Hazard model was used. The model was fit to the time-to-heal data using the survival\(^3\) and coxme\(^4\) packages in R version 3.3.1.\(^5\) This model incorporates a patient random effect to account for individual patient variability in healing rate. The difference in proportion healed between the two products at each timepoint was assessed with non-parametric bootstrap test. Approvals: Icelandic Medicines Agency (8.1.13.1/2017090010) and the Icelandic National Bioethics Committee (VSNb2018010033/03.01).

RESULTS
The fish skin group healed significantly faster with a hazard ratio of 2.37 (95% CI: 1.75-3.22) at a p-value of 0.0014 over dHACM (Figure 1). Wound healing was faster in the fish skin treated group at all timepoints: Day 14 - 68%, Day 18 - 83%, Day 21 - 50%, Day 25 - 26%, Day 28 - 10%. (Figure 2).

CONCLUSION/DISCUSSION
In this double-blind, prospective, healthy cohort study, more wounds treated with fish skin grafts healed in 28 days, and the wounds healed significantly faster than wounds treated with amnion membrane. Therefore, the results show that fish skin grafts are superior in time to heal on acute wounds compared to dHACM. Previous studies had shown that the fish skin grafts heal full thickness wounds significantly faster than a porcine sourced skin substitute.\(^1\) Amnion-membrane dHACM and also more cost effective treated wounds were 76% more expensive compared to fish skin treated wounds on average in this study (p=2.51*10^-16). Products have enjoyed increased clinical adoption in recent years, although comparative evidence for their efficacy has been scarce. Double-blind comparative studies such as these can help health-care practitioners to select the most efficacious treatment for their patients.

FOOTNOTE
*Kerecis® Omega3 Wound by Kerecis, #Epifix® by MiMedx

REFERENCES