Double-Blind, Prospective, Randomized Clinical Trial on 170 Acute Wounds Shows Significantly Faster Healing Rate with Intact Fish Skin Compared to Human Amniotic Membrane

John C. Lantis II MD, FACS; Kristin Petursdottir, MD; Baldur Baldursson; Robert S. Kirsner, MD, PHD, FAAD; Dot Weir, RN, CWON,

Mount Sinai St Luke’s and West Hospitals New York NY
Landspitali - The National University Hospital of Iceland Reykjavik Is,
Miller School of Medicine Miami University
Disclosures

- **Consultant**
  - Kerecis, Acelity, Smith & Nephew, Integra, Pluristem, MediWound, LimFlo, Ekare, Restorix, Molenyke

- **Principal investigator**
  - Pluristem, LimFlo, TissueTech

- **Grant Support**
  - Pluristem, LimFlo, TissueTech, Integra
Cellular and/or tissue based products (CTP's) derived from human and animal tissues have been used in the treatment of both hard-to-heal chronic and acute wounds.

A CTP derived from intact (freeze dried) fish skin grafts are a recent addition to the market. This graft (Kerecis Omega3™ Wound, Kerecis, Isafjordur, Iceland) from North Atlantic Cod is an acellular but otherwise structurally intact dermal tissue product.

A CTP derived from human amnio-chorionic membrane has been used for wound healing. A very efficacious product is a freeze-dried preparation that has been shown to be very effective in treating diabetic foot ulcers.
Both are modulatory products – in that in clinical trials and practice they require multiple applications.

While it is not entirely clear why fish skin speed healing, specific properties of the fish skin product include the natural content of omega 3 polyunsaturated fatty acids and the native extracellular matrix structure.

- An ECM which requires minimal processing due to the fact that fish is not known to transmit viral disease to humans.

The dHCAM relies on the presence of fetal derived growth factors, and cytoattractant properties, dHCAM has had many reports of very rapid healing of chronic diabetic foot ulcers in one week, this rapid healing effect was not noted in our acute wound study.

- Minimally manipulated human tissue
A prospective blinded assessment of time to healing of full thickness acute wounds, using a 4mm punch biopsy model to create standardized wounds, with the two different CTPs mentioned above.

The secondary objective was to compare the proportion of wounds fully epithelialized by day 28, incidence of pain, erythema and the rate of infection.
• After local anesthesia (lidocaine hydrochloride 10mg/ml and epinephrine 5 mcg/ml), two 4 mm punch wounds, 3 cm apart, were made on the proximal anterolateral aspect of the non-dominant forearm.

• Hemostasis was achieved with pressure and 30% ferrous chloride solution.

• The products were applied according to the randomization sequence followed by a secondary dressing consisting of a waterproof vapor transmitting, transparent plastic film with a centrally placed gauze pad.
• Over the 28-day study period, participants had a total of 7 visits.

• On day three, participants were contacted by phone by the trial physician to collect information on the status of their wounds. The participants were seen on days, 7, 14, 18, 21, 25 and 28 for assessment of wound status.

• Wounds were assessed for erythema, infection and reported pain or bleeding and a decision of healed vs. not healed was made by the evaluating health professional

• If the treatment material was intact, it was left in the wound. If it had reabsorbed or if treatment material was not visible, new material was applied to the wound.

• Standardized digital photographs were taken and healing assessment was performed by four wound healing professionals in an independent, blinded manner.
Results

• **Demography**
  
  85 healthy volunteers aged between 19 and 51 years were enrolled with no loss of follow up.
  
  • Their average age was 24.1, with a standard deviation of 4.6 years. 66.7% of the cohort were women.

• **Primary end point**

  Wounds treated with fish skin healed significantly faster with a hazard ratio of 2.37 (95% CI: 1.75-3.21) at a p-value of 0.001 over dHACM allograft treated wounds.
Proportional Hazard model
## Adverse Events

<table>
<thead>
<tr>
<th>Complication</th>
<th>Amnion/chorion membrane allograft, number of wounds (day of trial)</th>
<th>Fish skin graft, number of wounds (day of trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>2 (7), 2 (14)</td>
<td>4 (7), 2 (14)</td>
</tr>
<tr>
<td>Irritation and discharge</td>
<td>1 (7), 1 (14)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Limitations

• Small wounds
• Few applications - The fish skin graft received 1.6 applications per subject on average, while the dHACM received 1.4 per wound.
• Acute wounds
• Young healthy Caucasian subjects
Conclusions

- Full thickness acute wounds treated with intact fish skin grafts healed significantly faster than wounds treated with dehydrated human amnio-chorionic membrane.
- The number of adverse reactions such as mild erythema and irritation was not different.
- A previously reported like study - fish skin treated wounds also healed significantly faster than porcine small intestine submucosa
However, the immediate question is: What is the applicability of a study on acute wounds on the treatment decision for chronic wounds?

The aggressive debridement (wound excision or ulcerectomy), which, along with offloading is the centerpiece of the care of diabetic foot ulcers is explicitly or implicitly attempts or is “meant” to return the wound dynamics from a chronic to an acute phase.

Therefore the results on acute wounds may have implications for debrided chronic wounds. Also advantageous in this controlled experiment is that removes some biases inherent with clinical wound studies.
Double-Blind, Prospective, Randomized Clinical Trial on 170 Acute Wounds Shows Significantly Faster Healing Rate with Intact Fish Skin Compared to Human Amniotic Membrane

John C. Lantis II MD, FACS; Kristin Petursdottir, MD; Baldur Baldursson; Robert S. Kirsner, MD, PHD, FAAD; Dot Weir, RN, CWON,

Mount Sinai St Luke’s and West Hospitals New York NY
Landspitali - The National University Hospital of Iceland Reykjavik Is,
Miller School of Medicine Miami University