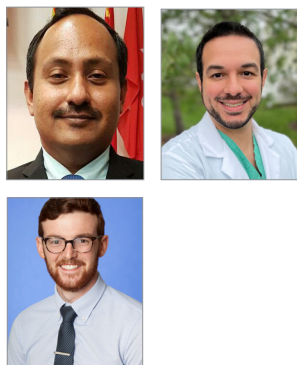


Use of an advanced extracellular matrix dressing in the treatment of acute and chronic wounds: a Malaysian case series



Chronic wounds are becoming an increasing burden on healthcare systems as the Malaysian population develops more complex comorbidities. These wounds present a challenge for health professionals to treat without having access to advanced wound healing technologies that have not been available in Malaysia. We report a retrospective case series (n=10) detailing one Malaysian wound care centre's initial experience with a novel decellularised extracellular matrix, ovine forestomach matrix (OFM), used in the treatment of both acute and chronic wound. At the 12-week mark, the principal investigator deemed 90% (9/10) wounds to be closed or improving.

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There is an ever-growing need for advanced wound care products in Southeast Asia as the region begins to see a dramatic rise in chronic wounds (Norman et al, 2020). In a 2015 survey assessing the rate of diabetes in Malaysia, it is estimated that 2.8 million (20.8%) Malaysians have type II diabetes (Hussein et al, 2016). It has been well documented that approximately 25% of patients with diabetes will sustain a wound over the course of their lives (Price, 2004; Singh et al, 2005) and these wounds are notoriously difficult to close due to the chronically inflamed wound environment (Spampinato et al, 2020). At present the standard of care for chronic wounds typically focuses on managing the symptoms of the wound (e.g., exudate and pain) rather than addressing the underlying wound pathophysiology to accelerate the wound healing process. With an increasing proportion of the Malaysian population becoming high risk for sustaining a chronic wound there is a growing demand for cost-effective technologies to achieve wound closure.

Recent advances in the field of regenerative medicine have identified tissue-based extracellular matrix (ECM) as a broad class of technology that can scaffold soft tissue regeneration and are particularly suited to wound repair (Pradhan et al, 2009; Gould, 2016). These products are not synthetic, but rather tissue-derived, being isolated from

intact mammalian tissues using processes to remove cellular components while keeping the structure and biology of the ECM intact (Gould, 2016). When placed in the wound bed, these products scaffold cellular infiltration and enhance the body's natural ability to heal. While these types of technologies have been widely available and readily adopted in many health care systems, global uptake has been slow due to economic barriers. For example, ECM-based technologies have not traditionally been available to Malaysian wound care professionals. Decellularised extracellular matrix derived from ovine forestomach, termed ovine forestomach matrix (OFM) is one of these ECM-based products. OFM acts as a scaffold to aid host cell migration and proliferation, and over time OFM is fully integrated into native tissue (Overbeck et al, 2020). OFM contains naturally occurring ECM proteins that provide structure to the site of injury and key resources for the regenerating tissue at different stages of healing (Lun et al, 2010). During the inflammatory phase, OFM modulates the innate immune response (Street et al, 2015) and modulates proteases leading to resolution of wound chronicity (Negron et al, 2012). During the proliferative phase of healing, OFM interacts with rebuilding cells such as mesenchymal stem cells, fibroblasts, endothelial cells and keratinocytes (Lun et al, 2010, Irvine et al, 2011, Dempsey et al, 2020) by providing a structural support for these cells and releasing

Key words:

- Ovine forestomach matrix
- Chronic wounds
- Wound care
- Case series

Table 1.					
Sex/age	Comorbidities	History	Wound age (weeks)	Wound area (cm ²)	Outcomes
M, 67	DM, HTN, HDL	Gangrene and 2 nd toe amputation	8	76.5	Healed at 10 weeks
M, 70	DM	DFU with cellulitis	2	14.0	Improvements in granulation tissue at 4 weeks
M, 82	CHF, HTN, BPH	Lower leg ulcer	55	3.0	Improvements in granulation tissue at 15 weeks
M, 66	DM	3 rd toe amputation	12	7.5	Healed at 3 weeks
F, 65	DM, HTN	Lower leg ulcer with prior cellulitis	68	15.0	Improvements in granulation tissue at 15 weeks
F, 58	DM, HTN	Surgical saucerisation of a carbuncle	48	9.0	Improvements in epithelial tissue at 7 weeks
M, 4	NKMI	Traumatic laceration with exposed fascia	2	18.0	Palmar fascia coverage at 1 week. Fully granulated after 4 weeks
M, 29	DM, HTN	Non healing ulcer post TMA	104	1.8	Healed at 2 weeks
M, 33	NKMI	Postoperative fasciotomy for compartment syndrome	36	24.0	Minimal change
M, 63	DM, HTN	Recurrent VLU	212	21.0	Improvements in granulation tissue at 5 weeks

M=male; F=female; DM=diabetes mellitus; HTN=hypertension; HDL=hyperlipidemia; CHF=congestive heart failure; BPH=benign prostate hypertrophy; NKMI=no known medical issues; TMA=trans-metatarsal amputation; VLU=venous leg ulcer

biologically active proteins that encourage the formation of granulation tissue, vasculature and ultimately new tissue ECM.

OFM has recently been made available in Malaysia for the management of acute and chronic wounds. This retrospective case series describes our early experience and clinical outcomes using OFM to treat wounds from the Malaysian patient population.

Materials and methods

As part of standard treatment, all patients provided written informed consent for their images and data to be used for research purposes. The study was conducted in accordance with World Medical Association Declaration of Helsinki ethical guidelines. Relevant de-identified patient data was collated

retrospectively, along with wound images. As this was a pilot evaluation of a new technology no inclusion or exclusion criteria were defined for patient selection.

The case series was conducted at a single wound care centre. Upon presentation at the clinic, all patients underwent an initial debridement of non-viable tissue. If the patient was identified by the principal investigator to be a suitable candidate for OFM (Endoform™ Natural Dermal Template, Aroa Biosurgery Limited, Auckland, New Zealand), it was placed into the wound bed, hydrated with a normal saline and wound exudate and allowed to adhere to the wound bed. The OFM was then covered with a non-adherent contact layer covered with an appropriately sized foam secondary dressing. All patients were instructed

to abide by the institutional guidelines for proper offloading, compression and/or use of any adjunctive therapies. Patients were seen once weekly in the wound care clinic for repeat applications of OFM and would undergo debridement at the clinician's discretion. All measurements were recorded using a paper ruler and digital photography was used to capture all wounds.

Results

A total of ten wounds were included in this case series, with one patient lost to follow-up during treatment (*Table 1*). The majority of patients were male (8/10), and the mean patient age was 53.7 years old. The aetiology of the wounds consisted of surgical wounds, diabetic foot ulcers (DFU), venous leg ulcers (VLU), and traumatic wounds (*Table 1*). Mean wound age at presentation was 55 weeks (range: 2–212 weeks) and mean baseline wound size was 19cm² (range: 1.8–76.5cm²). Wounds received treatment with OFM for up to 20 weeks. At the time of data collection, the principal investigator (HKRN) judged 90% (n=9) wounds had achieved either complete closure or improvement from the initial baseline status. The average percent area reduction at four weeks was 57%, with five wounds achieving at least 50% area reduction by four weeks.

Here we will present four examples of patients who received OFM as a part of their treatment regimen. The four examples highlight how OFM can be used to treat both acute and chronic wounds.

Case 1

A 67-year-old male with a past medical history of diabetes mellitus, hyperlipidaemia and hypertension presented to the clinic with an 8-week-old wound from a surgical dehiscence of a right foot 2nd toe amputation for gangrene (*Case 1a*). At the initial visit, the wound measured 17.5 cm x 4.5cm after the initial debridement of non-viable tissue. OFM was hydrated with saline and wound exudate upon application to the wound bed. This was followed by a non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap. The patient was instructed to properly offload the right foot and was given assistive devices to allow for this accommodation. The patient was instructed to change their foam dressing every three days with repeat application of OFM occurring at each weekly clinic visit. By week two the wound had begun to contract slight measuring 16.5 x 3.5cm and had a healthy bed of granulation tissue (*Case 1b*). By week 8 the wound had closed to 0.1 x 0.1cm (*Case 1c*) and by week 10 was completely reepithelialised with no drainage or dressing changes required (*Case 1d*).

Case 2

A 66-year-old male with a past medical history significant for diabetes mellitus presented to the clinic with a 12-week-old wound from a left 3rd toe resection for gangrene. At the initial visit, the wound measured 5 x 1.5cm after the initial debridement of non-viable tissue (*Case 2a*). OFM was hydrated with saline and

Case 1. Surgical wound dehiscence following a toe amputation gangrene.

- A 67-year-old male with diabetes mellitus, hyperlipidaemia and hypertension and a 8-week-old wound from surgical wound dehiscence of a right foot 2nd toe amputation for gangrene
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The patient was instructed to change their foam dressing every three days. Application of OFM occurring at each weekly clinic visit
- By week 10 was completely reepithelialised.



a. Initial defect, measuring 17 x 4.5 cm



b. 2 Week follow up, defect measuring 16.5 x 3.5cm



c. Week 8 follow up, defect measuring 0.1 x 0.1cm



d. Week 10, 100% reepithelialised

Case 2. Wound caused by a toe resection for gangrene.

- A 66-year-old male with diabetes mellitus and a 12-week-old wound from a left 3rd toe resection for gangrene
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The patient was instructed to change their foam dressing every three days. Application of OFM occurring at each weekly clinic visit
- Complete closure had occurred by the three-week visit.



a. Initial defect, measuring 5 x 1.5cm



b. Week 1 follow up visit, defect measuring 4.0 x 1.0cm



c. Week 3 follow up, defect 100% reepithelialised

wound exudate upon application to the wound bed. This was followed by a nonadherent contact layer, an absorbent foam dressing and secured with a gauze wrap. The patient was instructed to properly offload the left foot and was given assistive devices to accommodate this. The patient was instructed to change their foam dressing every 3 days with repeat application of OFM occurring at each weekly clinic visit. After one week post-application the wound size had decreased to 4 x 1 cm (Case 2b) with complete closure occurring at the three-week visit (Case 2c).

Case 3

A 4-year-old male with no significant medical history presented after sustaining a severe abrasion injury down to the palmar fascia of the left hand. At the initial visit, the wound measured 4.5 cm x 4cm after initial debridement of non-viable tissue (Case 3a). After debridement, OFM was hydrated with saline and serous wound exudate then applied to the wound bed. A secondary dressing was placed which consisted of a non-adherent contact layer and an absorbent foam dressing which was secured

Case 3. Severe abrasion injury.

- A 4-year-old male, no significant medical history presented with a severe abrasion injury of the left hand down to the palmar fascia
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The parents were instructed to change their foam dressing every three days or sooner if required. Application of OFM occurring at each weekly clinic visit
- At the 12 week follow up the wound was fully granulated with roughly 30% of the would remaining.



a. Initial defect, measuring 4.5 x 4.0cm, palmar fascia exposed



b. Week 1 follow up, pre-debridement, wound measuring 3.5 x 3.0cm



c. Week 10 follow-up, post-debridement, wound measuring 2.5 x 2.5cm



d. Week 12 follow-up, pre-debridement wound measurement 2.3 x 2.5cm

Case 4. Surgical wound dehiscence of a trans-metatarsal amputation two years ago

- A 29-year-old male with insulin-dependent diabetes mellitus and hypertension presented to the clinic for evaluation of a non-healing ulcer persisting on the left foot from a surgical wound dehiscence of a trans-metatarsal amputation two years ago
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The patient was instructed to change their foam dressing every three days. Application of OFM occurring at each weekly clinic visit
- Complete closure occurred by week two.



a. Initial defect measuring 2.7 cm x 0.7 cm



b. Week 1 follow up, pre-debridement wound measuring 2.0 cm x 0.5 cm



c. Week 3 follow up, defect 100% reepithelialised

by a gauze wrap. The patient's family was instructed to change the foam dressing every three days or sooner if the dressing became soiled or saturated. The patient was seen in the clinic weekly for repeat application of OFM. After one week, the palmar fascia was covered by granulation tissue ([Case 3b](#)) and at the 10-week follow up the wound size had decreased by over 60% ([Case 3c](#)). At the last clinic visit, the wound was fully granulated with reepithelialisation and roughly 30% of the wound remaining ([Case 3d](#)).

Case 4

A 29-year-old male with past medical history of insulin-dependent diabetes mellitus and hypertension presented to the clinic for evaluation of a non-healing ulcer persisting for two years on the left foot from a surgical dehiscence of a previous trans-metatarsal amputation. At the initial visit, the wound measured 2.7 x 0.7cm after initial debridement of non-viable tissue ([Case 4a](#)). After debridement, OFM was hydrated with saline and serous wound exudate and then applied to the wound bed. The wound was dressed with a non-adherent contact layer, secondary foam dressing and secured by a gauze wrap. The patient was instructed to properly offload the left foot and was given assistive devices to accommodate this. The patient was instructed to change their foam dressing every three days with repeat application of OFM occurring at each weekly clinic visit. After one week post-application the wound size had decreased to

2.0 x 0.5 cm ([Case 4b](#)) with complete closure at week two ([Case 4c](#)).

Discussion

Chronic wounds represent a global healthcare burden that requires a multidisciplinary approach to achieve wound closure. What makes chronic wounds such a challenge for clinicians to treat are the complexities of a wound, such as moisture management, the presence of tunnelling/undermining, and/or the presence of biofilm. In addition to these challenges, clinicians also must address the patient's underlying chronic comorbidities. With the global rising rates of obesity (Chooi et al, 2019), diabetes (Lin et al, 2020) and peripheral vascular disease (Fowkes et al, 2017), the number of patients dealing with chronic wounds is also projected to significantly increase (Sen, 2019). There are several compounding factors in addition to comorbidities that make achieving wound closure difficult. For example, it has been documented that developing countries have less access to quality healthcare, an inadequate healthcare structure, lack of universal healthcare and limited access to healthcare resources (Gupta et al, 2021). As the complexity of these wounds increases there is a growing need for advanced modalities to aid wound healing. Currently there are no ECM-based products accessible to Malaysian healthcare providers. Unfortunately, this situation is not isolated to Malaysia as many developing countries struggle with gaining access to these advanced technologies (Serena, 2014). By providing patients with an advanced wound

care technology such as OFM, there is potential to heal wounds quicker and improve their overall quality of life (Kapp and Santamaria, 2017). In our initial evaluation of OFM in a range of complex wounds and comorbidities 90% (9/10) of the wounds were deemed closed or improving at the 12 week follow-up with the remaining patient lost to follow-up.

Although developing countries have had limited access to these advanced ECM-based products, developed countries such as the US have been using OFM for over 10 years. To date OFM has been used in a variety of wounds ranging from chronic lower extremity wounds to acute surgical wounds (Liden and May, 2013; Simcock et al, 2013; Bohn and Gass 2014; Gonzalez 2016; Hughes et al, 2016; Ferreras, et al, 2017; Lullove 2017; Raizman et al. 2020). The patients in this retrospective case series demonstrate a similar mix of wound aetiologies including post-operative surgical dehiscence wounds, DFUs, VLU and acute traumatic wounds. Despite the complexities involved in this case series, there was a 57% area reduction at 4 weeks. Percentage area reduction is a key indicator of the likelihood of wound closure (Coerper et al, 2009). Given the difficulty in healthcare access, the average age of the wound on presentation, 55 weeks, was significantly higher than may be expected. Wound chronicity presents another challenge for the clinician as there is likely to be a high level of bacterial bioburden and associated biofilm present on presentation (Grice and Segre, 2012). This in conjunction with elevated levels of matrix metalloproteinases (MMP) in the wound bed can lead to significant difficulty in facilitating wound closure (Metcalf and Bowler 2013; Lazaro et al, 2016). This is where an advanced ECM-based product, such as OFM, can help advance the wound out of the chronic inflammatory phase and into the proliferative phase by modulating the imbalance of MMPs and tissue inhibitor of metalloproteinases (Negrón et al, 2012) as well as preventing biofilm formation (Karnik et al, 2019).

All wounds included in the case series showed significant changes in granulation tissue and 3/10 wounds closed at 12 weeks. Some of the factors that lead to delayed wound closure were difficulty with patient compliance in returning to the clinic for weekly application of OFM, difficulty with maintaining the agreed upon dressing change plan and patients being lost to follow-up for long periods of time. All these factors can elongate the time to full wound closure. Despite the previously mentioned compliance issues, the benefits of OFM can be seen by the improvement in wound bed appearance in 90% of the wounds after the

application of OFM. By providing more patient education, clinician education and improving access to healthcare, one can imagine how these factors would contribute to increasing the percentage of wound closure.

Limitations

As with all retrospective case series, this analysis lacks a control or active comparison, patient and physician blinding and standardisation of procedures. Also, given the difficult access to healthcare on a routine scheduled basis patients were lost to follow-up for periods of time when they were not receiving additional wound care. Additional limitations include a small sample size and uncertainty in previous treatments. On a separate note, patients were not able to provide additional OFM to the wound bed at interim dressing changes outside of the clinic visits. This is contrary to how the dressing is routinely used in other studies where frequent reapplications of OFM have been described to decrease closure times (Bohn et al, 2017).

Conclusions

In this study an ECM bioscaffold sourced from the forestomach of ovine was used by a single wound care clinic providing patients with an advanced healing technology previously not available to this patient population and an additional tool to aid wound closure. This retrospective case series highlights an initial positive experience implementing OFM as part of standard of care and demonstrated positive healing outcomes in complex chronic wounds. The favourable findings demonstrate the need for further study of OFM as an effective and accessible treatment modality for acute and chronic wounds in Malaysia and Southeast Asia.

WAS

Declaration of interest:

SGD and BAB are employees of Aroa Biosurgery Limited (New Zealand). EndoformR was provided by Aroa Biosurgery Limited.

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