Use of acellular intact fish skin grafts in treating acute paediatric wounds during the COVID-19 pandemic: a case series

Objective: More specific strategies are needed to support children requiring skin grafting. Our goal was to identify procedures that reduce operating times, post-operative complications, pain and length of hospital stay. Patient safety, optimal wound bed support and quick micro-debridement with locoregional anaesthesia were prioritised. Ultimately, a novel acellular fish skin graft (FSG) derived from north Atlantic cod was selected for use.

Method: We admitted consecutive paediatric patients with various lesions requiring skin grafting for definitive wound closure. All FSGs were applied and bolstered in the operating room following debridement.

Results: In a cohort of 15 patients, the average age was 8 years and 9 months (4 years 1 month–13 years 5 months). Negative pressure wound therapy (NPWT) was given to 12 patients. Rapid wound healing was observed in all patients, with a wound area coverage of 100% and complete healing in 95% of wounds. Time until engraftment in patients receiving NPWT was reduced by about a half (to an average 12 days) from our standard experience of 21 days. Ten patients received locoregional anaesthesia and were discharged after day surgery. The operating time was <60 minutes, and no complications or allergic reactions were reported. Excellent pliability of the healed wound was achieved in all patients, without signs of itching and scratching in the postoperative period. This case series is the first and largest using FSG to treat paediatric patients with different wound aetiologies. We attribute the rapid transition to acute wound status and the good pliability of the new epidermal–dermal complex to the preserved molecular components of the FSG, including omega-3.

Conclusion: FSG represents an innovative and sustainable solution for paediatric wound care that results in shorter surgery time and reduced hospital stays, with accelerated wound healing times.

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complex wounds • intact fish skin • paediatric complex wounds • skin substitutes • wound • wound care • wound dressing • wound healing

The COVID-19 pandemic has necessitated modifications to paediatric surgical practices to protect patients, families and health workers by minimising the possibility of viral transmission while maintaining reduced surgical site infections (SSIs) and post-operative complications to ensure optimal healing results. The development of a different approach for paediatric surgical grafting procedures, regardless of the cause, was therefore required during this unprecedented time. The following critical points during the admission process were reviewed and adapted into a novel approach:

1. Team-assisted wound care
2. Thorough counselling
3. Microsurgical debridement
4. Ideal graft choice
5. Appropriate choice of surgery
6. SSI prevention.

An updated and specialised dermal substitute pathway was established for children admitted to our hospital (Bambino Gesù Children's Hospital, Research Institute, Rome, Italy) for grafting procedures (for either a one- or two-step procedure) to provide optimal wound care with minimal likelihood of hospitalisation, as identified in Table 1. The COVID-19 pandemic further complicated the pre-existing challenges in wound management of paediatric populations as there was a lack of evidence-based clinical guidelines, so providers relied on published literature and expert opinion in many instances.

Paediatric patients requiring grafting can receive a temporary or a permanent dermal substitute (DS) depending on whether the wound is acute or hard-to-heal. Temporary skin substitutes can be considered a bridge for autografting or secondary intention healing, which can be realised using biologic epidermal substitutes or xenografts. When a permanent DS is advocated, as in wound burns, autologous cultured grafts or acellular allografts can be used, some of which are made of synthetic bilayer devices. Hard-to-heal wounds can be treated using composite allograft and/or

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Table 1. The dermal substitute procedure pathway during the COVID-19 pandemic for paediatric surgical wounds

1. Safety of paediatric patients and their families (proper, meticulous parental counselling)*
2. Appropriate care of all involved wound and periwound tissues
3. Locoregional anaesthesia/reduced general anaesthesia time procedures
4. Favour outpatient/day surgery procedures (early discharge plan)
5. Microsurgical debridement (using magnifying loops or an operating microscope for a meticulously prepared wound bed)
6. Quick dermal/epidermal skin substitute surgical fixation and dressing procedure
7. Simplified wound dressing procedures and related patient counselling
8. Hospital home-caring continuity plan

*Unicef. Coronavirus disease (COVID-19): Information for parents and caregivers on protecting yourself and your family (https://www.unicef.org/parenting/coronavirus-covid-19-guide-parents)

autologous cultured graft.[1] For our purpose of decreased hospital admission, shorter hospital stays and shorter operating times for paediatric patients requiring surgical grafting procedures, there was a need for a hypoallergenic composite skin substitute applied in a single-step procedure with good integration into the wound bed.[2,3]

To achieve the goal of optimal wound management, with shorter operating and inpatient times, we chose to evaluate the feasibility of using acellular fish skin grafts (FSGs) (Kerecis Omega3 Wound; Kerecis, Iceland) as a possible skin substitute option for definitive wound closure in paediatric patients.[4–6] The FSGs are made of intact skin from North Atlantic cod (*Gadus morhua*). FSG is homologous to human skin[7] and is used for tissue regeneration and grafting. FSG is CE marked and US Food and Drug Administration (FDA) cleared for multiple clinical applications in partial and full-thickness wounds. FSG is currently the only acellular dermal matrix product that does not originate from mammalian tissues. There is no known risk of a viral-disease transfer from cold-water fish to humans.[8] The fish skin needs only mild processing, thereby preserving the natural three-dimensional structure and porosity with its inherent chemical components, including collagen, fibrin, proteoglycans and omega-3 fatty acids.[9] When grafted onto damaged human tissue, such as a wound or burn, the FSG facilitates tissue regeneration by supporting revascularisation and cell ingrowth in the proliferation and remodelling phases of wound healing. Unlike mammalian and human-sourced skin substitutes, fish skin has no cultural or religious constraints for usage.[10] Clinical and scientific studies have shown that fish skin promotes faster healing, hard-to-heal wound closure, pain reduction and a reduction in the use of antibiotics, where omega-3 fatty acid content in combination with the skin-for-skin microstructure of the FSG plays a fundamental role.[11–24]

In this prospective case series, we aimed to evaluate the efficacy of FSG for definitive wound closure in the largest paediatric case series to date through reduced healing time while minimising the use of institutional resources such as operating room (OR) time and health provider labour during the COVID-19 pandemic.

Table 2. Patient demographics and wound characteristics

Patient	Age	Sex	Wound type	Wound size (cm^2)	Time to wound closure (days)	Follow-up (weeks)	Complications	Outcomes
1	13 years 5 months	F	AID	3.5	10	82	None	Stable*
2	13 years 1 month	F	MA	7.0	14	80	None	Stable*
3	7 years 5 months	F	PU	4.5	10	79	None	Stable*
4	12 years 3 months	F	SD	6.5	30	77	None	Quite stable**
5	5 years 5 months	M	Abite	14.0	21	75	None	Stable*
6	7 years 2 months	M	Abite	7.5	15	72	None	Stable*
7	5 years 9 months	M	AID	3.0	7	65	None	Stable*
8	5 years 2 months	F	PU	3.5	7	57	None	Stable*
9	11 years 2 months	M	Abite	5	9	49	None	Stable*
10	8 years 2 months	F	MA	12	13	45	None	Stable*
11	12 years 2 months	M	PU	3.7	14	38	None	Stable*
12	4 years 3 months	F	SD	2.0	7	30	None	Stable*
13	11 years 4 months	M	Abite	6.3	8	27	None	Stable*
14	12 years 1 month	F	PU	4.5	14	25	None	Stable*
15	4 years 1 month	M	SD	4.0	8	16	None	Stable*
Mean	8 years 9 months	7M/8F		5.8	12.4	54		

Abite—animal bite; AID—autoimmune disorder; F—female; M—male; PU—sacral pressure ulcer; MA—machinery accident; SD—surgical dehiscence
*Stable: favourable outcome, no retraction, no hypertrophic scar, no relapse, 100% wound care coverage, complete healing
**Quite stable: minimal fish skin graft edge detachment

Method

Patient demographics

A total of 15 consecutive patients were recruited from February 2020 to July 2021 by the Pediatric Division of Plastic and Maxillofacial Surgery (Bambino Gesù Children's Hospital, Research Institute) with complicated wounds of various aetiologies managed with acellular FSG for definitive closure. Data were documented regarding age, sex, wound size, type and time to wound closure, along with adverse events or complications. Table 2 lists patient demographics, wound characteristics and healing outcomes. The complex paediatric wounds managed by the hospital team included postsurgical, autoinflammatory, post-traumatic, pressure injuries and animal bite wounds.

Ethical approval and patient consent

Specific ethical approval was not required for this study; Kerecis FSG is already approved in the US and in Europe, including for paediatric cases. Kerecis has received FDA authorisation to market Kerecis Omega3 and has also been authorised in Europe to market it as the first fish skin substitute. All implants have been performed with products bearing the CE mark under the directive of the European Community (MDD).

Informed consent was obtained in all instances as required by the institutional protocols and detailed counselling was provided prior to any wound management procedure. In addition, all patients/parents/foster parents signed approval for each photograph or film and for use for scientific purposes in a separate hospital consent form.

FSG application method

FSG is supplied as solid, fenestrated or meshed sheets of various sizes, ready to be adapted to the wound bed. The wound bed preparation was performed as micro-debridement; this allows for precise debridement, which is particularly useful in paediatrics as it ensures the removal of all nonviable and necrotic tissue but spares any newly formed islands of epithelial tissue. Typically loops with 3.5–4.5× magnification or the operating microscope up to 8.0× magnification are used in our practice. FSG was handled using an aseptic technique and shaped to fit the wound bed with minimal overlap before or after hydration. The graft was hydrated in room temperature sterile saline for at least 30 seconds as per manufacturer instructions for use. In our experience, a polyhexanide–betaine solution can potentially be used in a contaminated wound field. The graft requires firm contact with the wound bed and can be fixed using sutures, staples or adhesive bandages. In our experience, sutures do not always need to be used to ensure graft stability, thus reducing procedure times. Finally, the FSG requires adequate bolstering to maintain firm contact with the viable wound bed.

The optimal procedure in our centre is to use negative pressure wound therapy (NPWT) to reduce the fixing time, possible SSI, and to limit the hospital length of stay. NPWT was used as a bolstering method in 12 out of 15 cases. When used instead of NPWT, the secondary dressings included sterile TNT gauze or silicone-coated polyurethane foam and a moderate compression with an elastic bandage. Application of backing protocols allowed the time from procedure until discharge to be minimised to 8–12 hours on average. The general procedure of FSG application and considerations regarding the procedure in the context of complex paediatric wounds is summarised in Table 3.

Table 3. The application and management pathway for fish skin graft (FSG) in pediatric complex wounds

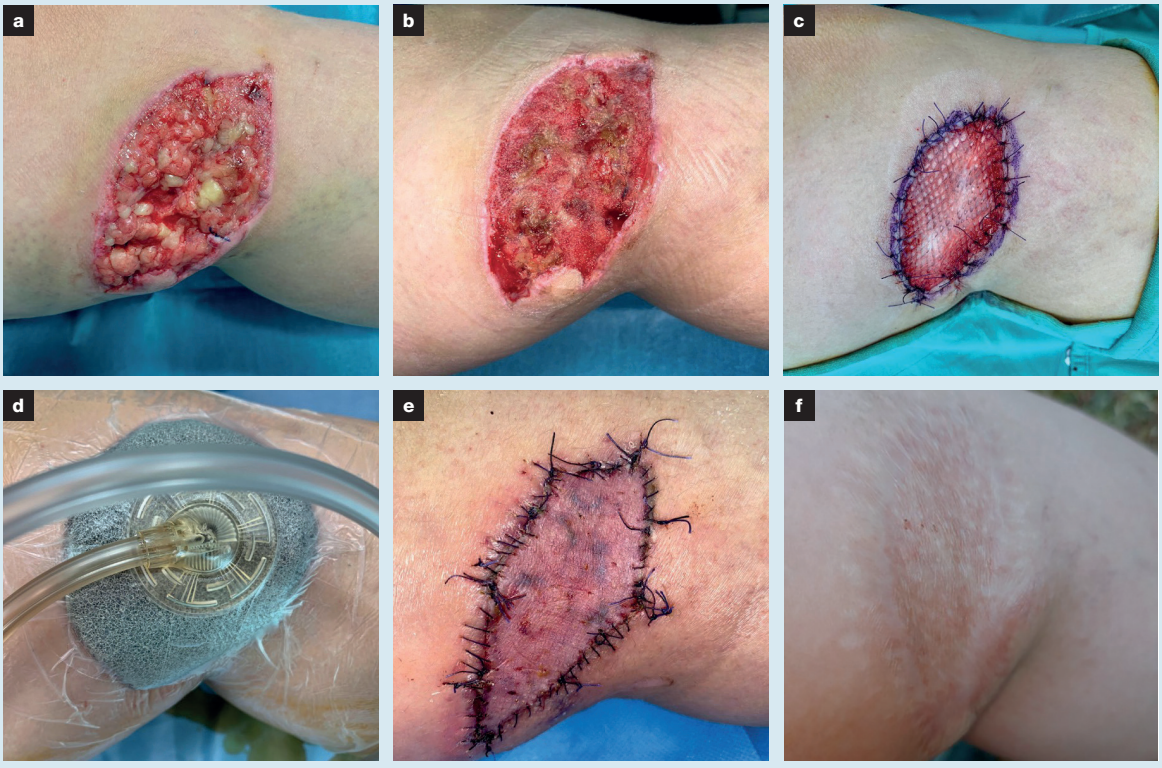
1. Application: various types of partial and full-thickness wounds and soft tissue defects
2. Anatomical area: dependent on wound aetiology
3. Local anaesthesia: used in 50% of the paediatric complex wounds managed with FSG
4. Elastic properties: FSG allows for contraction of wound borders
5. Undermining: separately treated with additional application of FSG to the specific area
6. Repeated applications: possible if required for complete granulation
7. Fixing: 40% of cases, FSG was secured with sutures
8. Best wound bed adherence: adjunctive management negative pressure wound therapy (NPWT)
9. Secondary dressing: standard dressings where NPWT was not used for the entire treatment duration
10. Pain control: achieved within the first 24 hours post application of FSG

Results

Included in the evaluation were 15 paediatric patients, eight female and seven male. The mean age was 8 years and 9 months, ranging from 4 years and 1 month to 13 years and 5 months. Six wounds were of post-traumatic origin (one horse bite, two dog bites, one pig bite, and two lawnmower injuries). Two wounds stemmed from autoimmune diseases (hypocomplementaemia vasculitis and scleroderma), three resulted from surgical dehiscence and four were sacral ulcer wounds.

All animal bite lesions were >5cm in diameter, were heavily contaminated and had extensively exposed subcutaneous tissue. Fig 1 and Fig 2 show the application process and follow-up in two of the animal bite cases. In the post-surgical dehiscence group, all patients had undergone the placement of spinal distractors (Harrington's device) for scoliosis operations: the algorithm in these cases involved the removal of necrotic and non-vital tissues in the operating room and the application of 2–4 cycles of NPWT. The next step was the positioning of the dermal–epidermal substitute (FSG, in this case) and a second cycle of NPWT which lasted on average 11 days for two consecutive changes. Since the back has thick skin and the fixators were only partially removed, all these grafts were covered with partial but high-thickness skin grafts (dermatome positioned 1.2–1.5mm thick). The two

Fig 1. A 6-year-old male patient with dog bite lesion with torn and frayed edges **(a)**, subjected to two cycles of negative pressure wound therapy (NPWT) **(b)**, then microsurgical debridement and graft with fish skin graft (FSG) **(c)** and immediate intraoperative dressing with NPWT (ACTIV.A.C; 3M+KCl, US), 100mmHg, with 50% thick V.A.C. Granufoam silver filler (3M, US), cut out on the lesion **(d)**. Photograph **(e)** indicates the perfect engraftment of the partial-thickness skin graft performed 15 days after the placement of the FSG. The attraction exerted on the edges of the wound by the FSG is clearly visible **(c)**, which also modifies the shape of the lesion itself, making it more oval and with uniform edges. At 14-month follow-up there is excellent aesthetic and functional outcome **(f)**



lawnmower injuries occurred incidentally in the home gardens. In both cases, the lesions resulted in the amputation of a bone segment (first and second toes of the left foot in the first case, and of the back of the foot and of the first toe the second). FSG was applied in both cases after preparing the wound bed with removal of sub-amputated bone fragments and smoothing of the residual stumps.

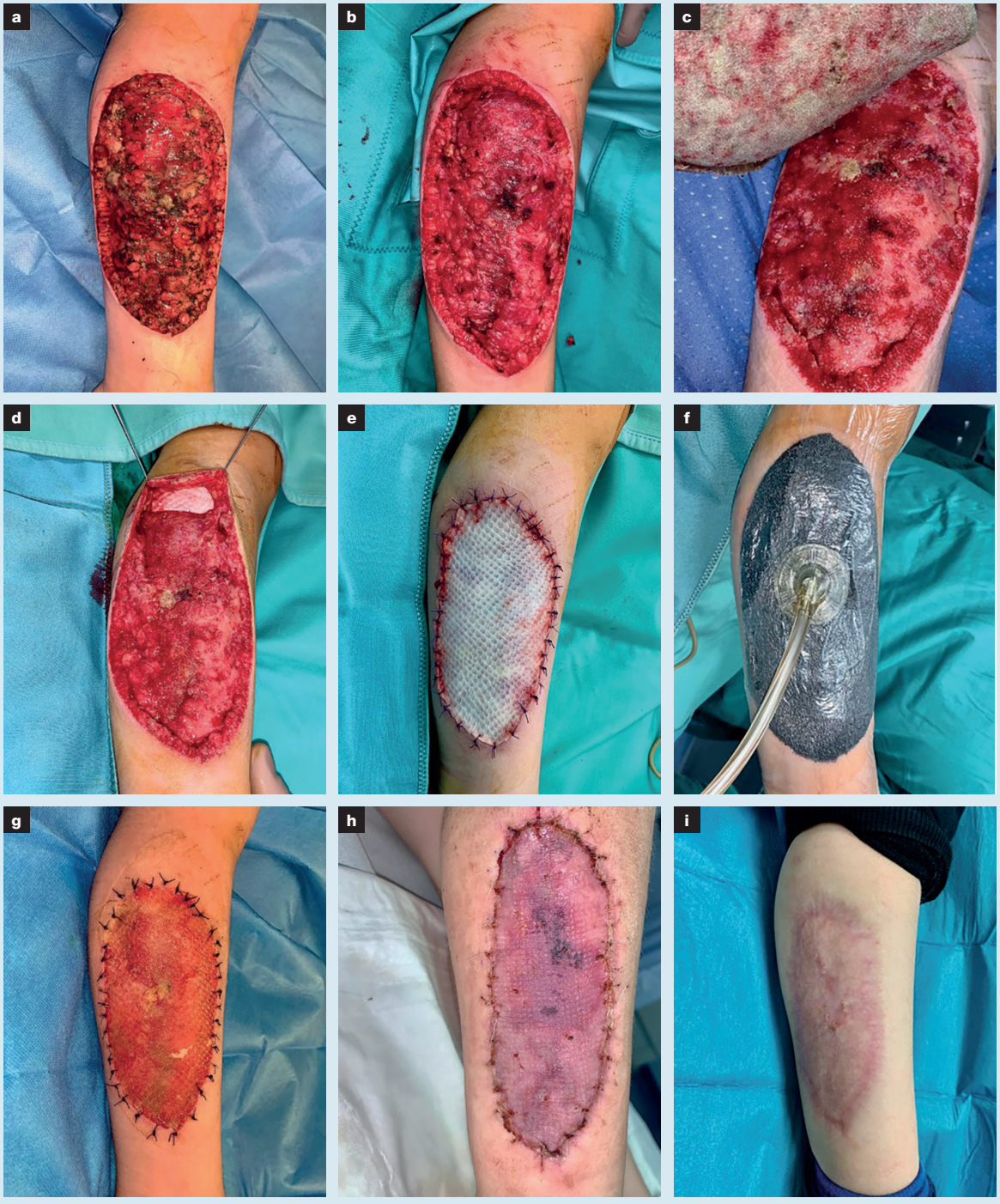
The mean wound area was 5.8cm^2 (range: 2–14cm^2). Patients were followed until up to 82 weeks post-injury, depending on the wound aetiology and healing progression. The average time for follow-up was 54 weeks. Complete healing of the area was achieved in 95% of wounds, with rapid wound healing with full granulation coverage seen in 100% of the patients. On average, two FSG applications were needed for definitive wound closure. The average healing time was 12.4 days.

Twelve patients were treated with FSG in combination with NPWT. The engraftment time in these patients was reduced by about a half to an average of 12 days compared to our standard expected time of 21 days. Only 2–3 dressing changes were required when NPWT was applied. The FSGs were secured with sutures in only 40% of the cases. Furthermore, the potential for staple retention and its associated complications was avoided, making this method potentially beneficial for both medical staff and patients.

Thirteen patients had outpatient surgery with local anaesthesia only and were discharged within 8–12 hours post-procedure. There was a reduction in operating time (average procedure time: 38 minutes, range: 14–50 minutes), depending on the wound area to be covered, compared to our typical procedure time of 60–90 minutes (average 75 minutes). The FSG allowed a 30% reduction of the lesion area due to the elastic properties of attraction exerted on the wound's borders. This effect is particularly useful for the paediatric population as greater natural elasticity of the tissues allows for excellent wound contracture after re-epithelialisation moving to the edges of the FSG.

All of the patients recovered fully without hypersensitivity or allergic reactions. No itchiness was reported, except for one case: in this patient, an itchy lesion was produced in the centre of the dermal substitute but, after 12 months, the desired aesthetic outcome was achieved with no residual scarring. Only a minor surgical dehiscence has been observed in a single patient, but with a final good result. No SSI, or

Fig 2. An 8-year-old male patient with a horse bite on the left leg, with a wound contaminated by herbaceous debris and a large loss of substance of 13×8cm **(a)**. Microsurgical debridement was performed, and then the wound bed preparation was completed with negative pressure wound therapy (NPWT) **(b,c)**. Extensive undermining was filled with fish skin graft (FSG) **(d)**, grafting was performed with FSG **(e)** and secured to the wound base with NPWT **(f)**. Two-week follow-up **(g)**, partial thickness skin grafting **(h)**, and 6-month follow-up **(i)**



other complications were observed. On follow-up, patients did not report any pain.

The skin-maintained sensitivity, important elasticity, and the absence of hypertrophic scars on the margins of the graft. The undermined area was filled with FSG with the intention to provide an optimal healing environment and minimise the risk of contractions or soft tissue defects.

Discussion

Paediatric patients have limited availability of donor tissue. Autografting is not ideal in children as there is an increased risk of donor site infection. Additionally, the dermal layer is thinner and less developed in children when compared to adults and does not allow for the optimal depth of tissue needed for a graft.[25] As children are more susceptible to hypertrophic scarring, functional and cosmetic outcomes require more careful consideration due to the child's continued growth; thus, avoiding scar contracture is particularly crucial. In general, the decision to use skin substitutes is driven by minimising or eliminating donor site deformity. There is a general lack of robust clinical evidence for paediatric wound management, especially for complex wounds.[24] However, the need for reduced OR times in paediatric patients is crucial.

The efficacy and safety of intact FSGs have been widely studied in the adult and geriatric populations. The superiority of FSG has been shown in two different randomised, controlled clinical trials against well-known marketed products: dehydrated human amnion/chorion membrane (dHACM) (EpiFix; MIMEDX, US) and porcine small intestine submucosa (SIS) matrix (Oasis; Smith+Nephew, US). Kirsner et al.[16] conducted a double-blind, prospective, randomised clinical trial comparing intact fish skin to dHACM in acute wounds. Wounds treated with FSG healed significantly faster (hazard ratio (HR) 2.37; 95% confidence interval (CI): 1.75–3.22; p=0.0014) than wounds treated with dHACM. Baldursson et al. conducted a non-inferiority study investigating the healing rate of FSG compared to a porcine matrix in acute wounds.[7] FSG was non-inferior at the primary endpoint, healing at 28 days. Furthermore, the wounds treated with FSG healed significantly faster than those with the porcine SIS product.

The LEG study is a randomised, open-label clinical trial comparing the efficacy of FSG plus standard of care (SoC) to Fibracol Plus Collagen Wound Dressing (3M+KCI, US) plus SoC in the treatment of diabetic foot ulcers (DFUs). The primary outcome measure is wound healing at 12 weeks. Data at an interim analysis showed 67% of wounds treated with the FSG were healed at 12 weeks compared with 36% with Fibrocol Plus, p=0.0318.[26] Full results will be published pending independent data analysis. The clinical effectiveness of FSG has been shown further in a multitude of published case reports and peer-reviewed articles.[7–9,14–22]

Kransnosky et al.[27] described several areas of paediatric wound care which should be considered. These were the cost of product, duration of treatment, ease of product application, accessibility of product, storage of product, and length of time taken to apply or perform the procedure. These were stated as being the most common barriers for use of advanced wound care products among various practices. FSG addresses these challenges by having room temperature storage, a shelf life of 3 years and a simple application procedure. As demonstrated in this study, FSG also reduces the surgical procedure time to under an hour and achieves early full closure of full-thickness paediatric wounds at an average of 12 days. In an independent study, Winters et al. showed that the use of FSG is more cost-effective than SoC in treating hard-to-heal DFUs. The model indicated that fish skin treatment would result in lower costs ($11,210 versus $15,075 per wound), more wounds healed (83.2% versus 63.4%), fewer amputations (4.6% versus 6.9%), and higher quality of life (0.676 versus 0.605 QALY) than with SoC.[28] The cost-saving associated with OR times and faster closure need to be evaluated further for the paediatric population.

The use of FSG has reduced overall procedure times and allowed for prompt discharge, compounded with accelerated healing and good scarring outcomes on follow-up. When used in combination with a non-secured FSG, although not directly assessed, the authors observed a trend towards reducing the time of NWPT.[29] Overall, fewer resources were required to apply intact FSG.

Reflective questions

- What are some of the challenges or barriers to the use of skin substitutes in the paediatric population?
- How does the use of fish skin graft (FSG) address the challenges of managing complex wounds in the paediatric population during the COVID-19 pandemic?
- What are the safety and efficacy outcomes of using FSGs in the paediatric population?

Limitations

The limitation of the study is the small patient number and lack of a control arm to compare against SoC practices.

Conclusion

Intact FSG provides a unique, sustainable and biocompatible clinical solution that improves wound healing in both adult and paediatric patient populations, and is an effective solution in children with complex wounds requiring grafting. This study has successfully demonstrated efficacy, accelerated healing of complex wounds, and safety in the paediatric population. Further controlled clinical investigations using intact FSG for wound management in the paediatric population should be considered to make conclusive decisions regarding its place in wound management in this specific population. JWC

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