Abstract

A 70-year-old female presented with a sacral wound measuring 38 cm^2 in circumference and 1.6 cm in depth. Patient's wound was treated using DermaBind TL (formerly AmnioBind), a terminally sterilized, dehydrated, full-thickness placental membrane allograft consisting of amnion, chorion, and the associated intermediate (spongy) layer. Treatment consisted of covering the wound with DermaBind TL, spraying the membrane with a zinc solution and covering the wound with gauze. Every 6 days the gauze was removed and new DermaBind TL allograft applied over the proceeding allograft. Treatment proceeded for 4 weeks in which time the wound was reduced to 16 cm^2 in circumference and 0.9 cm in depth.

Introduction

As the largest organ of the human body, the skin has a significant impact on various human activities and functions, including protection from pathogens, sensing of the external environment, and thermoregulation [1]. However, as the outermost part of the human body, the skin, due to its elastic and soft nature, is prone to develop wounds [2, 3]. Although human skin is able to repair itself spontaneously to restore its structural and functional integrity, wound care is still paramount to prevent infection and dehydration, relieve pain, protect the open site, accelerate the healing process and prevent scarring, especially in large and open wounds or burns [4-6]. In 2014, there were 17.2 million hospital visits for acute wounds in the United States [7]. Currently, approximately 1-2% of the population in developed countries suffer from chronic wounds [8]. Meanwhile, chronic wounds such as diabetic ulcers, vascular ulcers and pressure ulcers, which have a long and cruel healing time due to disease, aging or inappropriate treatment, not only affect patients' daily lives, but are also associated with high morbidity and mortality [9, 10].

To date, the physiology of wound healing is well understood [11]. The healing process involves four overlapping phases: hemostasis, inflammation, proliferation, and remodeling [5, 12-14]. There are many types of wounds: acute incisional and excisional wounds can undergo a normal healing process, while chronic wounds have aberrant healing conditions [10]. In the clinic, wound healing management varies according to tissue characteristics, intrinsic regenerative capacity, wound classification, and other environmental variables [6, 10, 15-17]. Therapeutic strategies for wounds are diverse and include hyperbaric oxygen therapy [18-20], negative pressure therapy [21], vacuum-assisted closure [22], ultrasound [23], electrotherapy [24, 25], autografts/allografts and xenografts [4, 26, 27], cell-based therapy and engineered skin grafts [4, 28, 29], and topical drug and growth factor delivery [30-32]. Regardless of the wound class and the chosen wound management strategy, a wound dressing is required [33]. Traditional passive wound dressings such as gauze, bandage, and cotton wool would adhere to the skin tissue, causing dehydration and re-injury when removed. In contrast, allograft wound dressings integrate the multifunction of maintaining a moist

environment, managing exudate and protection from pathogens, adhesiveness, and suitable mechanical properties have recently surged and demonstrated extraordinary advantages in more complicated situations [4, 34, 35].

Case

Patient in this case report is a 70-year-old female. When this patient was presented at the clinic, she was non-verbal and incapacitated. Patient had previously been diagnosed with lung disease/lung cancer. In addition, there was a non-healing bedsore wound on the left cheek/sacrum measuring 38 cm^2 in circumference and 1.6 cm in depth.

Treatment of the sacral wound was immediately commenced. The existing bandage was removed, the wound area was then rinsed lightly with saline, and a DermaBind TL allograft (6.5 cm x 6.5 cm) was placed directly on the wound. The allograft was covered with cotton gauze and a zinc solution spray. The allograft was left on the wound for 6 days at which time a new allograft was placed over the previously applied grafts. When a new allograft was applied (approximately each week), the circumference of the wound and depth of the wound were measured to assess progression of the wound toward closure. This treatment regimen continued for 4 weeks.

Based on previous uses of DermaBind TL, the expectation was that the wound would progress from the non-healing state to a healing state. A four-week timeline was not expected to result in a full closure of the wound but significant progress was expected to occur.

Initial visit: 38 cm^2 circumference, 1.6 cm depth, no infection present
Week 1: 30 cm^2 circumference, 1.0 cm depth, no infection present
Week 2: 24.5 cm^2 circumference, 1.0 cm depth, no infection present
Week 3: 17.4 cm^2 circumference, 0.9 cm depth, no infection present
Week 4: 16 cm^2 circumference, 0.9 cm depth, no infection present

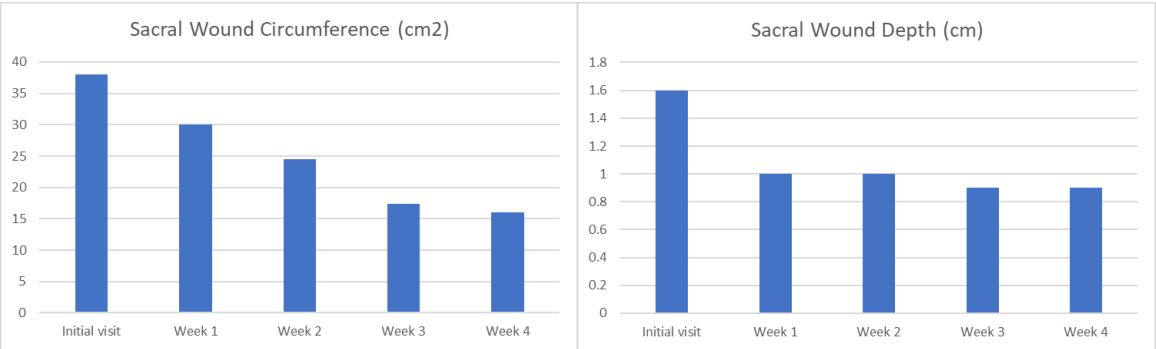

Figure 1. Graphical representation of wound circumference and depth reduction over a 4 week span

Discussion

A patient, 70F, with a non-healing sacral wound, was treated using DermaBind TL for 4 weeks. During this 4 week period, there was a significant reduction in the circumference and the depth of the sacral wound. Through the four weeks of treatment, the wound circumference was reduced by an average of nearly 7 cm^2 per week. This patient's treatment was scheduled to be extended to 12 weeks with the expectation that the use of DermaBind TL could bring this wound to a complete closure. Unfortunately, this patient was deceased before the study could be reached 5 weeks.

The purpose of this case study was to assess the feasibility, ease of use and safety associated with the use of this novel full-thickness placental membrane allograft. The sacral wound treated with DermaBind TL experienced at least a 50% reduction in wound area within 3 weeks of initial application. The authors believe that this is the only case reported in the literature of the use of this therapy. Considering that this patient had previously failed conventional wound treatments, the results obtained support the hypothesis that full-thickness placental membrane allografts are effective in promoting wound healing. No adverse events were observed in the study.

Human amniotic membrane has been used to promote granulation tissue in wounds for over a century. It has been shown to promote new vessel formation in leg ulcers and has bacteriostatic properties [36]. It is sometimes used in developing countries as a low-cost treatment for burns because it has been shown to reduce pain and speed healing [37]. It has been shown to increase the success rate of skin grafting in burn patients [38]. Amniotic membrane tissue is harvested from the placenta after elective cesarean section from mothers who are seronegative for HIV, sexually transmitted diseases (STDs), hepatitis C (HVC), and hepatitis B (HBS) tests, although it is often not feasible to use or store fresh amniotic membrane. Several amniotic membrane products are available to the clinician for use in wound management. These products may be dehydrated or cryopreserved and may contain amnion alone or amnion and chorion. The full-thickness placental membrane product used in this evaluation is composed of both amnion and chorion layers of amniotic membrane derived from the placenta.

In the clinical setting, a randomized controlled trials suggest that placental membrane derivatives can be used to effectively treat diabetic neurotrophic ulcers [39]. In the study by Zelen et al, patients were randomized to receive standard care alone or standard care with the addition of dehydrated Amnion Chorion Membrane (dHACM) every two weeks [39]. Significant differences in wound reduction were observed at 4 weeks after the first application of dHACM, with a mean wound reduction of 32-0% ± 43-7% with standard care (n = 12) versus 97-1% ± 7-0% (P <0-001) with dHACM (n = 13). Overall healing rates after 4 and 6 weeks of treatment with dHACM were 77% and 92%, respectively, compared to 0% and 8-0%, respectively, with standard care (P <0-001). The treatment protocol used by Zelen et al. included biweekly application of a dHACM allograft, which is more longer than the once-per-week application protocol in this study [39]. Although our observations were more limited in scope, the results obtained by

other investigators suggest that research into multiple dHACM applications on wounds of different sources is warranted and will likely yield further positive results in addition to those we observed. In fact, another randomized trial evaluated weekly versus bi-weekly application of dHACM for the treatment of diabetic foot ulcers and found that wounds treated with weekly dHACM application healed faster than those treated bi-weekly [40]. The mean time to healing was only 2-4 ± 1-8 weeks in the weekly dHACM group compared to 4-1 ± 2-9 weeks in the biweekly dHACM group (P = 0-039) [40]. Faster healing with weekly application provides an economic benefit in that these patients require fewer visits and dressing changes to the wound care center and reduce their risk of adverse events.

Chronic wounds are burdensome in terms of both the negative impact on patient quality of life and the financial costs associated with their management. The development of effective, affordable and durable techniques for rapid wound closure is a priority for healthcare systems. Future research comparing the efficacy of skin substitute products and classes is clearly needed, as the current literature can only be used to evaluate product efficacy compared with standard wound dressing techniques. In addition to the efficacy of various skin substitutes, the cost of application must be considered. The investigation of shelf-stable, low-cost allografts could address current clinical concerns by making advanced allografts more widely available to both clinicians and patients by limiting expensive handling practices and production costs. Human amniotic membrane (dHAM) has unique biochemical properties that make it potentially applicable to wound care. dHACM has been developed as a potential vehicle for these properties in a shelf-stable form, limiting product cost and allowing for greater ease of use. The dHACM has been shown to be both clinically and cost effective compared to other advanced wound care products for the treatment of diabetic lower extremity ulcers [41-42]. Considering that DermaBind TL contains the amnion, chorion, and the intermediate (spongy) layer, it follows that a full-thickness placental membrane would have at least similar, if not better, results.

In conclusion, this non-randomized product study supports the hypothesis that placental membrane allografts can be used in chronic wound therapy. These data are consistent with data obtained in similar studies and build on the established history of placental membrane derivative use for non-healing wounds. Future research would require the performance of multicenter randomized controlled trials to evaluate the efficacy of placental membrane in the treatment of chronic wounds of various causes and whether full-thickness placental membrane is more effective in the treatment of these wounds than other currently available products.

Conclusion

DermaBind TL offers an effective and easy-to-use treatment alternative for the management of chronic wounds. Clinical improvement results strongly suggest significant and faster healing, resulting in complete wound closure, in wounds treated

with full-thickness placental membrane-containing products. Chronic wounds that do not respond to other standard treatment options show significant healing and wound coverage with placental membranes. Easy storage and extended shelf life promote clinical acceptance in the wound care environment. Lower complication rates compared to other similar products have been reported in numerous clinical studies. Although DermaBind TL has a higher unit (dressing) cost compared to standard wound care, the overall cost is similar or lower considering the faster healing and presumably lower rate of complications and clinical sequelae such as amputations.

References

1. Colonna M. Skin function for human CD1a-reactive T cells. *Nat. Immunol.* 2010;11:1079–1080. doi: 10.1038/ni1210-1079.

2. Strodtbeck F. Physiology of wound healing. *Newborn Infant Nurs. Rev.* 2001;1(1):43–52. doi: 10.1053/nbin.2001.23176.

3. Harper D, Young A, McNaught CE. The physiology of wound healing. *Surg. Infect. (Larchmt.)* 2014;32(9):445–450. doi: 10.1016/j.mpsur.2014.06.010.

4. Sun BK, Siprashvili Z, Khavari PA. Advances in skin grafting and treatment of cutaneous wounds. *Science.* 2014;346(6212):941–945. doi: 10.1126/science.1253836.

5. Nethi SK, Das S, Patra CR, Mukherjee S. Recent advances in inorganic nanomaterials for wound-healing applications. *Biomater. Sci.* 2019;7(7):2652–2674. doi: 10.1039/c9bm00423h.

6. Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, et al. Burn wound healing and treatment: review and advancements. *Crit. Care.* 2015;19:243. doi: 10.1186/s13054-015-0961-2.

7. Sen CK. Human wound and its burden: updated 2020 compendium of estimates. *Adv. Wound Care.* 2021;10:281–292. doi: 10.1089/wound.2021.0026.

8. Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haughtm R, et al. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. *Value Health.* 2018;21(1):27–32. doi: 10.1016/j.jval.2017.07.007.

9. Powers JG, Morton LM, Phillips TJ. Dressings for chronic wounds. *Dermatol. Ther.* 2013;26(3):197–206. doi: 10.1111/dth.12055.

10. Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. *Adv. Ther.* 2017;34:599–610. doi: 10.1007/s12325-017-0478-y.

11. Singh S, Young A, McNaught CE. The physiology of wound healing. *Surg (Oxford)* 2017;35(9):473–477. doi: 10.1016/j.mpsur.2017.06.004.

12. Mandla S, Huyer LD, Radisic M. Review: multimodal bioactive material approaches for wound healing. *APL Bioeng.* 2018;2(2):021503. doi: 10.1063/1.5026773.

13. Schultz GS, Davidson JM, Kirsner RS, Bornstein P, Herman IM. Dynamic reciprocity in the wound microenvironment. *Wound Repair Regen.* 2011;19(2):134–148. doi: 10.1111/j.1524-475X.2011.00673.x.

14. Li J, Zhang YP, Kirsner RS. Angiogenesis in wound repair: angiogenic growth factors and the extracellular matrix. *Microsc. Res. Tech.* 2003;60(1):107–114. doi: 10.1002/jemt.10249.

15. Rivera AE, Spencer JM. Clinical aspects of full-thickness wound healing. *Clin. Dermatol.* 2007;25:39–48. doi: 10.1016/j.clindermatol.2006.10.001.

16. Madaghiele M, Demitri C, Sannino A, Ambrosio L. Polymeric hydrogels for burn wound care: advanced skin wound dressings and regenerative templates. *Burns Trauma.* 2014;2(4):153–161. doi: 10.4103/2321-3868.143616.

17. Ambrosio L. The role of biomaterials in burn treatment. *Burns Trauma.* 2014;2(4):150–152. doi: 10.4103/2321-3868.143608.

18. Huang X, Liang P, Jiang B, Zhang P, Yu W, et al. Hyperbaric oxygen potentiates diabetic wound healing by promoting fibroblast cell proliferation and endothelial cell angiogenesis. *Life Sci.* 2020;259:118246. doi: 10.1016/j.lfs.2020.118246.

19. Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M, et al. Oxygen in acute and chronic wound healing. *Br. J. Dermatol.* 2010;163(2):257–268. doi: 10.1111/j.1365-2133.2010.09804.x.

20. Rodriguez PG, Felix FN, Woodley DT, Shim EK. The role of oxygen in wound healing: a review of the literature. *Dermatol. Surg.* 2008;34(9):1159–1169. doi: 10.1111/j.1524-4725.2008.34254.x.

21. Huang C, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr. Probl. Surg.* 2014;51(7):301–331. doi: 10.1067/j.cpsurg.2014.04.001.

22. Agarwal P, Kukrele R, Sharma D. Vacuum assisted closure (VAC)/negative pressure wound therapy (NPWT) for difficult wounds: a review. *J. Clin. Orthop. Trauma.* 2019;10(5):845–848. doi: 10.1016/j.jcot.2019.06.015.

23. Kloth LC. Discussion: advanced technologies to improve wound healing: electrical stimulation, vibration therapy, and ultrasound—what is the evidence? *Plast. Reconstr. Surg.* 2016;138(35):105S–106S. doi: 10.1097/prs.0000000000002699.

24. Rajfur J, Pasternok M, Rajfur K, Walewicz K, Fras B, et al. Efficacy of selected electrical therapies on chronic low back pain: a comparative clinical pilot study. *Med. Sci. Monit.* 2017;23:85–100. doi: 10.12659/msm.899461.

25. Ashrafi M, Alonso-Rasgado T, Baguneid M, Bayat A. The efficacy of electrical stimulation in lower extremity cutaneous wound healing: a systematic review. *Exp. Dermatol.* 2017;26(2):171–178. doi: 10.1111/exd.13179.

26. Norouzi M, Boroujeni SM, Omidvarkordshouli N, Soleimani M. Advances in skin regeneration: application of electrospun scaffolds. *Adv. Healthcare Mater.* 2015;4(8):1114–1133. doi: 10.1002/adhm.201500001.

27. Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, et al. Advances in skin regeneration using tissue engineering. *Int. J. Mol. Sci.* 2017;18(4):789. doi: 10.3390/ijms18040789.

28. Horst B, Chouhan G, Moiemen NS, Grover LM. Advances in keratinocyte delivery in burn wound care. *Adv. Drug Deliv. Rev.* 2018;123:18–32. doi: 10.1016/j.addr.2017.06.012.

29. Phua QH, Han HA, Soh BS. Translational stem cell therapy: vascularized skin grafts in skin repair and regeneration. *J. Transl. Med.* 2021;19:83. doi: 10.1186/s12967-021-02752-2.

30. Martino MM, Briquez PS, Ranga A, Lutolf MP, Hubbell JA. Heparin-binding domain of fibrin(ogen) binds growth factors and promotes tissue repair when incorporated within a synthetic matrix. *PNAS.* 2013;110:4563–4568. doi: 10.1073/pnas.1221602110.

31. Braund R. The role of topical growth factors in chronic wounds. *Curr. Drug Deliv.* 2007;4(3):195–204. doi: 10.2174/156720107781023857.

32. Wang W, Lu KJ, Yu CH, Huang QL, Du YZ. Nano-drug delivery systems in wound treatment and skin regeneration. *J. Nanobiotechnol.* 2019;17:82. doi: 10.1186/s12951-019-0514-y.

33. Lei J, Sun L, Li P, Zhu C, Lin Z, et al. The wound dressings and their applications in wound healing and management. *Health Sci. J.* 2019;13(4):662. doi: 10.36648/1791-809X.1000662.

34. Pereira RF, Barrias CC, Granja PL, Bartolo PJ. Advanced biofabrication strategies for skin regeneration and repair. *Nanomedicine.* 2013;8(4):603–621. doi: 10.2217/nnm.13.50.

35. Veld RC, Walboomers XF, Jansen JA, Wagener F. Design considerations for hydrogel wound dressings: strategic and molecular advances. *Tissue Eng. Part B.* 2020;26(3):230–248. doi: 10.1089/ten.TEB.2019.0281.

36. Faulk WP, Matthews R, Stevens PJ, Bennett JP, Burgos H, Hsi BL. Human amnion as an adjunct in wound healing. *Lancet* 1980;1:1156–8.

37. Ramakrishnan KM, Jayaraman V. Management of partial-thickness burn wounds by amniotic membrane: a cost-effective treatment in developing countries. *Burns* 1997;23(Suppl 1):S33–6.

38. Mohammadi AA, Seyed Jafari SM, Kiasat M, Tavakkolian AR, Imani MT, Ayaz M, Tolide-ie HR. Effect of fresh human amniotic membrane dressing on graft take in patients with chronic burn wounds compared with conventional methods. *Burns* 2013;39:349–53.

39. Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J* 2013;10:502–7.

40. Zelen C, Serena T, Snyder R. A prospective randomized comparative study of weekly versus biweekly application of dehydrated human amnion/chorion membrane allograft in the management of diabetic foot ulcers. *Int Wound J* 2013;10:1–14.

41. Fetterolf DE, Istwan NB, Stanziano GJ. An evaluation of healing metrics associated with commonly used advanced wound care products for the treatment of chronic diabetic foot ulcers. *Manag Care* 2014;23:31–8.

42. Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J* 2014; doi: 10.1111/iwj.12395 [Epub ahead of print].