The Use of Dehydrated Human Amnion/Chorion Membranes in the Treatment of Burns and Complex Wounds

Current and Future Applications

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Abstract: Historically, biologic materials found in nature have been used for a wide variety of medicinal purposes, although their widespread use may be limited due to challenges in obtaining and properly preparing the material for safe clinical use. Amniotic membrane has long been recognized to possess unique properties favorable for healing. Dehydrated human amnion/chorion membrane allografts are commercially available for use in multiple sizes and configurations applicable for a variety of clinical settings and presentations. The purpose of this article is to review the therapeutic properties of amniotic membrane.

Key Words: burns, complex wounds, human amniotic membrane

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The ability to cover a wound is both soothing and protective. Exposed nerve endings are calmed, fluid and heat losses are slowed optimizing moisture balance, underlying tissues protected from shear and further trauma, inflammatory and autolytic responses modulated, cellular interactions promoted, and all effected to improve the overall healing process. Familiarity with, and the ever-increasing availability of commercially processed and engineered biologic and biosynthetic constructs have significantly altered the way we conceptualize, understand, cover, and treat our patient's wounds. Although certainly true for current generations of health care providers, there is a long and storied history to the incorporation of biologics found in nature.

Once considered medical waste, amniotic membrane with its unique properties has gained popularity as a treatment for a wide variety of medical conditions and is an example of the current quest for natural agents with regenerative properties. Application of placental membranes for skin grafting and treating burns and ulcerations is found in the Western medical literature as far back as the early 1900s.[1–3] Before the emergence of human immunodeficiency virus and hepatitis C, placental membranes were commonly available from the obstetrical unit in many hospitals and well accepted as modalities for the management of a wide variety of wound types, particularly those of thermal origin, yet due to fear of the potential for disease transmission and other operational issues, the use of freshly acquired amniotic tissue was largely abandoned.

Recently, there have been renewed efforts to preserve placental tissue in ways that retain their natural biological activities so the material can be safely and conveniently used as an allograft in a wide variety of clinical settings. Although there are many methods for processing human tissue, most result in complete removal of cells and DNA, soluble macromolecules, and antigenic and immunogenic macromolecules, leaving only an extracellular scaffold. Recently, a gentle cleansing and dehydration process was developed to preserve and maintain the biological activities inherent in the native amniotic membranes, retaining the natural growth factors and regulatory molecules naturally found in these placental tissues.[4,5] This process has resulted in commercially available dehydrated human amnion/chorion membrane (dHACM) allografts (EpiFix, AmnioFix, EpiBurn; MiMedx Group Inc., Marietta, Ga) that may be stored at ambient conditions with a 5-year shelf life.

THERAPEUTIC CHARACTERISTICS OF HUMAN AMNIOTIC MEMBRANES

Biologics and biosynthetics are generally thought to effect progressive wound healing by a variety of mechanisms. Perhaps, most fundamentally, their focal presence and action serve as a protective dressing, minimizing pain, trauma, shear, local contamination, and fluid loss. Perhaps, even more important is their ability to promote an endogenous cascade modulating the inflammatory response while promoting cellular migration to the wound site and optimizing conditions for repair and/or epithelialization.

The dHACM allograft material matrix contains intact but nonviable cells and is known to contain more than 226 growth factor cytokines and chemokines involved in the regulation of wound healing and inflammation.[5–8] The highest concentrations of growth factors tend to derive from the chorion layer with a notable exception of epidermal growth factor which is found in higher concentrations in the amnion layer.[8] In vitro testing of these constituents are thought to be responsible for fibroblast and endothelial cell proliferation.[6] The propensity to recruit endogenous progenitor cells to the wound site further upregulating the biosynthetic processes while modulating the inflammatory response makes these type of commercially available and easily stored allografts particularly appealing to the wound and burn care specialist.

BURN WOUNDS

Thermal injuries are associated with a wide variety of presentations dependent on depth and extent of the injury, and pathophysiology of both the insult and form, as well as patient health and characteristics, the physical location of the injury, and so many other factors. Delays in presentation and quality of care provided all play important roles in not only the presentation and manifestation of the injury but also in establishing the likelihood of quality and successful healing. True no doubt for a wide variety of wound types.

Application of dHACM for Treatment of Partial Thickness Burns

For many health care providers, the application of human amniotic membranes has proven particularly beneficial in the management

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of partial thickness burns. For a biologic, such as dHACM, to work, it must adhere, protect, and biointegrate into the wound bed. The bed must be clean of debris or eschar and the wound environment neither desiccated nor macerated. A slightly moist quality to the wound bed facilitates this integration and presents a more hospitable environment for cellular migration and proliferation. A gentle cleansing or debridement can often effect this when needed. On removal from the package, the dHACM allograft is parchment-like in nature and imprinted for proper orientation, in this state, it is easy to transfer and fix (Fig. 1). Once moistened by wound fluid, the biologic allograft becomes transparent and sticky, making reorientation a bit more challenging. Our preference is to overlap uninvolved adjoining skin with the allograft by a few millimeters or so, and fix it with either a few drops of tissue adhesive or more commonly in our practice with Steri-Strips (3M). Whenever possible, we prefer to cover the allograft with a nonadherent greasy dressing. Overlying dressings or splints as necessitated by the location of the wound and patient specifics are then applied. With clean partial thickness wound sites, we generally leave it be with few if any dressing changes for 3 to 7 days. It will peel and separate easily when the wound reepithelializes.

Use of dHACM in Deeper and Mixed Burns

Deeper burns are always very challenging wound presentations because the determination of absolute depth and quality of the injury pattern can be difficult, particularly early on, reflecting the dynamic nature of the wound state in evolution. Tissue preservation strategies generally remove inhibitory elements using a variety of technologies, such as enzymatic debriding agents, mechanical tools, waterjet, and in many centers, the application of allogenic skin or xenograft. In our practice, if wounds are demonstrating a propensity to heal but either have plateaued or failed to progress in a timely fashion, we will often change tack and replace the allograft with dHACM. Over the past 3 years, this has proven to be a very valuable and effective way of favorably "jump starting" the wound healing course. We have recently submitted this experience for publication.

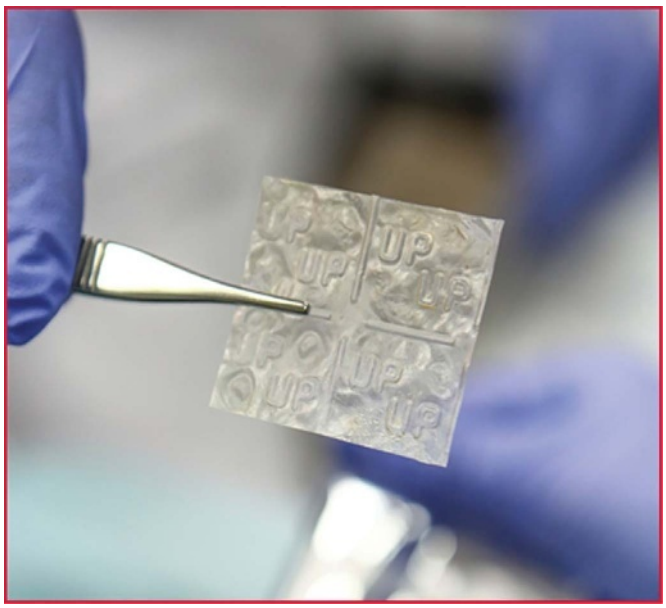

FIGURE 1. The commercially available dHACM allograft (EpiFix; MiMedx Group Inc.).

EVIDENCE SUPPORTING USE OF dHACM FOR WOUND HEALING

Several randomized controlled trials have documented significant improvements in healing both venous stasis as well as diabetic wounds using dHACM.[9–13] In addition, multiple clinical observations of use of dHACM in various wound types, including a diabetic patient with a full-thickness plantar burn,[14] a case of pyoderma gangrenosm,[15] and other patients with challenging nonhealing wounds of various origin[16] have also been published and/or presented as poster presentations at clinical meetings. Of particular note was the clinical observation of improvement in wound bed quality, fill, and closure over exposed vital structures.[17,18] This observation has led several centers to present their experience in the burn setting at a recent conference.[19] These observations although preliminary in nature, stimulated much interest in the use of dHACM as a treatment for thermal injury. As always, time will tell us more as to its ultimate efficacy and reliability as a therapeutic measure.

PERSONAL EXPERIENCE WITH dHACM

As clinicians, we are informed and academically influenced by scientific, peer-reviewed published evidence, complementarily, it is our personal experience and observations that ultimately guide our artful practice of medicine. My first experience using dHACM in the clinical setting presented in 2013 when called to see if I might be able to help treat a premature infant of 24 weeks, a twin, who presented with neonatal candidal sepsis, cardiac and ophthalmic pathologies, respiratory insufficiency, dense tethered band-like constrictions, and what appeared to be deep dorsal as well as ventral cutaneous wounds. The wound sites were gently cleansed and a preliminary allograft dressing placed. I recalled my experience gained as a medical student having witnessed and participated in the care of several patients treated with fresh placental-derived biologics for the management of their burns. With concerns of skin grafting, a very ill and premature neonate weighing heavily on us, we decided to proceed with the newly available (at the time) commercial formulation of amniotic membrane, dHACM. The initial allograft was removed, and the wound site treated with dHACM (EpiFix) covered by a nonadherent greasy silver containing dressing (Restore; Hollister Wound Care, Libertyville, Ill). The child and his wounds responded well with this therapy, rapidly reepithelializing.[20] This treatment regimen algorithm has become a standard part of the therapeutic armamentarium of our burn center.

FUTURE TREATMENTS FOR THERMAL INJURY

In the current state, human amniotic membranes have shown particular benefit as adjuncts in improving healing in a wide variety of wound types. As is always the case, we continue to look to the future for further improvements in the quality and efficacy of our interventions. Economies of scale will hopefully continue to lower the total costs of our interventions. One can easily envision recombinant tissue-engineered derivations, such as: (a) trauma bandages that would not only cover and protect the wound but also encourage healing and hemostasis, (b) the incorporation or further promotion of cellular integrations and vascularization. Improved structural integrity for potential regenerative endeavors, and (c) its potential application as an antiadhesion and reparative agent. Hopefully, in the coming years, we will gain further insight into its effect on scar formation or prevention. There is so much to be studied and learned.

CONCLUSIONS

It is reasonable to envision that as our knowledge and understanding of the complex pathophysiology of the wound and healing states evolve, along with gained experience with the use of human amniotic

membranes, our ability to care for our patients will be optimized. A noble attribute of those dedicated is our propensity to expand horizons, and to develop newer and better ways of caring for our patients. Biologics, such as dHACM, I envision, will play an increasing role in this endeavor.

A mentor and dear friend ingrained in me many salient lessons with regard to the management of wounds. Most notably is that "one must never solely focus on the wound, but rather focus on the whole of the patient," second, "there are wounds and there are wounds … and they are not all the same, they are dynamic in nature and state" and finally "preventive efforts and education while often overlooked are probably the most important determinants of long lasting results and quality of life for our patients."

Optimizing the wound state requires optimizing the patient. Attention to improving overall nutritional status cannot be overstated. Improving hemodynamic, physiologic and vascular status is imperative. Comorbidities and cofactors detrimental to the wound healing process must be managed. Blood sugar control is critical as is the control of edema, both overall as well as that of focal volume status. Minimizing further trauma and pain, meticulous attention to wound bed preparation and protection, minimizing bacterial and biologic burden are all critical for patient healing. Despite the beneficial qualities of biologics and biosynthetics, our efforts are often compromised or doomed to fail without adequately attending to these elements.

The healing and medicinal benefits of amniotic membrane and placental tissue have long been observed. Today, we are gaining a better understanding of the proteins, cytokines, and growth factors contained within the tissue, and methods to obtain, cleanse, and preserve the material allow for its widespread use in a variety of conditions and clinical settings. Treatment modalities, such as dHACM, when used appropriately, are proving to be powerful adjuncts in our rapidly evolving armamentarium. In the future, as more data become available, we will recognize how best to incorporate various biologics into the clinical pathways for the treatment and management of thermal injuries.

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