

Review Article

Hyaluronic Acid Dressings for Burn and Acute Wound Treatment: A comprehensive literature review.

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Citation: Tenenhaus M, Mulder GD, Schultz G (2017) Hyaluronic Acid Dressings for Burn and Acute Wound Treatment: A comprehensive literature review. *Plast Surg Mod Tech* 2: 112. DOI: 10.29011/2577-1701.100012

Received Date: 15 March, 2017; **Accepted Date:** 22 March, 2017; **Published Date:** 30 March, 2017.

Introduction

The treatment of all wound etiologies, including chronic, burn and acute (trauma) wounds has significantly evolved over the last three decades. Thousands of products, including wound dressings, biological matrices, regenerative tissues, growth factors, and topical agents are available to assist with the wound healing process. Extensive literature is available related to the treatment of chronic wounds [1-5]. Changes in the treatments of burns and trauma related wounds are of particular interest as they are often life threatening and pose problems with effective tissue repair [6-8]. The use of biological, synthetic and semi-synthetic matrices are particularly important as they may provide a skeletal structure for cell migration, attachment and activity leading to tissue regeneration and wound closure.

The number of well-designed randomized clinical trials with matrix products for burns and traumatic wounds are comparatively small compared to publications related to chronic wounds. Limited clinical publications are available on the use of hyaluronic acid (HA) for the treatment of complicated wounds despite the important role HA may play in expediting tissue repair and wound closure.

The intent of this manuscript is to review the available rel-

evant publications on HA and HA matrix, particularly an HA Ester, for the treatment of traumatic wounds and burns, and to provide information supporting its potential and beneficial use as an effective and relatively low cost treatment for the surgeon. Extensive literature is available on the use of HA in vivo and in vitro, including the treatment of chronic wounds and scar revision [9-18].

The focus of this review is to provide a brief background on the role of HA in tissue repair and to review published data on the use of a FDA approved HA matrix ester for burns and acute wounds.

Importance of Wound Coverings in Burn and Acute Wound Care

The number of well-designed randomized clinical trials with matrix products for burns and traumatic wounds are comparatively small with reference to publications related to chronic wounds. Limited clinical publications are available on the use of hyaluronic acid (HA) in the complicated wound despite the important role HA may play in expediting tissue repair and wound closure.

Importance of Wound Coverings and Matrices in Burn and Acute Wound Care

Wounds of all types share many commonalities with re-

spect to care and treatment strategies, and yet we have all come to respect the unique pathophysiology and characteristics of the varied wound presentations and etiologies. Thermal injuries and their respective wound presentations pose unique challenges. Burn wounds are generally characterized by depth of injury, evolution in progression as well as total body surface involvement and systemic consequences including the presence of associated inhalation injury for example. To further complicate the issue, thermal injuries may result from a variety of injurious mechanisms such as scald, chemical, radiation, contact, flame, flash, electrical, etc. Delays in presentation or treatment, individual pre-morbid physiologic considerations notwithstanding each wound type presentation remains unique, and while individualized in requisite care, similarly they share common generalized approaches to optimizing wound healing.

Skin is a remarkable and sensate organ, critical for survival, homeostasis and human interaction with the environment and others. It protects us from trauma and pathogens by virtue of its barrier and immunologic function. Skin is crucial in maintaining fluid balance and temperature balance, solar protection, Vitamin D synthesis, while maintaining potent capabilities to heal regenerate and scar. A comprehensive characterization of skin's function and import to life extends well beyond the scope of this text.

The larger the surface area involvement, the more significant the devastating contributions of temperature, fluid and heat losses become. The loss of an external barrier and tissue trauma results in inflammation, exposed pain fibers, pain and swelling. The exposure, desiccation or direct injury to adnexal structures inhibits regenerative healing and wound closure while extending the inflammatory insult, augmenting apoptotic contributors to injury and cell death. Early protection and coverage of clean open wounds helps modulate these effects reducing pain and inflammation, protecting critical underlying structures while reducing fluid and heat losses. These preliminary efforts cannot be overstated in importance as they not only optimize wound healing probability, but potentially limit injury progression and systemic consequence, especially in more extensive surface area wound presentations. It is the amelioration of pain, which contributes so much to the compassionate quality of our care.

Wound dressings have evolved to afford not only a direct barrier coverage function but also to participate or modulate the wound bed. Transudative and exudative elements are absorbed in a variety of wound dressings in an effort to minimize their contribution to impaired re-epithelialization while maintaining a moist (non macerated) wound environment. Semi-occlusive dressings may contribute to autolytic debridement. Slough, exudate, eschar and devitalized tissue components are directly addressed by dressings and topical products containing enzymatic debriding agents.

The use of topical antimicrobial agents, historically proven beneficial in delaying invasive pathogenicity, contributed strongly (in addition to early excisional strategies, nutritional supplementation, specialized burn centers, etc.) to improved mortality rates. The use of biologic matrices such as allograft and xenograft have proven particularly beneficial to the management not only of excised burn wounds, but also as appropriate tissue coverage strategies to facilitate re-epithelialization in more superficial wound states. Biosynthetic matrices bio-integrate into the wound, affording not only a protective element but also contributing physiologically as a matrix for cellular interaction, promotion and migration of local and systemic cell populations.

As is the case in specialized wound care, there is no single ideal wound dressing, matrix or biological cover universally appropriate for wound treatment. The stage and quality of the wound, regenerative potential, functional and aesthetic consequence, distribution, practice, demographics and patient status remains critical determinants. Allergies, pain, availability, cultural and economic sensitivities must all be taken into consideration.

Patients are surviving devastating thermal injuries with increasing frequency. The ultimate determinant of timely and effective wound care can no longer be judged merely by closure or mortality rates but rather must take into account the ultimate functional and aesthetic result.

Hyaluronan Technology

General Background

Hyaluronan, also called hyaluronic acid or hyaluronate or HA, is an anionic, non-sulfated, glycosaminoglycan that is widely distributed throughout connective, epithelial, and neural tissues [2]. Glycosaminoglycans (GAGs) are large linear polysaccharides constructed of repeating disaccharide units with the primary configurations containing an amino sugar, either N-acetyl glucosamine (GlcNAc) or N-acetyl galactosamine (GalNAc) and an uronic acid, either glucuronic acid and/or iduronic acid. Hyaluronan is composed of alternating residues of β -D-(1 \rightarrow 3) glucuronic acid (GlcA) and β -D-(1 \rightarrow 4)-N-acetyl glucosamine (GlcNAc) (Figure 1).

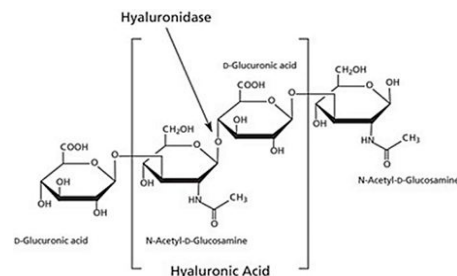


Figure 1: Hyaluronic acid is composed of alternating residues of β -D-(1-3) glucuronic acid and β -D-(1-4)-N-acetyl glucosamine, and is cleaved by hyaluronidases at the β -(1-4) link.

There are five identified glycosaminoglycan polymer chains

Hyaluronan, Chondroitin, Dermatan, heparin/heparin and keratan. Hyaluronan is unique among GAGs because it is non-sulfated, it is synthesized by enzymes that are located in the plasma membrane instead of the Golgi, it is not attached to proteins to form proteoglycans, and it can be very large, with its molecular weight often reaching the millions. For example, Hyaluronan molecules can contain 25,000 disaccharide repeats in length, and the average molecular weight in human synovial fluid is 3 to 4 million Daltons, and hyaluronan purified from human umbilical cord is 3.1 million Daltons [20]. Due to the uronic acid residues, Hyaluronan polymer chains have a strong negative charge at physiological pHs. The average 70 kg (154 lb) person has roughly 15 grams of Hyaluronan in the body, one-third of which is turned over (degraded and synthesized) every day [21].

Biological Synthesis of Hyaluronan

Hyaluronan is synthesized by a class of integral membrane proteins called Hyaluronan synthases (HAS), and vertebrates have three types: HAS1, HAS2, and HAS3. These enzymes lengthen hyaluronan chains by repeatedly adding glucuronic acid and N-acetyl glucosamine to the nascent polysaccharide as it is extruded via ABC-transporter through the cell membrane into the extracellular space [22]. The HAS require UDP-N-acetyl glucosamine and UDP-glucuronic acid as sugar donors, and can generate a 1,000,000 Dalton polymer in less than a minute. A strain of *Bacillus subtilis* has recently been genetically modified (GMO) to synthesize hyaluronans in a patented process producing human-grade Hyaluronan product [23].

Biological Degradation of Hyaluronan

Hyaluronan is degraded by a family of enzymes called hyaluronidases. In humans, there are at least seven types of hyaluronidase-like enzymes. Testicular hyaluronidases degrade hyaluronan to tetrasaccharides, while bacterial hyaluronidases degrade hyaluronan to disaccharides. In lysosomes, hyaluronan is degraded to the monosaccharide's N-acetyl glucosamine, which is recycled, and glucuronic acid, which is further metabolized via the pentose phosphate pathway. The oligosaccharides and very low-molecular-weight hyaluronan degradation products exhibit pro-angiogenic properties [24]. In addition, recent studies showed hyaluronan fragments, not the native high-molecular mass of hyaluronan, can induce inflammatory responses in macrophages and dendritic cells in tissue injury and in skin transplant [25,26].

Physiological Effects and Cell Receptors for Hyaluronan

Until the late 1970s, hyaluronan was described as a "goo" molecule, a ubiquitous carbohydrate polymer that is part of the ex-

tracellular matrix.[27] For example, hyaluronan is a major component of the synovial fluid, and was found to increase the viscosity of the fluid. Along with lubricin, it is one of the fluid's main lubricating components. Hyaluronan is also an important component of articular cartilage, where it is present as a coat around each cell (chondrocyte). When aggrecan monomers bind to hyaluronan in the presence of link protein, large, highly negatively charged aggregates form. These aggregates imbibe water and are responsible for the resilience of cartilage (its resistance to compression). The molecular weight (size) of hyaluronan in cartilage decreases with age, but the amount increases [28].

Hyaluronan is also a major component of skin, where it is involved in tissue repair. When skin is exposed to excessive UVB rays, it becomes inflamed (sunburn) and the cells in the dermis stop producing as much hyaluronan, and increase the rate of its degradation. Hyaluronan degradation products then accumulate in the skin after UV exposure, and as described above, hyaluronan fragments can induce inflammatory responses in macrophages and dendritic cells through toll-like receptor 2 (TLR2), TLR4, or both TLR2 and TLR4 in tissue injury [25,26,29].

As one of the chief components of the extracellular matrix (ECM), hyaluronan contributes significantly to cell proliferation and migration [30]. Three main groups of cell receptors for hyaluronan have been identified: the CD44 receptor protein, the receptor for HA-mediated motility (RHAMM), and the intercellular adhesion molecule-1 (ICAM-1). CD44 and ICAM-1 were well known as cell adhesion molecules with other recognized ligands before their hyaluronan binding was discovered [31].

CD44 is widely distributed throughout the body, and the formal demonstration of HA-CD44 binding was proposed by Aruffo et al. in 1990.[32] To date, it is recognized as the main cell surface receptor for hyaluronan, and the binding of hyaluronan to CD44 functions as an important part in various physiologic events [25,33], such as cell aggregation, migration, proliferation and activation, cell-cell and cell-substrate adhesion, endocytosis of Hyaluronan, which leads to hyaluronan catabolism in macrophages, and assembly of pericellular matrices from hyaluronans and proteoglycans. Two significant roles of CD44 in skin were proposed by Kaya et al. [34]. The first is regulation of keratinocyte proliferation in response to extracellular stimuli, and the second is the maintenance of local hyaluronan homeostasis [33].

ICAM-1 is known mainly as a metabolic cell surface receptor for hyaluronan, and this protein may be responsible mainly for the clearance of hyaluronan from lymph and blood plasma, which accounts for perhaps most of its whole-body turnover [31,35]. Hyaluronan binding to the ICAM-1 receptor triggers a highly coordinated cascade of events that includes the formation of an endocytic

vesicle, its fusion with primary lysosomes, enzymatic digestion to monosaccharide's by hyaluronidases, active transmembrane transport of these sugars to cell cytoplasm, phosphorylation of GlcN Ac and enzymatic deacetylation [19,31,36]. As indicated by its name, ICAM-1 may also serve as a cell adhesion molecule, and the binding of hyaluronan to ICAM-1 may contribute to the control of ICAM-1-mediated inflammatory activation [33].

Hyaluronan in Skin Wound Repair

Healing of skin wounds is a complex process that normally proceeds through the four phases of hemostasis, inflammation, repair, and remodeling.

Hemostasis and Platelet De-granulation.

In vascularized tissues, the first major process that occurs is the activation of pro-thrombin to thrombin which cleaves fibrinogen to fibrin, leading to the formation of the fibrin clot that tamponades the damaged blood vessels and prevents excessive hemorrhage. Equally important to the formation of the blood clot, however, is the activation of platelets, which leads to the release into the fibrin clot and surrounding tissue of preformed, active growth factors and cytokines that are stored in alpha granules. These growth factors and cytokines play a major role in initiating the inflammatory phase by chemo tactically drawing neutrophils and macrophages from the blood into the area of the skin injury [33].

Inflammation.

The wound tissue in the early inflammatory phase of wound repair is abundant in HA, probably a reflection of increased synthesis [33]. Hyaluronan acts as a promoter of early inflammation, which is crucial in the whole skin wound-healing process. In a murine air pouch model of carrageen an/IL-1-induced inflammation, hyaluronan was observed to enhance cellular infiltration [33,37]. Kobayashi and colleagues [33,38]. showed a dose-dependent increase of the proinflammatory cytokines TNF- α and IL-8 production by human uterine fibroblasts at hyaluronan concentrations of 10 μ g/ml to 1 mg/ml via a CD44-mediated mechanism. Endothelial cells, in response to inflammatory cytokines, such as TNF- α , and bacterial lipo-polysaccharide, also synthesize hyaluronan, which has been shown to facilitate primary adhesion of cytokine-activated lymphocytes expressing the hyaluronan-binding variants of CD44 under laminar and static flow conditions [33,39]. It is interesting to note that hyaluronan has contradictory dual functions in the inflammatory process. Hyaluronan not only can promote inflammation, as stated above, but hyaluronan also can moderate the inflammatory response, which may contribute to the stabilization of granulation tissue matrix, as described below in the Repair Phase.

Although inflammation is an integral part of wound healing, inflammation needs to be moderated for normal tissue repair to

proceed. The initial granulation tissue formed is highly inflammatory with a high rate of tissue turnover mediated by matrix degrading enzymes (especially the matrix metalloproteinase's, MMPs) and reactive oxygen species (ROS) that are products of inflammatory cells [33]. Stabilization of granulation tissue matrix can be achieved by moderating inflammation. Hyaluronan functions as an important moderator in this moderation process, which contradicts its role in stimulating inflammation, as described above. Hyaluronan can protect against free-radical damage to cells by its free-radical scavenging property, a physicochemical characteristic shared by large poly-ionic polymers. In a rat model of free-radical scavenging property investigated by Foschi and colleagues, hyaluronan has been shown to reduce damage to the granulation tissue [40,41].

In addition to the ROS scavenging role, hyaluronan may also function in the negative feedback loop of inflammatory activation through its specific biological interactions with the biological constituents of inflammation [33]. For example, hyaluronan also forms a stable complex with TNF-stimulated gene 6 (TSG-6) which in turn binds the serum proteinase inhibitor I α I (Inter- α -inhibitor) and aids its inhibition of plasmin, which ultimately reduces the activation of pro-MMPs by plasmin.

Repair Phase

Cell migration is essential for the formation of granulation tissue, which is the fibrous connective tissue that replaces the early provisional fibrin clot in healing wounds. It typically grows from the base of a wound and is able to fill wounds of almost any size it heals. Hyaluronan is abundant in granulation tissue matrix. A variety of cell functions that are essential for tissue repair may attribute to this hyaluronan-rich network. These functions include facilitation of cell migration into the hydrated provisional wound matrix, and studies show that cell movement can be inhibited, at least partially, by HA degradation or blocking HA receptor occupancy [42]. Cell proliferation and organization of the granulation tissue matrix are also influenced by hyaluronan [33].

Hyaluronan also plays an important role in the normal epidermis. Hyaluronan also has crucial functions in the re-epithelialization process due to several of its properties. It serves as an integral part of the extracellular matrix of basal keratinocytes, which are the major constituents of the epidermis, and it scavenges free-radicals and promotes keratinocyte proliferation and migration [33].

In normal skin, hyaluronan is found in relative high concentrations in the basal layer of the epidermis where proliferating keratinocytes are found [43]. CD44 is co-located with hyaluronan in the basal layer of epidermis where additionally it has been shown to be preferentially expressed on plasma membrane facing the hyaluronan-rich matrix pouches [33,44]. Maintaining the extracel-

lular space and providing an open, as well as hydrated, structure for the passage of nutrients are the main functions of hyaluronan in epidermis. Tammi and other colleagues found Hyaluronan content increases at the presence of retinoic acid (vitamin A) [43]. The proposed effects of retinoic acid against skin photo-damage and aging may be correlated, at least in part, with an increase of skin Hyaluronan content, giving rise to increase of tissue hydration. It has been suggested the free-radical scavenging property of Hyaluronan contributes to protection against solar radiation, supporting the role of CD44 acting as a Hyaluronan receptor in the epidermis [33].

Epidermal Hyaluronan also functions as a manipulator in the process of keratinocyte proliferation, which is essential in normal epidermal function, as well as during re-epithelialization in tissue repair. In the wound healing process, HA is expressed in the wound margin, in the connective tissue matrix, and collocating with CD44 expression in migrating keratinocytes [43,45]. Kaya et al. found suppression of CD44 expression by an epidermis-specific antisense transgene resulted in animals with defective Hyaluronan accumulation in the superficial dermis, accompanied by distinct morphologic alterations of basal keratinocytes and defective keratinocyte proliferation in response to mitogen and growth factors. In addition, decreases in skin elasticity, impaired local inflammatory response, and impaired tissue repair were also observed [35]. These observations strongly support the important roles Hyaluronan and CD44 have in skin physiology and tissue repair [33].

Lack of fibrous scarring is the primary feature of fetal wound healing. Hyaluronan content in fetal wounds is higher than that in adult wounds, which suggests that hyaluronan may, at least in part, reduce collagen deposition and therefore lead to reduced scarring [46]. This suggestion is in agreement with the research of West et al., who showed in adult and late gestation fetal wound healing, removal of hyaluronan results in fibrotic scarring [33].

Medical Uses

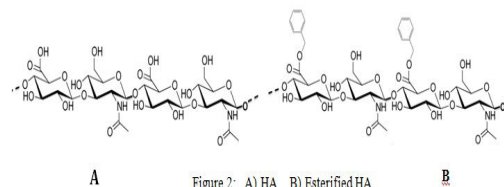
In the late 1970s, intraocular lens implantation was often followed by severe corneal edema, due to endothelial cell damage during the surgery. It was evident that a viscous, clear, physiologic lubricant to prevent such scraping of the endothelial cells was needed [47,48]. A formulation of hyaluronan isolated from rooster combs, sold as Heal on, was very effective as a viscoelastic solution for intraocular surgery that maintained a deep anterior chamber and helped to prevent sheer injuries to the corneal endothelium.

Hyaluronan has also been used in the synthesis of biological scaffolds for wound-healing applications. These scaffolds typically have proteins such as fibronectin attached to the hyaluronan to

facilitate cell migration into the wound. This is particularly important for individuals with diabetes suffering from chronic wounds [49]. However, native hyaluronan has a relatively short half-life (shown in rabbits) [50], so various manufacturing techniques have been deployed to extend the length of the chain and stabilize the molecule for its use in medical applications. These include the introduction of protein based cross-links [51], or the benzylation of the carboxylic acid group of the glucuronic acid units (Hyalomatrix®), which prevents the hyaluronidases from cleaving the hyaluronan chains. As the benzyl ester groups are slowly hydrolyzed off the carboxylic groups by natural hydrolases, the degradation of the hyaluronan undergoes the typical breakdown pathway by hyaluronidases that cleave the hyaluronan chains leading to natural turnover and metabolism of the chemically modified hyaluronan.

Hyaluronic Acid Ester: A Matrix for Clinical Use

Extensive non-clinical literature is available on Hyalomatrix® [HA Ester] as well as HA, supporting the positive effects of HA and HA Ester in expediting wound repair [52-56]. The structures of HA and HA Ester are provided in (Figure 2).



Although the purpose of this brief paper is to review clinical data, a list of publications related to animal and in vitro use is provided in the references [57].

Prospective, single-center, non-randomized study involving 300 pediatric patients with deep partial-thickness burns treated with Hyalomatrix® dermal matrix post debridement of necrotic tissue. A majority of the patients [83%] healed within 21 days, avoided an escharectomy procedure and exhibited healed tissue quality similar to superficial injuries. Results suggested a treatment regime involving dermabrasion with the application of Hyalomatrix® dermal matrix can provide an effective and expeditious wound closure in deep partial-thickness burns and potentially improve tissue quality outcomes [58].

Prospective case study review of 15 patients with extensive full-thickness traumatic wounds treated with Hyalomatrix® dermal matrix. Wounds were large in size averaging 104.4cm² [6 - 490cm²] with a majority involving tendon and/or bone exposure. The wounds were the result of trauma, burns and surgical procedures. Within the six-week study, sixty-six percent [66%] of the burns healed without requiring a surgical graft. The remaining third of the wounds that required a graft procedure to complete

closure had developed sufficient dermal tissue post application of the Hyalomatrix® to support the graft procedure and subsequent healing. Development of infection was avoided in 93% of the cases [59].

Prospective, non-randomized 24-week study of surgical reconstruction for large tissue loss areas after tumor removal. Thirty-six wound sites in 27 patients were evaluated using four different surgical methods: full-thickness skin graft, split-thickness graft, Hyalomatrix® plus split-thickness skin graft or Integra® plus a split-thickness skin graft. The study utilized a standardized measurement device, ultrasound and a 3D scan to evaluate corneometry, transepidermal water loss [TEWL], elastometry, colorimetry, skin thickness and 3D surface patterns of the healed sites. The study was under powered therefore no statistically significant differences were noted between the groups. The authors concluded Hyalomatrix® and Integra “could be recognized as first-choice surgical treatment for both functional and cosmetic soft tissue loss reconstruction in selected cases, and no longer a simple salvage second-line therapy.” Hyalomatrix® provided better cell regulation and stimulation activity, with subsequent production of a regenerated extracellular matrix, and most closely approached the hydration and TEWL of normal skin.

Comparative Evaluations

Comparison study of three burn treatments [60], Hyalomatrix® [HA Ester], Burn shield® [hydrogel] and Derma silk® [semipermeable adhesive film] in two patients with three deep second-degree burns to examine the effect of various new treatment materials for their effect on skin pH variations and epithelialization. Each burn was treated with a separate product to evaluate the pH curve during the healing process. The study concluded that the Hyalomatrix® was similar to other materials used (Burn shield® hydrogel and Derma silk® semi permeable adhesive film,) with respect to the pH curve during the healing process, suggesting a similar effect on the wound bed. No adverse reactions were noted.

Retrospective Studies

Multi-center [61], retrospective study review of 57 patients from 11 burn centers with deep partial and full-thickness burns treated with Hyalomatrix® used as a temporary skin coverage prior to a skin graft procedure or to promote primary healing. Forty-Six percent [46%] of the burns achieved closure without the need for a skin graft procedure. The Vancouver Scar Scale (VSS) score showed no significant differences when patients were classified according to age groups or burn depth. The VSS score also showed no significant differences between patients who underwent grafting versus those who did not, following the Hyalomatrix® treatment. The treatment was found to be a safe and effective approach for deep partial-thickness and full-thickness burns, with-

out adverse reactions, when used as a temporary covering before grafting or alone for wound healing. The authors suggest the HA derived matrix can be used after dermabrasion or surgical debridement to protect the residual dermal layer and possibly stimulate the re-epithelialization from the wound edge and skin appendages in deep partial thickness burns. In full-thickness burns where a full thickness graft cannot be immediately performed, Hyalomatrix® matrix may be used as a “bridge” treatment to temporarily cover the areas that underwent escharectomies to protect and optimize the wound environment until the time of definitive treatment with skin grafts or cultured autologous keratinocytes.

Case Study

Publication reports on six patients [62], age 10 months to 10 years, treated with Hyalomatrix® [HA Ester] on deep second-degree burns and two patients with serious third-degree burns involving 40% and 60% total body surface area. The author has used Hyalomatrix® in burns for three years and reports the product is an effective and practical skin substitute. No adverse events were noted.

Evidence Based Recommendations for Clinical and Surgical Applications

Prior to the application of Hyalomatrix®, wound bed preparation is critically important for the removal of non-viable tissue and bacterial burden. Avoid applying Hyalomatrix® when the wound bed is infected or cannot be adequately prepared. Moderate to high levels of exudates may displace the product and contribute to matrix degeneration. Fenestration is recommended to allow fluid trapped beneath the matrix to escape.

A secondary dressing may be selected and applied based on wound characteristics

Moderate to High Exudates: Absorbent dressings including hydro cellular non-adhesive foams.

Low exudate wounds: May not require a secondary dressing as the silicone layer acts as a protective barrier.

Low exudate wounds with a higher risk of exposure to external disruption or contamination: May be covered with a secondary dressing including gauze or foam dressings.

Gauze dressings or rolls may be used to further secure the Hyalomatrix® between dressing changes or wound examination.

The matrix may be secured with sutures, staples or simply kept in place with a light pressure bolster. Staples and sutures need to be removed in a time span that is customary with the use of these products. It is important that the matrix be in direct contact with

the wound bed and not be disrupted by any external patient or movement.

The secondary dressing should be changed as needed, and the wound site monitored based on the wound and patient status.

The HA derivative is slowly hydrolyzed after application, followed by tissue and capillary in growth. When such growth is optimal, which may be seen between an average of six to ten days, the silicone layer may be detached and separated from the base HA (derivative) layer with ease.

When maximum or desired granulation has been reached, the surgeon may proceed with the treatment of choice, which may include skin grafting or use of topical wound dressings. Additional Hyalomatrix® may be applied when further granulation is desired

Depending on the location, status and etiology of the wound, primary closure may also be considered.

The surgeon will determine the specific treatment protocol, as there are significant differences between patients and wounds, based on wound etiology, medical status and planned subsequent interventions.

Authors' Summary

Limited publications are available on the use of hyaluronic acid derivatives or HA Esters for the treatment of burns and acute (traumatic or surgical) wounds. Clinical trials and presentations were considered to be a low level of evidence with certain trials having poor controls making conclusions difficult to assess

All clinical publications as well as published reviews of the literature conclude that hyaluronic acid products, including HA Ester are safe and effective and are associated with improved wound healing outcomes as well as positive results and benefits for the patients.

Numerous wound dressings and matrices, which vary significantly in cost, ease of application, and recommended use, are available on the global market, for the treatment of burns and acute wounds. Hyaluronic acid based products appear to offer similar advantages to other burn and acute wound dressings, few disadvantages, no significant adverse effects, high level of patient and physician acceptance, and comparatively low cost, making them an excellent choice for the healthcare provider concerned with optimal outcomes in a rapidly changing health economics driven medical world. Despite the data supporting their use, it appears that a significant number of surgeons and healthcare providers are not familiar with the beneficial characteristics and outcomes from using hyaluronic acid dressings, specifically HA Ester. Although large well-designed prospective randomized controlled trials are important and will be forthcoming, the current literature strongly

suggests that surgeons should consider using Hyalomatrix® as a part of their treatment approach for the burn and trauma patient.

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