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Exploring Hyaluronic Acid as a Potential Standard Dressing for Burn Wound

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ABSTRACT

A massive loss of dermis layer such as in deep burn wounds brings several important consequences and complications which contribute to major problems, personally and economically, for the burn patients and their families. Ideal burn wound treatment should not focus merely on removing devitalized tissue, controlling bacterial growth, and promoting healing, but also on accelerating the healing process and preventing scar-related complications. The evolution of biomaterial science for burn wounds has provided physicians with novel dressing materials based on natural and also synthetic polymers, and the latest development introduces the use of hyaluronic acid (HA) as a potential burn wound dressing. HA has been studied to have involvement in many phases of the wound healing process, such as inflammation, granulation, and re-epithelialization. Dealing with the unfavorable physical properties of the native polymer such as solubility and rapid degradation, modification and improvement are designed to produce insoluble molecules to facilitate hyaluronic acid-based (HA-based) wound dressing products as a valuable option for the treatment of deep burns. Our literature review shares the development and the outcome of the use of these products in burns. The currently available clinical experience suggests that these HA-based wound dressing products provide a safe therapeutic method useful for the treatment of acute burns and minimize scar-related complications, although further improvements are still required to make an ideal HA-based wound dressing product for standard burn wound treatment.

KEYWORDS: Burns; hyaluronic acid; wound healing; dressings

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INTRODUCTION

Burns remains a significant, preventable cause of morbidity and mortality worldwide. Each year, over 300,000 people are estimated to die from fire-related burn injuries. Burn-related disability and disfigurements are also major problems which cause secondary effects, personally and economically on the patient and the family. It is estimated that annually 10 million Disability Adjusted Life Years (DALYs) are lost globally due to fire-related burn injuries, among which are more than three million South-East Asian's.[1]

Managing a burn wound is challenging because of its dynamic process; it can progress or regress into a more severe form over time, depending on the initial injury and subsequent environmental insults. Wound conversion can occur as the viable tissue beneath the layer of necrosis can become non-viable over time. Therefore, treatment must be continuously adapted to the changing wound biology which depends on the burn injury process, the host response to injury, and the wound environment.[2]

Most topical therapy for burn wounds focuses on removing devitalized tissue, controlling bacterial growth, and promoting healing but ideally, burn wound treatment should also aim to accelerate the healing process and prevent complications by maintaining the deposition of collagen in scar tissue. The decision of choosing the right wound dressing must also consider the effects of healing, the feasibility of application and removal, the comfort of the patient, and cost-effectiveness.[3]

Hyaluronic acid (HA) has been used widely as one of the biological materials which contain essential features such as biocompatibility and show no immunogenicity-inducing component.[4] It has been used for treating dermal and

epidermal injuries, including burns. HA has been shown to modulate the three phases of wound healing through migration of cells, inflammatory response, and angiogenesis.[5,6] However, some research also found that HA had unfavorable mechanical properties, a fast degradation rate, a high swelling ratio, and non-controlled drug delivery which limit its use as an optimal burn wound dressing.[7]

METHOD

Taking the complexity of burn injury into account and considering HA's conflicting evidence as burn wound dressing, we made this literature review to conduct a further investigation about the potential use of HA in burn wound healing, the rationale behind hyaluronic acid-based (HA-based) materials for burn wounds, the types of HA-based dressing for burns with related clinical evidence of their application, and the effectiveness and safety of HA-based dressing compared to the other existing wound dressings. We assembled scientific articles that met the keywords "hyaluronic acid", "burns", "wound healing", and "wound dressing" from the last 20 years as the references for our review.

RESULTS

HA in wound healing

HA is one of the structural components of a human extracellular matrix (ECM) which is important for fluid homeostasis and beneficial for tissue hydration and wound healing. HA molecules can swell up to 1000 times in volume[6] and absorb up to 3000 times their weight when absorbing water[8]; these may be the main reasons behind many of its biological properties.[6] The solutions of HA are extremely osmotic because of their high hygroscopicity, and this factor plays important role in the regulation of skin tissue hydration as it facilitates the re-epithelialization process by maintaining a moist environment.[6]

HA has also been observed to have different roles in the human body depending on its molecular weight property, and one of its roles is in the wound healing process. Many studies suggest that HA play role in every phase of wound healing, from the initial formation of clot and platelet plug to remodeling. During clot formation, HA binds to fibrinogen and helps to loosen the clot while at the same time aiding in stabilizing it.

In the inflammatory phase, intermediate-sized HA fragments help attract polymorphonuclear (PMN) leukocytes while high molecular weight-hyaluronic acid (HMW-HA) limits the intensity of the myeloperoxidase reaction and free-radical injury of tissues, thus decreasing the inflammation intensity. Furthermore, HA fragmentation also induces mononuclear cells into the wound.

In the proliferation phase, HA fragments prompt mitosis, sprouting, and tropism of endothelial cells, which provide for angiogenesis and neovascularization. HA also plays role in the differentiation of fibroblasts into myofibroblasts and constituting the matrix of granulation tissue. Furthermore, HA stimulates migration and proliferation of fibroblast, synthesis of collagen type III by fibroblast, and provides extracellular matrix together with fibronectin.

In the remodeling phase, HA level decreases and this possibly stimulates continuous deposition of collagen type I which contributes to the greater tensile strength of the wound. During re-epithelialization, it is found that HA, bound to a transmembrane glycoprotein CD44, faces the wound margin, and this complex may continue regulating keratinocyte proliferation and migration until the wound heals completely.[5] Therefore, HA is an advocate of the entire process of wound repair by driving both the inflammatory and reparative processes of wound healing through changes in its polymer size.

Endogenous HA is found in relatively high concentrations in the basal layer of the epidermis, and especially high in granulation tissue during the proliferative phase of the wound healing process. Its primary function is associated with the three-dimensional architecture of the extracellular space, the hydration structure for nutrient flow, and the involvement in keratinocyte proliferation and migration. On the subject of exogenous HA, as a modulator of many biological processes, it is very much involved in the early phases of tissue repair and wound healing, and notably crucial in controlling the angiogenic process.[5,6] Angiogenesis inhibition is related to HMW-HA, while angiogenesis acceleration and collagen production in endothelial cells is associated with the oligosaccharides of low molecular weight-HA (LMW-HA). Some research also found that the matrix cells responsible for scar formation might also be inhibited in an HA-rich environment.[6]

Exogenous HA has thus been investigated in wound healing topical applications and various studies supported the effectiveness of HA even in various challenging types of wounds. However, this potential substance has limitations in its natural state, such as short residence time in vivo and its solubility, hence several modifications must be applied to enhance HA resistance to degradation.[6]

The rationale behind HA-based materials for burn wounds

Burn wounds, especially partial-thickness and full-thickness types, involve losing the dermal layer of the skin massively, and their healing can only occur by restoration of the full-thickness dermal layer. Re-epithelialization and the resulting wound closure are possible only when a proper dermal bed has been developed. The gold standard is by applying autologous skin (i.e. skin grafts) to cover the wound, but this procedure is not always possible: for example if the burn wound area is larger than 50% total body surface area. Should the skin grafts be harvested from cadaver skin and cryopreserved, the risk of viral transmission is not favorable

for the ideal outcome. Therefore, a synthetic dermal substitute together with advanced wound dressings is crucial for promoting wound healing and minimizing scarring and contracture. Studies on various biomaterials to find and develop a biocompatible and biodegradable polymer which is effective and safe for burns have been conducted, including studies on HA.[6]

The effectiveness of HA for burn wound treatment is based on its regulatory activity at every phase of wound healing. As previously stated, HA is actively involved in the inflammatory, proliferation, and remodelling phase of the wound healing process, therefore it has a significant role in accelerating wound healing as well as improving the quality of the scar.[5,6] As the goals of burn wound treatment revolve around accelerating wound healing and reducing the scar-related risk of complications like contractures, hypertrophic scar, and keloid[9], it is reasonable to take HA into account when considering a suitable candidate for an effective burn wound dressing.

In the aspect of patient safety, adverse events following HA administration should not be expected as it is a physiological bio-component of the human body and reported adverse events related to HA administration are rare and transient. Different forms of HA may have different risks of adverse events[10], and current clinical evidence suggested that HA is likely safe when taken by mouth, applied to the skin, given as a shot, and applied to the eye when used appropriately, with the rare case of allergic reaction and local side effect.[11]

Types of HA-based dressing for burns and their clinical evidence

Various HA-based dressing products have been studied, applied, and evaluated for their effectiveness and safety profile in burn wounds. The purposes of the substantial combination include achieving the optimal benefit of all substances involved and enhancing HA resistance against bio-degradation, hence prolonging its bioavailability.

HA derivative polymer

A HA derivative polymer obtained by the esterification of the free carboxylic group of glucuronic acid with benzylic alcohol, called HYAFF® 11, has been developed and applied in the clinical setting. This process aims to improve the polymer stability with the preservation of the starting molecule's biological and safety characteristics. In vivo study showed that HYAFF® 11 is bio-compatible and safely degraded within the human body.

Examples of HA-based medical devices using HYAFF® 11 are Hyalomatrix and Hyalosafe. Hyalomatrix is a sterile, bi-layered dermal substitute with the character of being flexible and conformable, designed for immediate wound closure and promoting the permanent regeneration of the dermis. The HA is released from the HYAFF® 11 fibrous matrix layer once it comes in contact with the wound bed in a prolonged manner which allows epidermal cell migration, resulting in new dermal tissue reconstruction, or even spontaneous re-epithelization.

Hyalomatrix is used for immediate coverage following surgical excision and before skin-grafting of deep burns for wound bed protection. In second-degree burns, it can also be used to protect the residual dermal layer and stimulate the re-epithelialization of the wound after the removal of necrotic tissues.[6] A histological study on adult patients undergoing surgery for hypertrophic scar or keloid and subsequently treated with Hyalomatrix PA demonstrated that it increased collagenization and decreased vascularisation, supported clinically by the improvement of the Vancouver Scar Scale.[12]

Hyalosafe is a transparent film wound dressing using the same technology HYAFF® 11 for the effective coverage of first and superficial second-degree burns. The film containing HYAFF® 11, when applied to the wound, releases HA as a result of HYAFF® 11 degradation, and thus creating the ideal condition for rapid re-epithelialization and facilitating the renewal of the epithelium. The removal of this film is painless since it is not adherent.[6] This HYAFF® 11 film has also been reported in the treatment of second-degree face burn in pediatric patients, showing very good healing properties and aesthetic results.[13] A retrospective study of 54 adult patients with facial partial-thickness facial burn injury who were treated with Hyalosafe also showed good effectiveness and safety, with additional benefits i.e. acceptable pain scores and scar formation, single application, no-repeat dressing change required, outpatient treatment, and no specific tools for fixation needed.[14]

The combination of HA with other substances

The conjugation with antitumor necrosis factor-α (anti-TNF-α).

Tumor necrosis factor-α (TNF-α) is one of the pro-inflammatory cytokines which drive many of the cellular processes in association with burn progression. The level of this cytokine is significant in burn wound tissue and wound fluid, and it is involved in the inflammatory processes including leukocyte chemo-attraction, increased cytokine production, and the expression of cell adhesion molecules.[15] It has been suggested by some studies that dysregulation of inflammation may slow the healing process or promote scar tissue formation and that targeting TNF-α signaling in early responses to injury may be beneficial for therapy.[16] To achieve the localized delivery of TNF-α inhibitors, conjugation of an anti-TNF-α antibody to a high molecular weight polysaccharide such as HA is a solution.[17] HMW-HA itself has been shown to have some benefits in wound healing such as supporting migration, proliferation, and cytokine production of fibroblasts while showing immunosuppressive effects and radical scavenging properties.[18]

The conjugation of HA into anti-TNF-α is beneficial in terms of prolonging the latter's time in the injured tissue,

thus increasing its effect. An animal study found that the conjugation of the antibody to HMW-HA slowed antibody diffusion in the wound bed by a factor of 6. A study of diffusion measurements in collagen matrices also showed a significant decrease in the mobility of antibodies due to HA conjugation. Antibody clearance was found to be delayed as well, due to the large molecule of intact (anti-TNF-α)-HA hindering it to be cleared through blood vessels until it was extensively degraded. This pattern change in the antibody distribution was also found to be correlated with changes in inflammatory-cell infiltrate, suggesting the importance of the increased residence time for preventing inflammation-induced necrosis on burn tissue.[19]

Another study found that there was a decrease of PMN infiltrate thickness in the HA- containing groups compared with free anti-TNF-α and saline controls, with more dispersed PMN found in a higher dose of treatment. This difference in PMN infiltration and accumulation may be related to the physical or biochemical blockade of HA, probably by an inhibitory effect on PMN chemotaxis and phagocytosis.[16]

The combination with silver sulfadiazine (SSD)

Since SSD is widely adopted as the topical therapy of choice for burns, HA combination with SSD has been studied to find the combined benefit of both materials for burn wound healing. A double-blind, controlled clinical study by Koller assessing the efficacy of HA and SSD for partial thickness burn patients suggested this combination can reduce both healing time and local edema, and demonstrated good antibacterial, anti-edematous and local analgesic effects, with a clear stimulatory activity on the re-epithelialization process compared to single therapy of SSD.[20] Another clinical study by Costagliola et al. on the same objective and population also found statistically significant faster healing of burn wound compared to single therapy of SSD. Both studies found no significant adverse effect of this combination, hence it was safe locally and systematically.[21]

The combination with other substances as scaffolds

One of the innovations in burn therapy is the use of scaffolds containing biomaterials, which is important in various dressings and tissue-engineered constructions. The concept is the imitation of skin ECM, which consists of collagen, elastin, proteoglycans, nidogen, laminin, and perlecan and its properties. Collagen provides the skin's strength, elastin ensures its elasticity and flexibility, with its hydration and viscosity provided by proteoglycans. There are many choices of biomaterials of various origins (natural, synthetic, or semi-synthetic) used in scaffold fabrication but the main requirements are biodegradability, temporary mechanical support, and permeability. Scaffolds may be with or without cells; the latter can further be grouped into dermal, epidermal, and epidermal-dermal composites.[22]

The consideration of HA as one of the biomaterials in constructing a scaffold is reasonable as it is one of the important polysaccharide components of the ECM, and HA-containing scaffold application in burn treatment had been studied widely. Various materials have been studied in combination with HA as a scaffold, such as chitosan, pullulan, gelatin, glycosaminoglycan (HA and chondroitin sulfate), and dextran for burn treatment, mostly in vitro. The majority of the result showed that the combination of HA with other substances as the scaffold was beneficial in comparison to control, with evidence including significant progress in re-epithelialization, collagen fibers arrangement, and angiogenesis; a decrease of TNF-α and an increase of matrix metalloproteinase (MMP) 2 expressions; long-duration drug release, effective antibacterial activities and wound regeneration ability; faster healing process supported by the finding of complete re-epithelialization with less damaged tissue zone diameter compared to the control.[23–27] One study stated that HA's role as one of the components was helping in swelling and slow release of the active ingredients into the system.[25] Based on current studies, HA seems to have the potential to be one of the biomaterials to fill in a scaffold.

The combination with other substances as hydrogels

Hydrogels are polymer-based materials which have a three-dimensional (3D) structure formed by the cross-linked hydrophilic polymer chains, with high water content and physical characteristics mimicking the native ECM. Due to the favorable characteristics e.g. similarity to native ECM, high biocompatibility, tuneable physical, chemical, and biological properties; and versatility in fabrication, hydrogels have been used in a wide range of applications, one of those being an appropriate drug delivery system.[28]

HA combination with various substances in a form of hydrogel therapy for burn injury has been studied for its biocompatibility and roles in wound healing. The majority of the studies showed that HA is effective as a component of the topical system which enables the achievement of the desired mechanical properties in terms of antimicrobial and wound healing effects while being relatively safe.[29–32]

Current evidence of HA-based dressing effectiveness and safety compared to other dressings

Some studies have been conducted to compare the safety and effectiveness of HA to the other modalities in burn treatment. One study compared the cytotoxicity and wound healing effects of HA and two commonly used hydrogel matrices—carbomer and sodium alginate—on skin cells in vitro. The repairing ability for thermal-injured keratinocytes and the effects on cell migration were investigated to evaluate the wound-healing effects. The result of this trial showed that different molecular weights of HA showed no toxicity, even at the concentration of 0.5%, while mild or moderate cytotoxicity was found in carbomer and sodium alginate when their concentrations were higher than 0.1%. HA was

also superior compared to carbomer and sodium alginate in repairing the thermal-injured cells and proliferation and migration of keratinocytes.[33]

The other study comparing the clinical effect of the topical application of ozonated oil versus HA for 12 weeks in the phase of re-epithelialization of second-degree skin burns in vivo in 30 patients showed that HA was as potent as ozonated oil in reducing symptoms related to skin burns (erythema, tension, itching and burning sensation reported by patients) when topically applied for 12 weeks, but less effective in preventing the post-lesional hyperpigmentation. The major limitation of this study is the lack of a histological comparison due to ethical reasons, therefore evaluation of the mechanisms that regulate the effects of HA and ozonides on burned skin could not be conducted.[34]

A systematic review involving two randomized controlled trials with a random distribution of 143 patients, evaluating the outcome of partial-thickness and/or deep partial-thickness burn complete healing using HA compared to other covers and/or solutions found that there was a statistically significant mean healing time in favor of intervention groups (HA and SSD) compared to controls (single therapy of SSD).[35]

There is also a systematic review and meta-analysis done on randomized controlled trials regarding HA derivatives and their healing effect on burns and other wounds which suggested that overall, the positive effect of HA was found in the healing of burns, and other included types of wounds no matter the form in which HA was delivered topically. This review analyzed three trials examining the effect of HA versus placebo and HA combined with SSD versus single therapy of SSD in the healing of burn patients. For the former, two studies involving a total of 125 patients evaluating the complete healing and rate of healing found that complete healing occurred faster significantly with placebo in one study but faster healing was observed with HA in another one. For the latter, a study involving 110 patients resulted in significantly faster complete healing with a combination of HA with SSD compared to single therapy of SSD.[36]

Most studies on HA-based dressing for burn treatment are conducted on partial-thickness burns. For deeper burns, a multicentre retrospective study of HA-based dressing (Hyalomatrix PA) on deep partial and full-thickness burns found that only 32.7% of participants achieved complete wound closure after 29 days, and 85.7% in 37 days.[37] Normal healing times of deep partial-thickness burns and full-thickness burns are estimated to be 14-21 days and over 21 days respectively[9], so the healing time in this study was prolonged. These unfavorable results could be attributed to the higher risk of infection in deeper burns, hence the incorporation of HA with antimicrobial agents has been studied to overcome this issue.[38]

DISCUSSION

HA plays role in every phase of wound healing, from the initial formation of clot and platelet plug to the last phase of remodeling. The hyperosmocity and hygroscopicity of HA plays important role in the regulation of skin tissue hydration and in creating the ideal moist environment that facilitates the re-epithelialization process.[6]

While endogenous HA—established mainly in the basal layer—is associated with the three-dimensional architecture of the extracellular space, the hydration structure for nutrient flow, and the involvement in keratinocyte proliferation and migration during the first week of wound healing, exogenous HA is notably crucial in controlling the angiogenic process during the proliferative phase.[5,6] With controlled angiogenesis, the risk of hypergranulation can be avoided, the re-epithelialization process can take place in an ideal environment, and the risk of hypertrophic scarring is minimized.

The effectiveness of HA for burn wound treatment includes—based on its regulatory activity at every phase of wound healing—both accelerating wound healing progress and improving the quality of the scar, which subsequently minimizes the scar-related risk of complications like contractures, hypertrophic scars, and keloids.[5,6,9] Numerous experimental studies, both in vitro and in vivo, have shown that HA-based dressing is effective and safe for burn wound treatment, especially in partial-thickness burns (grade IIA and IIB). For deeper burns, less favorable results still need further attention, which is probably due to the higher risk of infection in deeper burns. Incorporating HA with antimicrobial agents has been evaluated to successfully overcome this matter.[38]

HA-based materials used for burns dressing are also available in a wide range of preparation, such as cream, hydrogel, transparent film dressing, dermal substitute, and scaffold, with various concentrations. Adverse events following HA administration are rare and transient, and current clinical evidence suggests that HA is likely safe when taken by mouth, applied to the skin, given as a shot, and applied to the eye when used appropriately, with the rare case of allergic reaction and local side effect.[11] Such a broad variety of HA preparation and concentration in the market needs future research with a focus on which preparation and concentration of HA-based dressing are most effective for burn wound treatment, especially for partial and full-thickness burns.

CONCLUSION

The superiority of HA namely its bio-compatibility, its absence of immunogenicity-inducing risk, and its role in all phases of wound healing supports its use in various wound treatments, including for burn wounds. Burns involving partial or complete dermal loss need wound dressings and/or dermal substitutes to promote wound healing, and all of the studies reviewed in this article suggested that HA-based

dressing —as a single modality or in combination with other substances— can serve as an effective and safe solution not only to achieve that goal but also to improve scar quality and minimize scar-related complication such as keloids and contractures. There is still room for improvements, especially regarding its effectiveness for deeper burn wounds, but with more research and clinical trials on its effective preparation, combination, and concentration, the HA-based dressing may live up to the expectancy as a potential standard dressing for burn wounds.

Author Contributions

Agustini Song: data collection, data analysis and interpretation, writing the paper

Ahmad Fawzy: study concept and design, data analysis and interpretation, writing the paper

Conflict of Interest

The authors declare that there is no conflict of interest.

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