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Healing and Antimicrobial Properties of Connext® Surgical Matrix

Introduction

Proper management of wounds and surgical site defects is a critical aspect of plastic, reconstructive, and general surgery procedures. Wound healing is a complex physiological process involving tissue repair and regeneration. Inherent variables such as tissue pathology, closure technique, patient health status and procedure-related trauma are significant factors that can disrupt the normal healing cascade. Altered or impaired wound healing is marked by interruption of the healing process by adverse events such as persistent inflammation, infection, seroma and adhesion formation. Surgical site infections have shown to increase mortality, readmission rate, patient suffering, poor surgical outcomes and financial costs.[1] In the case of mastectomy procedures, the incidence of infection rates was 10.7% for patients requiring mastectomy with implants.[2]

Connext® Surgical Matrix is a purified, low pH, 100% type I bovine collagen powder indicated for the management of complex wounds. The powder format is provided in an easy to use bellows applicator that allows the surgeon to consistently administer the desired amount of Connext® Surgical Matrix to the site easily and efficiently. Connext® delivers a highly absorbent matrix (up 30x its weight) that neutralizes wound exudate and forms a protective gel moisture barrier which supports all phases of normal wound healing. The type I collagen composition delivers a structural protein to the wound site that signals key cellular processes in all phases of wound healing, an effect that is enhanced by its low pH, fragmented powder form.[3-8] In addition, the collagen used in Connext® creates a low pH healing environment, which has been shown to increase fibroblast proliferation, promote epithelization and angiogenesis, regulate MMP activity, increase oxygenation of damaged tissues, and inhibit growth of pathogens.[8]

Connext® Surgical Matrix is indicated for use in the management of partial and full thickness wounds, pressure (stage I-IV) and venous ulcers, ulcers caused by mixed vascular etiologies, venous stasis and diabetic ulcers, first and second-degree burns, cuts, abrasions, and surgical wounds.

Hemostatic Effect of Collagen Powder

Native intact collagen has shown to be an ideal scaffold material for use in wound dressings. Due to its fibrous, biocompatible composition and structure, it functions as a natural extracellular matrix (ECM) that can support all phases of wound healing. Besides its function as an ECM scaffold, collagen plays a pivotal role as a signaling molecule for cellular regulation for optimal wound healing. Acute wounds may heal in a predictable pattern, but chronic wounds fail to heal without proper wound care interventions.

During acute wound healing, MMPs (Matrix Metalloprotienases) lead to the proteolytic degradation of native intact collagen in the remodeling phase.[6] Polypeptide fragments released by proteolytic degradation of native collagen exhibit chemotactic properties and facilitate cellular differentiation, migration, and recruitment of cells.[6] This allows a highly vascularized granulation bed to form and encourages the formation of new granulation tissue and epithelium on the wound.[6]

Chronic wounds exhibit abnormally elevated levels of MMPs, and this imbalance leads to excess degradation of viable endogenous collagen, thereby inhibiting the ECM scaffold formation needed for cellular remodeling. Protecting native collagen from MMP destruction is critical for restoring normal biochemical healing processes. The addition of exogenous collagen (Connext®) provides a stable scaffold material for cellular ingrowth, organized collagen deposition, and to act as a "sacrificial substrate" for degradation by MMPs.[6]

Collagen promotes thrombosis (clotting) by enhancing platelet aggregation and releasing protein to form fibrin, resulting in hemostasis at the wound site.[9] The powdered collagen used in Connext® is fabricated though proprietary processes that breaks down larger collagen structures into smaller particles (~0.6 µm) to facilitate easy application.[7] Powdered collagen has significantly greater surface area compared to 3D scaffolds, which improves function and bioavailability in the wound bed, and is more readily incorporated into the wound healing cascade.

Healing Mechanism of Connext®

Connext® is processed using a proprietary, low pH processing method that renders the collagen with a higher absorption capacity (30X its weight) and bioavailability upon application to the wound site. Low pH treatment of fibrillar collagen causes an ion-induced, osmotic swelling of the collagen triple helix.[10] The low pH environment surrounding the collagen molecule causes a discharge of negative side chains via hydrogen ions, requiring an equal number of free negative ions to remain at the collagen bands, thereby producing a local osmotic gel formation.[10] The gelling action contracts the collagen structure axially, causing widespread relaxation of inter-fibrillar unions without major damage to the triple-helical structures.[10] The resultant modified structure renders the collagen with greater hydrophilicity (absorption capacity) and enhances bioavailability for immediate signaling in the wound bed, while maintaining a viable ECM structure for MMP mitigation and wound remodeling.[10]

The mechanism of wound healing is well described complex cellular interaction that can be divided into several integrated processes. After hemostasis, the inflammatory response plays an important role in both normal and pathological healing. Temporary inflammation is a typical response in acute wound healing and is a time-limited, orchestrated process. The local macrophage population transitions from predominantly pro-inflammatory (M1) to anti-inflammatory (M2) which are required in the proliferation and remodeling phases of healing.[11, 12] In chronic wounds, the inflammatory phase does not resolve within the expected timeframe, and several factors afftect this delay in healing. The evolution of macrophage phenotypes needed for successful healing is greatly impeded. The pro-inflammatory macrophages persist without transitioning to anti-inflammatory phenotypes, which leads to impairment in tissue repair.[13,14]

An acidic healing environment tends to polarize macrophages to the M2 phenotype, evidenced by the downregulated expressions of M1-related genes as well as upregulated gene expression of M2 surface markers.[15] The low pH properties of Connext® support proper macrophage polarization that help switch macrophages from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes leading to the healing of chronic wounds.

Antimicrobial Effectiveness of Connext®

Wound healing is influenced by both intrinsic and extrinsic factors. Hemostasis and inflammation, proliferation, and maturation or remodeling are the distinct, overlapping phases involved in wound healing. Altered or impaired wound healing, as seen in chronic wounds, is marked by an interruption of this process.

Infection is one of the most prevalent causes for nonhealing and chronicity of wounds. The presence of bacteria and bacterial products, such as endotoxins and metalloproteinases, can cause disturbances in the orderly scheme of wound healing, thereby negatively affecting each of the phases of healing.[16,17] Most of the pathogenic bacteria associated with infected wounds in humans need a pH value > 6 to thrive whereas their growth is inhibited by lower pH values.[18-20] The pH value within the wound milieu directly and indirectly influences all biochemical reactions taking place in the process of wound healing.[21] It has been shown that low pH helps wound healing by controlling wound infection, increasing antimicrobial activity, altering protease activity, releasing oxygen, reducing toxicity of bacterial end products, and enhancing epithelization and angiogenesis.[8]

A low pH collagen surgical matrix like Connext® can effectively lower the pH of the infected surfaces and create an environment unsuitable for the growth and multiplication of the bacteria. Connext® low pH and high surface area (as shown in Figure 1) allows it to absorb excess wound exudate and forms a biodegradable gel or sheet over the surgical site. It keeps the balance of wound moisture environment, thus promoting healing. The powder format and low pH of Connext® maximize the gelling effect, as shown in Figure 2.

Figure 1: High surface-area of micronized collagen in Connext® Surgical Matrix allows it to readily absorbs wound exudate and form a occlusive biobarrier that keeps the wound environment moist.

Connext® was tested for antimicrobial activity according to AATCC Test Method 100, using organisms common to wound infections in the clinical setting.[2,3] Test samples (N=3) were inoculated, incubated for 24 hours and enumerated to determine the log reduction compared to the initial inoculum count.[22] Connext® demonstrated a > Log 6 (% 99.9999) microbial reduction after 24 hours of exposure. The organisms tested and log reduction results are shown in Table 1.[22] These results indicate that Connext® Surgical Matrix is a wound dressing that can effectuate antimicrobial activity in complex reconstructive and surgical wounds.

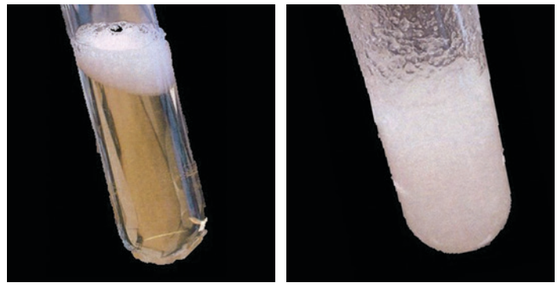

Figure 2: Gel forming capability of soluble hydrolyzed collagen powder (left) compared to non-soluble fibrillar collagen used in Connext® (right).

Table 1: Antimicrobial Testing Results for Connext® Surgical Matrix

Organism	Type	Log Reduction	% Reduction
S. aureus	Gram-positive Bacteria	> 6.13	99.9999
MRSA	Gram-positive Bacteria	> 6.33	99.9999
E. coli	Gram-negative Bacteria	> 6.05	99.9999
E. faecalis	Gram-positive Bacteria	> 6.11	99.9999
C. albicans	Yeast	> 6.33	99.9999
A. brasiliensis	Mold	> 6.39	99.9999

Summary

- *Biocompatible, ready to use and easy to apply*
  - Connext® consists of purified, low pH, type I bovine micronized collagen that is supplied in easy to use Bellows Bottle. No reconstitution, mixing, thawing or special storage conditions required.
- *Bioresorbable and promotes healing in complex and draining wounds*
  - Connext® has low pH and high surface area that maximizes absorption of wound exudate (30X weight) and increases the bioavailability of collagen. Connext® forms a protective gel moisture barrier while retaining a structural ECM for MMP mitigation and tissue remodeling
- *Antimicrobial*
  - Localized reduction in blood pH results in antimicrobial activity, and Connext® showed a >6 log reduction (%99.9999), against broad range of gram-positive, gram-negative, yeast and mold organisms (S. aureus, MRSA, E. coli, E. faecalis , C. albicans, and A. brasiliensis).