SAR Journal of Anatomy and Physiology

Abbreviated Key Title: *SAR J Anat Physiol*
Home page: https://sarpublication.com/journal/sarjap/home
DOI: 10.36346/sarjap.2022.v03i01.001

ISSN 2707-7713 (P)
ISSN 2709-6874 (O)

Review Article

Recent Progression in Wound healing Technologies

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Article History: | Received: 13.01.2022 | Accepted: 24.02.2022 | Published: 28.02.2022 |

Abstract: Optimizing patient local and systemic circumstances, as well as creating an optimum wound healing environment, are essential components of successful wound care. Many products have been developed to impact the wound environment in order to offer a pathogen-free, protected, and moist environment in which to heal. In the wound healing cascade, newer items are being employed to replace or supplement various substrates. The latest applications of silver in microbial prophylaxis and treatment, including issues involving resistance and side effects, the latest uses of negative pressure wound devices, advanced dressings and skin substitutes, biologic wound products, including growth factor applications, and hyperbaric oxygen as an adjunct in wound healing are all covered in this review of the current state of the art in wound-healing products. With so many options, it's easy to get overwhelmed.

Keywords: Wound healing, dressing, Hydrogel & Technologies.

INTRODUCTION

Wound is defined as the disruption of the cellular and anatomic discontinuity of a tissue [1] .Wound may be produced by chemical, physical, thermal, microbial or immunological insult to the tissue. Wound cause discomfort and are more prone to infection and other troublesome complications [2]. Some diseases like diabetes, Immune compromised conditions, ischaemia and conditions like malnourishment, ageing, local infection, local tissue damage due to burn or gunshot often leads to delay in wound healing. Infection is the major complications of burn injury and is responsible for 50-75% of hospital deaths [3]. Wound healing consists of an orderly progression of events that reestablish the integrity of the damaged tissue. Many of the synthetic drugs currently used for the treatment of wounds are not only expensive but also pose problems such as allergy, drug resistance etc and this situation has forced the scientists to seek alternative drugs[4]. More than 80% of the world population still depends upon traditional medicines for their ailments [5]. Especially for wound management [6] as they provide a moist environment to encourage the establishment of the suitable environment. Many medicinal plants are claimed to be useful for wound healing in the traditional system of medicine though their mechanism of action and efficacy have not been evaluated scientifically. Wound in a normal state of body get healed by various processes which is fundamentally a connective tissue response, initial stage of this process involves an acute inflammatory phase followed by the synthesis of collagen and other extra cellular macromolecules which are later remodeled to form a scar [7]. Wound is a physical trauma where the skin is torn, cut, burn or punctured [8]**.** Normally on wound site various mechanisms of body participate in wound healing i.e. white blood cell [9] fibroblasts, keratinocytes etc. While carbohydrates [10], lipids [11], and proteins [12] metabolism increases with the increase in the resting energy expenditure (RES). Wound healing is also affected by the other diseases such as diabetes etc, antineoplastic drug and antibiotics may also interfere with the wound healing. Wound infection is one of the most common diseases in developing countries because of poor hygienic conditions.[13]Wounds are the physical injuries that result in an opening or breaking of the skin and appropriate method for healing of wounds is essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin [14]. In other words wound is a break in the epithelial integrity of the

skin and may be accompanied by disruption of the structure and function of underlying normal tissue and may also result from a contusion, haematoma, laceration or an abrasion [15]. Healing of wounds starts from the moment of injury and can continue for varying periods of time depending on the extent of wounding and the process can be broadly categorized into three stages; inflammatory phase, proliferate phase, and finally the remodeling phase which ultimately determines the strength and appearance of the healed tissue [16]. 70% of the wound healing Ayurvedic drugs are of plant origin, 20% of mineral origin, and the remaining 10% consisting of animal products and these drugs are stated to be effective in different conditions such as *Vrana* (wounds or ulcers), *Nadivrana* (sinuses), *Vidradhi* (abscess),*Visarpa* (erysipelas), *Upadamsha* (syphilitic ulcers), *Vranajakrimi* (maggots in wounds), *Dustavrana* (septic wounds), *Vranashotha* (inflammatory changes of wounds), *Vranavisha* (cellulitis), *Ugravrana* (purulative ulcer), *Netravrana* (hordeolum or stye sepsis), *Pramehapidaka* (diabetic carbuncle), and *Bhagandara* (fistula-inano) [17]. Some very common plants like *Aloevera, Azadirachta indica, Carica papaya, Celosia argentea, Centella asiatica, Cinnamomum zeylanicum , Curcuma longa, Nelumbo nucifera, Ocimum sanctum, Phyllanthus emblica, Plumbago zeylanica, Pterocarpus santalinus, Terminalia arjuna and Terminalia chebula* have been extensively reported in ayurveda, siddha and unani systems of medicines for their wound healing potentials [17]. Research on wound healing agents is one of the developing areas in modern biomedical sciences and many traditional practitioners across the world particularly in countries like India and China have valuable information of many lesser-known hitherto unknown wild plants for treatingwounds and burn [18]. Traditional forms of medicine practiced for centuries in Africa and Asia are being scientifically investigated for their potential in the treatment of wounds related disorders [19, 20]. According to various traditional medicinal practices throughout the world, wounds have been treated mostly topically with different medicinal herbs or with their extracts solely or in combination with some other plant parts [20].

Ancient history of wound healing plants

In ancient times men tried out different plants to see which ones helped cure certain diseases. They probably watched to see what plants the animals ate, especially when they are sick. By trial and error, over the ages, men came to use thousands of plants as remedies for their ills. For example, many American Indian tribes used willow bark to treat rheumatism. How they selected it is not known, but scientists have found that the willow bark contains a pain killing chemical related to one used in aspirin. Many medicinal plants discovered by primitive people are still in use today. The leaves of 'Foxglove' furnish digitalis for the treatment of heart ailments. Quinine, from the bark of the South American Cinchova tree was long used to combat malaria. Curarae, a powerful poison applied by South American Indians to the tips of their arrows, is valuable in the treatment of disease that causes muscular spasms and anesthesia. Rauwolfa, used in the treatment of high BP is derived from the root of a plant that grows in Southeast Asia. It has long been used to treat fevers, insomnia and nervousness. Belladonna and atropine, obtained from the deadly night shade are important in the treatment of eye diseases. Painful spasmodic conditions and other ailments. Ephedrine, used for hay fever and in nose drugs is one of the few drugs that are derived from conifers. Spagnum moss is used for surgical dressings. Antibiotics produced by molds are the most important medicinal discoveries of 20th century. Many plants are rich source of vitamins. Some plant drugs are violent poisons and habit-forming narcotics. About 4500 years ago, when the great civilizations arose in ancient China, India, Babylon and Egypt, men put their knowledge of plant remedies in writing. These written accounts were called 'herbals'. The earliest herbal known was probably written by the Chinese emperor, Shen Nung, about 2700 BC. It contains the accounts of the healing value of about 250 plants. In India, the references to the curative properties of some herbs in the Rigveda seem to be the earliest records of use of plants in medicine. But references to plants in the Rigveda are very brief. More detailed account is available in the Atharva-veda. The period of Rigveda is estimated to be between 3500 and 1800 BC. After the Vedas, there is no information on the development of this science in India for a period of about 1000 years. Charak-Samhila (1000 BC), one of the earliest treatises on Indian Medicine, records the use of over 340 drugs of plant origin; some of these drugs were not indigenous to India. In Egypt carvings on tomb and temple walls show that people used plants for medicine as early as 3000 BC. A long document written about 1500 BC describes more than 800 remedies for all sorts of ailments, from headaches to heart trouble and from sore throats to insect bites. India recognizes more than 2500 plant species as having medicinal value, Sri Lanka about 1400 and Nepal around 700. In Ayurveda about 2000 plant species are considered to have medicinal value. The Indian Pharmacopoiea (1966) recognized 85 drug plants whose ingredients are used in pharmaceutical preparations. The Chinese Pharmacopoiea lists over 5700 traditional medicines, most of which are of plant origin. It has been estimated that out of about 2000 drugs that have been used in curing human ailments in India, only about 200 are of animal origin and a similar number are of mineral origin. The rest, i.e., about 1500 are of plant origin [21].

Phases of Wound Healing

Wound healing involves continuous cell–cell and cell–matrix interactions that allow the process to proceed in three overlapping phase's viz. inflammation cellular proliferation and remodeling.

Phase 1

It is a coagulation and inflammatory phase (0–3 days) and this involves migration of neutrophils at margin of incision, moving towards the fibrin clot.

Phase 2

It is a proliferative phase (3–12 days) in which the neutrophils are largely replaced by the macrophages. Granulation tissue progressively invades the incision space and the incissional space is filled with granulation tissue. Collagen fibrils become more abundant and begin to bridge the incision.

Phase 3

It is a remodeling phase (3–6 months), involving continuous accumulation of collagen and proliferation of fibroblasts. There is marked reduction in leukocyte infiltration and edema. The phase involves synthesis of collagen fibers, leading to increase in tensile strength of the skin. Healing requires the collaborative efforts of many different tissues and cell lineages. It involves platelet aggregation and blood clotting, formation of fibrin, an inflammatory response to injury, alteration in the ground substances, angiogenesis and re-epithelization. Healing is not complete until the disrupted surfaces are firmly knit by collagen. Wound healing is a process by which a damaged tissue is restored as closely as possible to its normal state and wound contraction is the process of shrinkage of area of the wound. three different phases constitute the physiologic process of wound healing (i***) substrate phases (ii) proliferative phase (iii) remodeling phase.*** All these steps are orchestrated in controlled manner by a variety of cytokines including growth factors. Some of this growth factor like platelet derived growth factor, transforming growth factor B, fibroblast growth factor and epidermal growth factor etc. has been identified in self healing wounds. In chronic wound the application of some growth promoting agents or some compounds which can enhance the in situ generation of these growth factors is required to augment the healing process [22].

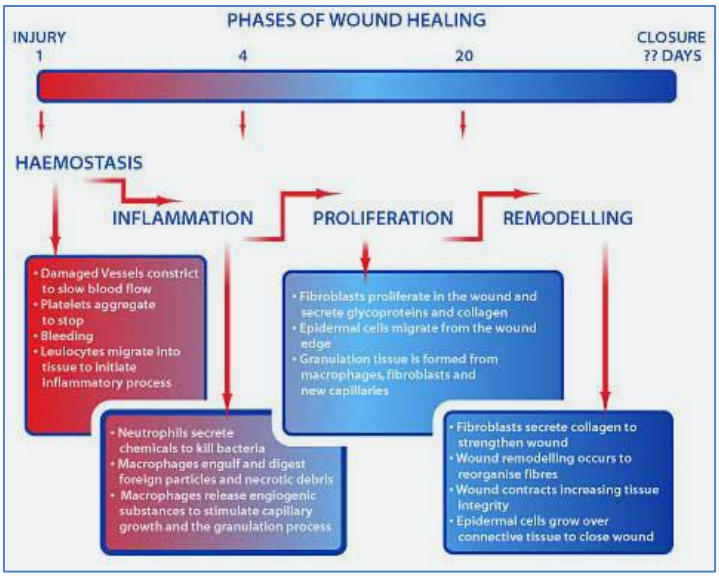


Fig-1: Phases of wound healing

Role of Cell Signaling in Tissue injury

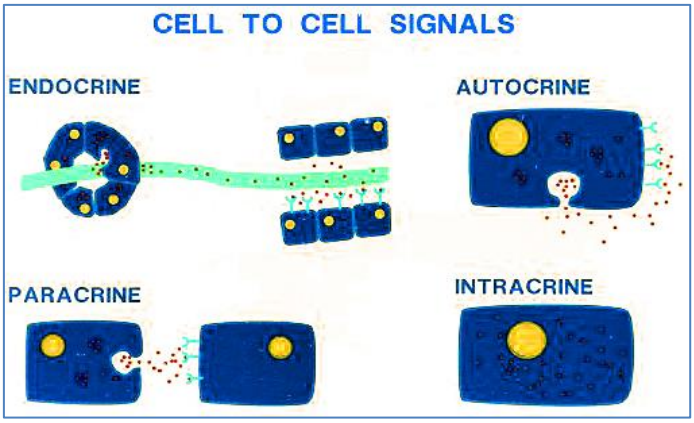


Fig-2: Cell signaling by cytokine

Fig-3: The four possible responses following tissue injury

The Healing Cascade

The healing cascade begins immediately after injury when platelets come into contact with exposed collagen. When platelets aggregate, clotting factors are released, resulting in the deposition of fibrin clots at the site of damage. Fibrin clots serve as temporary substrates and form the basis for subsequent healing processes. In addition to releasing clotting factors needed to control bleeding and loss of fluid and electrolytes, platelets provide a set of chemical signals known as cytokines or growth factors that initiate a healing response. The two most important signals are platelet-derived growth factor (PDGF) and transforming growth factor beta (TGFß). PDGF starts Homotacia neutrophils, macrophages, smooth muscle cells and fiber acetopes. It also stimulates the mitogenesis of fiber aceto and smooth muscle cells. TGFβ initiates cascade healing and stimulates cascade healing to start cascade healing and to emphasize additional cine, including FGF (fiber-aceto growth factor), PDGF, TNFA (alpo necrosis), PDGF, TNFA (Alpha necrotic tumor) and IL1 (interleukin1) . In addition, TGFβ also improves fiber aceta and smooth muscular cell chemale and adjust collagen expression and collage. The net result of this excessive signal is the energetic response of the matrix production cells to ensure rapid deposition of new coupling tissues at the impairment site during the following proliferation during the following proliferation. Neutrophils are the next predominant cellular marker in wounds up to 24 hours post-injury. The main function of neutrophils is to remove foreign substances, bacteria and non-functional host cells, as well as damaged matrix components that may be present at the wound site. Bacteria provide a chemical signal by attracting neutrophils, which engulf the neutrophils through a phagocytosis process. During bacterial protein synthesis, a waste product represented by f-MetLeuPhe tripeptide is released to attract inflammatory cells. The neutrophils swell until they are full of bacteria and form “pus" in the wound 48 hours after injury, fixed tissue monocytes are activated to become wound macrophages. These specialized wound macrophages are perhaps the most important inflammatory cells involved in the normal healing response. Inhibition of macrophage function delays the healing response. When activated, these wound macrophages release PDGF and TGFß to further recruit fibroblasts and smooth muscle cells to the wound site. These highly phagocytic macrophages are also responsible for clearing non-functional host cells, bacteria-filled neutrophils, damaged matrix, foreign debris, and any remaining bacteria from the wound site.

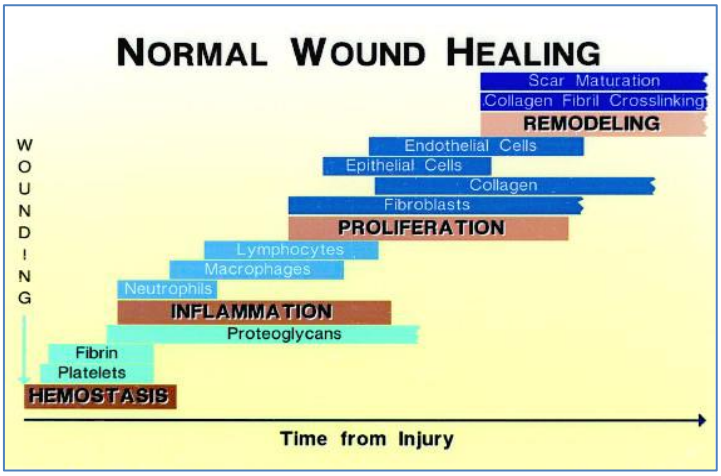


Fig-4: The sequence of events during normal wound healing

Phases of wound healing

PHASES OF HEALING	*DAYS POST INJURY*	*CELLS INVOLVED IN PHASES*
Hemostasis	Immediate	Platlets
Inflammation	Days 1-4	Neutophils
Proliferation	Days 4-21	Macrophages
Granulation		Lymphocyte
		Angiocytes
		Neurocytes
Contracture		Fibroblasts
		Keratinocytes
Remodelling	Days 21-2 yrs	Fibrocytes

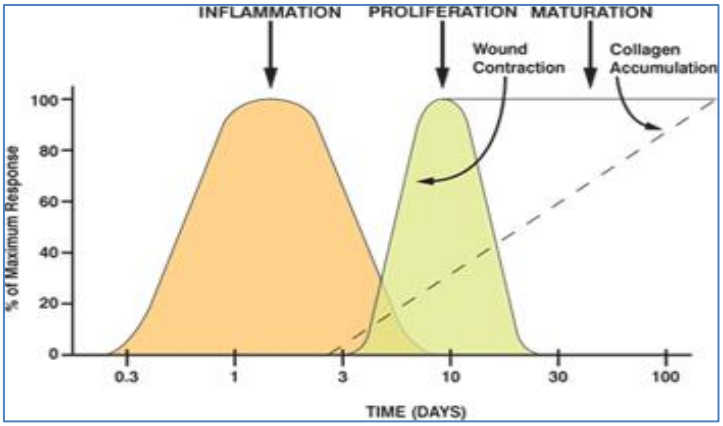
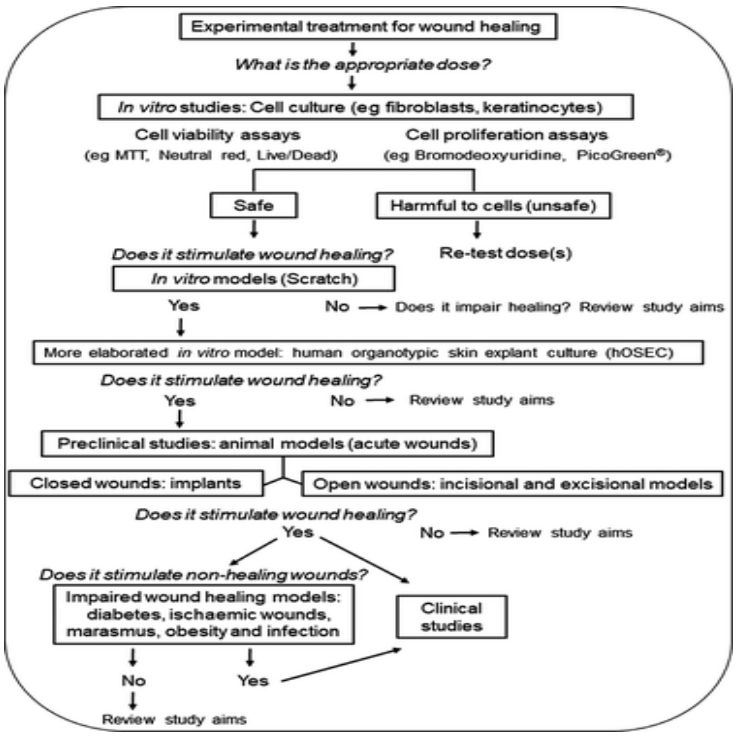
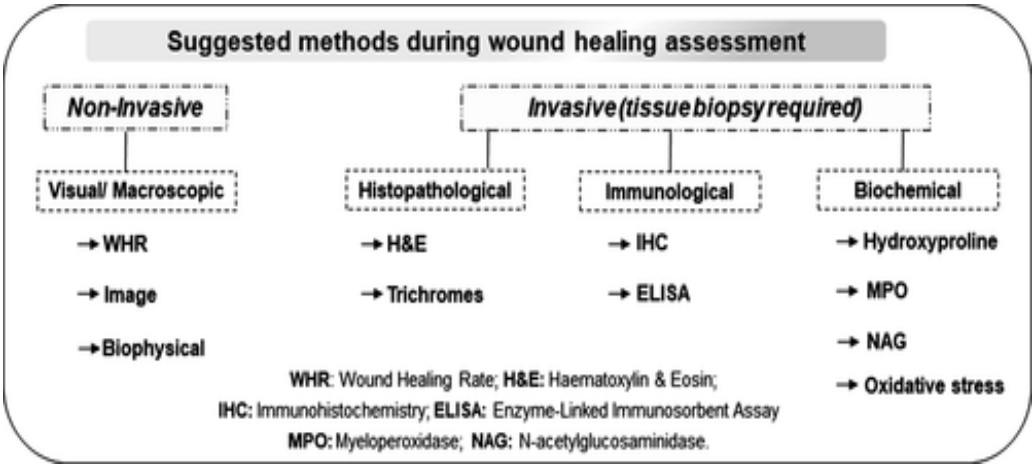


Fig-5: Graphical representation of wound healing phases

Advancement in Screening of Wound healing Potential





Biophysical Model of wound Healing Activity

Optical coherence tomography (OCT) is a new technique for diagnosing and monitoring inflammatory dermatological disorders. It produces high-resolution real-time images of the cutaneous architecture.

Greaves *et al.* evaluated OCT and histological assessments of in vivo acute wound healing to see how well they agreed on inflammation, proliferation, and remodelling. The authors proposed that OCT may be used as a diagnostic option to punch biopsies because the results were equivalent [23].

Tsai *et al.* used optical coherence tomography (OCT) to study in vivo wound healing following non-ablative fractional laser or ablative fractional laser treatments. The treated areas were scanned at several time periods to monitor the wound healing process, and an algorithm was devised to quantitatively quantify the morphological changes at different tissue depths during recovery [24].

Recent advancement in dressings for wound

Hydrogel dressings for wound

Hydrogels are applied to the wound as gels; they required a second cover such as gauze. Besides, if they are applied as films to the wound area, they can be used both as a primary and secondary dressing.

Hydrogels suitable for wound dressing as they

- Aid to the rehydration of dead tissues and elevated the healing of debridement
- Suitable for cleansing of dry or necrotic wounds
- Act as inert with biological reactants
- Penetrable to metabolites

Hydrogel is a cross-linked polymer matrix which has the potential to absorb and hold water in its network structure. Hydrogels act as a moist wound dressing medium and have the ability to absorb and retain the wound exudates along with the foreign bodies, such as bacteria, within its network structure. In addition to this, hydrogels have been found to encourage fibroblast proliferation by minimized the fluid loss from the wound surface and protect the wound from external harm necessary for rapid wound healing. Hydrogels help to support a micro-climate for biosynthetic reactions on the wound surface necessary for cellular activities. Fibroblast proliferation is requisite for complete epithelialisation of the wound, which starts from the edge of the wound. Since hydrogels help to keep the wound moist, keratinocytes can voyage on the surface. Hydrogels may be transparent, depending on the nature of the polymers, and provide soften and cooling/ soothing effects to the wound surface. The main advantage of the transparent hydrogels includes examined the wound healing without removing the wound dressing. The process of angiogenesis can be begins by using semi-occlusive hydrogel dressings, which is initiated due to temporary hypoxia. Angiogenesis of the wound ensures the growth of granulation tissue by maintaining appropriate supply of oxygen and nutrients to the wound surface [25].

Skin substitutes

Bioengineered skin replacements, including biosynthetic skin substitutes and cultured autologous engineered skin, are available in large quantities and pose no danger of infection or immunologic difficulties, making them ideal for temporary or permanent coverage. The cost of these items is their biggest drawback. We will briefly review currently available products and then go through some of them that may have an advantage over autologous tissue in terms of wound healing potential in chronic wounds. Bio-membrane is a temporary dressing made up of a knitted nylon mesh that is attached to a thin silicone membrane and covered with porcine polypeptides. It's used to cover donor areas in split-thickness skin grafting and clean superficial and mid-dermal depth burns It's used to cover donor areas in split-thickness skin grafting and clean superficial and middermal depth burns. It has been found in studies to be just as effective as silver sulfadiazine in wound healing without the need for frequent dressing changes. TransCyte is a biosynthetic dressing that combines a semi-permeable silicone membrane with a nylon mesh coated with porcine

collagen and newborn human fibroblast cells to create a biosynthetic dressing. It's used as a temporary cover for excised burns before grafting or as a dressing for superficial burns that don't require skin grafting. In terms of healing time, infections, and scar formation, it has been demonstrated to be superior to antibiotic creams or silver sulfadiazine in several investigations, particularly on facial burns [26].

Hyperbaric oxygen

For the past 40 years, hyperbaric oxygen has been used as an adjuvant in wound healing. It entails putting the patient in a sealed chamber with 100 percent oxygen at 1.5 to 3 atmospheres absolute (ATA) for 60 to 120 minutes over the course of several sessions. It has indications for use in carbon monoxide poisoning, crush injuries, compartment syndrome, acute traumatic ischemia, ischemia-reperfusion injury, radiation injury, compromised skin grafts, infections with anaerobic organisms, and refractory osteomyelitis. It was originally designed for use in decompression illness in deep sea divers. In addition, HBO treatment has particular special indications in chronic wounds [27].

CONCLUSION

The field of wound healing is constantly expanding with technological advances. There is still no good alternative to reconstruction using the patient's own tissue and carefully designed reconstruction procedures. The new product provides preventative measures against healing barriers, increases wound healing factors, delays and a bridge time to final repair, and optimize the outcome of final wound reconstruction and helps to promote good healing. Current wound healing products and modality expand the surgeon's arsenal to consider all aspects of wound healing.

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