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Techniques in Chronic Wound Management: Review of the Literature and Recent Concepts

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Abstract

Chronic wounds are very distressing for the patient and a difficult problem to manage. Many treatment modalities exist for this condition, making it difficult for the health care professionals to choose the appropriate treatment. This article deals mainly with the definition and local management of these wounds, and has been subdivided into debridement techniques, techniques to stimulate the healing process and dressing methods available. A mention has been made of the recent advances in the management of these wounds.

Keywords: Chronic wound; Ulcer; Wound management

Introduction

There is no consensus on the definition of the term "chronic wound". Werdin et al. defined chronic wounds as "wounds that have not proceeded through orderly and timely reparation to produce anatomic and functional integrity after 3 months [1]." Leaper and Durani defined chronic wounds as those wounds which, even after 2-4 weeks of optimal treatment did not show 20-40% reduction in size [2]. Sharma and John opined that "chronicity may be considered when there is no complete healing after 6 weeks or if there is poor response to a treatment change [3]." Chronic wounds cause financial and emotional strain to the patient as well as pose a difficult challenge for the healthcare staff. Although any wound has the potential to become chronic, certain medical conditions are commonly associated with chronic/non-healing wounds. They include diabetes mellitus, chronic venous congestion, arterial insufficiency and pressure sores. Some rare causes include rheumatoid arthritis, sickle cell anemia, hemolytic anemia, leukemia, Marjolin's ulcer etc. [1]. Furthermore malnutrition and immunodeficiency may complicate wound healing.

Normal healing of wound occurs in four interlinked stages which often overlap and include Stage1-hemostasis, Stage2-inflammation, Stage 3-cell proliferation, Stage4-remodeling [4]. The cellular events that take place during various stages include: Stage 1-activation of platelets and start of coagulation cascade; Stage 2-activation of neutrophils, macrophages and lymphocytes, release of cytokines and proteolytic enzymes; Stage 3-fibroblast migration into the wound, epithelial cells proliferation and migration, production of collagen and matrix metalloproteinases by fibroblasts, angiogenesis; Stage 4-continuous laying down of collagen by fibroblasts, covalent cross-linking of collagen molecules [4].

According to Ayello et al. [5] "chronic wounds are 'stuck' in the inflammatory and proliferative stages, so the wound never reepithelializes and closes." 5The successful outcome of chronic wounds requires aggressive local management as well as treating the underlying systemic cause, using a multidisciplinary approach including surgeons, physicians, and podiatrists and nursing staff. The aim of this article is to review the available local management options for chronic wounds to prepare the wound bed till definitive wound cover is provided.

Management of chronic wounds

The "T.I.M.E." acronym advocated by International Wound Bed Preparation Advisory Board identifies the important events responsible for delay in wound healing. The T stands for nonviable tissue which should be debrided, I stand for inflammation and infection which should be controlled, M is for moisture imbalance which should be corrected and E stands for edge (non-advancing/nonmigrating) and epithelialization which should be restored [5]. This concept has been subsequently updated twice, with emphasis being laid on management of systemic causes and patient related holistic approach which takes into consideration other factors like pain management etc. [6,7].

The principles of local management of chronic wounds include firstly, effective debridement; secondly, stimulating the intrinsic process of wound healing and thirdly, wound support with the use of appropriate dressing techniques till the wound bed is ready for final wound closure. Though these steps are usually performed concurrently rather than sequentially, they have been dealt with separately in this article for convenience of presentation and ease of understanding.

Debridement

Local debridement of the wound helps in healing by removing the dead necrotic tissue, particulate matter, or foreign materials, and reducing bacterial load. These devitalized tissues hinder cell migration necessary for healing and predispose to infection, thus necessitating removal [1,8,9].

Surgical debridement

Surgical debridement involves the use of sharp instruments like scalpels or scissors to remove the devitalized tissue to make a chronic wound look like an acute wound. The removal of the devitalized tissue hastens healing by allowing for the granulation tissue to grow. Chronic wounds require a series of debridement also known as "maintenance

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debridement" which should be accurate and efficacious [1]. Surgical debridement allows rapid clearance of the devitalized tissue and is optimal for wounds with extensive and adherent eschar [10]. The disadvantage is associated inadvertent viable tissue removal as there is lack of any objective biological/molecular marker to discriminate impaired and nonimpaired tissue to direct the extent of debridement [11]. The limiting factors include inadvertent bleeding and poor pain tolerance by the patient [10].

The use of high pressure saline beam to debride the devitalized tissue from wound bed has been advocated in place of scalpel debridement [12,13]. This hydrodissection or hydrocision with the use of Versa jet (Smith and Nephew) acts tangentially over the soft tissue surface and creates a smooth wound bed while preserving dermal tissue [13]. It has been found to be effective modality in treatment of chronic leg ulcers and burns [14,15].

Physical debridement

Wet-to-dry dressings: Wet-to-dry dressings include the use of moist gauze over a wound and its removal when dry. The gauze moistened with saline is kept on the wound and covered by another layer of dry gauze. The moistened gauze dries after a period of time and adheres to the underlying tissue, and upon dressing removal the adherent tissue is also removed. However these dressings are not selective in removal of no vitalized tissue as some healthy neo-epithelium can also be inadvertently removed thus causing pain and damage to the reparative tissue. Other disadvantages are the need for frequent dressing change, increased risk of infection and prolonged inflammation. Furthermore, these dressings on drying have a local cooling effect at the wound site, which is detrimental to healing [16].

Pressure irrigation

Continuous and pulsatile irrigation using saline or tap water through a syringe [17] or power irrigator/jet-lavage systems have been used to achieve local wound cleansing. Both saline and tap water have been found to be comparable in terms of bacterial load reduction when used as irrigant [18,19]. The high pressure cleansing has shown to reduce local bacteria counts. Increased pressure removes more debris and bacteria but can come at a price of damage to bone and soft tissue [20]. The advantage of using pulsatile irrigation over traditional irrigation is unclear [20]. The other disadvantage of this type of debridement is that the use of high pressure may drive the bacteria into healthy soft tissue [21].

Biological debridement

Biological debridement with use of larvae of common green bottle fly (*Lucilia sericata*) has gained popularity [22,23]. The larvae of this fly thrive on necrotic tissue, but are unable to ingest healthy tissue. They act by releasing proteolytic enzymes to selectively digest the slough and devitalized tissue. They are effective against methicillin-resistant staphylococcus aureus (MRSA) and beta hemolytic streptococci and have a wound regeneration effect. Owing to their photophobic nature, these larvae often reach deep crevices of the wound inaccessible through surgical debridement [24].

The disadvantages as stated by Sarabahi are, "local discomfort, itching, unaesthetic appearance to the patient along with cost of the therapy and short half-life of maggots [21]."

Enzymatic debridement

One of the reasons why chronic wounds fail to epithelialize is because of inefficient debridement of temporary extracellular matrix components like fibrin and fibronectin [24], which can be improved with the use of exogenous enzymes like collagenase and papain. They are available as ointment preparations and are applied once or twice daily directly to the wound surface. The enzymatic debridement can be used as an alternative when surgical debridement is contraindicated. The disadvantages are hypersensitive reaction and a transient stingy feeling on application [25]. It can also be combined with surgical debridement in a serial manner. This has been suggested as more effective in removing adherent necrotic tissue in selected wounds [25].

Autolytic debridement

Autolytic debridement is achieved with the help of moisture retaining dressings through the endogenous enzymes present in the wound that digest the necrotic slough and allow the dressing to separate. These moisture-retaining dressings include hydrogels, hydrocolloids and transparent films (discussed later). This method of debridement is easy to use and relatively painless. At the same time it is slow and may lead to maceration of wound edge [10]. A randomized control trial found both autolytic and enzymatic debridement to be equally effective in terms of amount of slough, healthy granulation and reepithelialization [26].

Affecting the intrinsic process of wound healing

Antimicrobials: Chronic wounds usually contain microorganisms. The bacterial presence can be staged as contamination, colonisation, critical colonisation and infection. Critical colonisation or covert infection and infection delays wound healing. Antimicrobials are used against these organisms and include a variety of substances like antiseptics, antibiotics and disinfectants which are used to get rid of microorganisms like bacteria, fungi, virus, protozoa and prions. However, disinfectants are too toxic to be used for topical application, and hence only the other two are used extensively in topical therapy of wounds. Antiseptics are non-specific in action and kill all microorganisms, thus no resistance against them have been reported so far [27]. Commonly used antiseptics include povidine iodine, chlorhexidine, hydrogen peroxide, silver nitrate, silver sulfadiazine, boric acid, acetate, alcohol, Eusol and sodium hypochlorite [28]. The rationale for the use of topical antibiotics is the fact that optimal concentrations may be obtained directly where they are required. On the other hand, unlike antiseptics their indiscriminate use may lead to development of bacterial resistance. The commonly used topical antibiotics include Bacitracin A, Neomycin, Fucidin, Mupirocin, Retapamulin [21]. As there is gradual development of bacterial infection in chronic wounds, clinical assessment and good quality wound cultures are recommended [29].

Negative pressure wound therapy (NPWT): This technique implies topical application of sub-atmospheric pressure over the wound surface whereby the exudate is contained in a sealed environment and drained out with a tube connected to an external container. A thorough debridement is done before application of NPWT. Foam dressing conforming to size and contour of the wound is cut and kept over the wound. A hole is made in the dressing for insertion of the drainage tube, which in turn is attached to a vacuum pump. The foam dressing is covered with a transparent adhesive drape to create a sealed environment. The vacuum device creates a sub-atmospheric pressure of about 125 mmHg that drains the exudate out through the tube. This pressure can be applied in continuous or intermittent manner. NPWT promotes wound healing by improving oxygenation, cellular proliferation, granulation and reducing bacterial load and inhibitory cytokines [30]. Furthermore, by removing the exudate

without drying the wound, it conforms to the principles of moist environment treatment as the adhesive dressing provides a semi-occlusive environment and allows for gas exchange. Various studies support the use of NPWT in management of chronic wounds [31-35].

Plikaitis and Molnar [30] suggested that the term sub-atmospheric pressure therapy is more apt than NPWT as the pressure created is not negative i.e. <0 mmHg. The disadvantages of this technique are pain and bleeding during foam changing and trauma to surrounding skin while removing adhesive drape especially in patients with thin skin [36]. It is contraindicated in neoplastic wounds [36].

Hyperbaric Oxygen Therapy (HBOT): HBOT increases local oxygen tension and hastens wound healing by promoting growth of fibroblasts and collagen, improving leukocyte function, reducing detrimental cytokine production and promoting angiogenesis [37,38]. The patient is placed in an airtight chamber and 100% oxygen is administered at 1.5-3 atmosphere absolute (ATA:1 ATA is 760 mmHg, which is atmospheric pressure at sea level) [39]. Once or twice daily sessions, each lasting 45-120 minutes are conducted for a total of 20 to 30 sessions in the treatment of chronic wounds [39].

HBOT leads to systemic hyperoxia, thus fulfilling the required need for oxygen at the wound site [40]. As Niinikoski stated, "At 2 to 2.5 ATA oxygen pressure, physically dissolved oxygen in plasma increases over tenfold", leading to, "a favorable gradient for oxygen diffusion from functioning capillaries to ischemic tissue sites" [37]. Another mechanism of action of HBOT is mediated through production Nitric oxide (NO). NO acts as a vasodilator and has positive effect on wound healing [41].

A recent systematic review concluded that HBOT is useful in reducing the risk of major amputations in diabetics with chronic foot ulcers [42]. The limiting factors of HBOT are that unlike debridement, it cannot remove the devitalized tissue from wound surface and its role as universal modality for all types of chronic wounds is not validated. Presently HBOT is used as an adjunct to other modalities of wound management for selected group of patients. The contraindications of HBOT include acute pneumothorax, recent ear or sinus surgery, seizure disorders, claustrophobia and febrile disorders [40].

Growth Factors (GF): Growth factors and cytokines are small polypeptides that bind to cell surface receptors and influence the process of wound repair. Cytokines are chemotactic for white cells and fibroblasts, while the growth factors initiate fibroblast and keratinocyte proliferation [43]. In chronic wounds these GF get caught in the capillaries or extracellular matrix leading to their deficiency and subsequent arrest of the wound repair process. Ten Studies have demonstrated the beneficial effect of growth factors on healing of chronic wounds due to various etiologies [44-48]. One study found GF therapy no better than conventional moist dressings in treatment of simple wounds [49].

Growth factors can be used alone or as an adjunct with other wound bed preparation techniques in treating chronic wounds [50]. The US Food and Drug Administration (FDA) have approved recombinant human PDGF (rhPDGF) for clinical use in wounds [51].

Bioengineered skin substitutes: Bioengineered skin substitutes are another therapeutic option for management of chronic wounds. They can be derived from autologous or allogenic skin cells after growing these cells *in vitro* on biodegradable scaffolds like collagen or polylactic acid [52]. These tissue engineered skin substitutes are categorized according to their use into epidermal, dermal or their combination [52].

Their beneficial effect is by "promoting revascularization, cellular migration, and repopulation of wound fields through provision of an appropriate scaffold material to facilitate these processes" [53]. These products do not integrate into the host skin and provide temporary coverage of the wound area till definitive procedure like skin grafting is done. The ideal skin substitute should "function as an alternative to autologous skin, form an effective barrier against bacterial invasion, minimize inflammation and scar formation, improve fibrovascular tissue in growth, and have excellent reproducibility" [54]. The disadvantages include high cost, limited availability, risk of transmissible diseases and immunological rejection [52].

Honey: Honey has been used for ages as a topical agent for wound healing, but renewed interest in honey as a wound dressing agent developed in the 1980s [55]. The properties of honey depend on its source and processing. Superior healing properties have been claimed for honey obtained from Australia and New Zealand [56]. The most studied and widely marketed medicinal honey is obtained from the plants of genus *Leptospermum* which is mostly endemic to Australia [55]. The wound healing effect of this medicinal honey is exerted through its antimicrobial, immunomodulatory and anti-inflammatory properties [55]. Honey can be applied as such or in combination with sterile dressings. The indications of medicinal honey in management of chronic wounds include diabetic, arterial, venous and pressure ulcers. Overall it is a safe product, theoratic risk of complications like wound-botulism have been highlighted [57]. Gamma irradiation has been used to get rid of the clostridium botulinum spores.

Ultrasound: Ultrasound has found a place in management of chronic wounds. The wound healing actions include collagen synthesis, angiogenesis, fibroblast stimulation, reduction of inflammation and cellular proliferation. In chronic wounds it has been found to facilitate transition to the stage of granulation from the stage of inflammation. A typical effect of ultrasound is cavitation i.e. formation of holes/gas bubbles in liquid medium. With respect to chronic wounds it causes holes in bacterial cell membrane leading to increased uptake of antiseptics and antibiotics, thus facilitating their action [58]. Low frequency ultrasound at 40 kHz at low intensity coupled with saline mist has been found as a novel alternative to surgical debridement [59]. Multiple studies have demonstrated the beneficial effect of ultrasound in treatment of chronic wounds [59-61].

Electrical stimulation: Electrical stimulation accelerates the wound healing process by mimicking the current of injury that normally occurs during injury to skin [62,63]. The movement of cells along the path of the electrical current may be important in the inflammatory and proliferative stage of wound healing. This stimulation may be applied from periphery of wound towards the wound bed using direct, alternate or pulsed current [63]. This is "usually achieved by placing one electrode in contact with the wound bed and another in contact with the periwound skin close to the wound margin" [63]. The plethora of delivery systems for electrical stimulation makes it difficult to evaluate its effect [63]. A commercially available bio-electric wound care dressing, POSiFECT™ RD (Biofisica, Hampshire, UK) has been shown to be beneficial in treatment of chronic wounds [63,64]. Furthermore, the amount of current applied and the duration of treatment also varies, warranting further research before it can be uniformly established as a modality for chronic wound healing.

Dressings: Dressings contribute to local wound care by physical, chemical and biological means. They are useful for non-surgical wound debridement and also protect the wound by providing a protective

wound covering. This in turn reduces pain and psychological distress caused by these wounds. Jones described an ideal dressing as one that "maintains a moist environment, manages wound exudates, facilitates autolytic debridement, protects the periulcer skin, protects against contaminants, minimizes shear and friction, causes no trauma on removal, leaves no debris in the wound bed, reduces or eliminates pain, provides thermal insulation and induces no allergic reactions." [65]. Presently, moisture-retaining (occlusive) dressings are favored over the dry or wet-to-dry gauze dressing. These occlusive dressings maintain the moisture content of the wound environment that is conductive to healing. The commonly used dressings are described in table 1 [21,66,67].

Miscellaneous: Topical phenytoin been used to promote wound healing in a variety of chronic wounds like pressure ulcers, venous ulcers, diabetic ulcers, burns, and leprotic ulcers [68,69]. The exact mechanism of action of phenytoin in wound healing is unknown and is thought to be multifactorial. Also the optimal topical dose and delivery form is not known. It has been used as powder and in combination with saline gauze dressings. A study comparing topical phenytoin and saline dressings for chronic wounds found greater reduction of wound area as well as bacterial load in the phenytoin group [70]. Another study in the recent past found accelerated healing of excisional wound in albino rats treated with topical phenytoin [71].

Its use is not FDA approved and further clinical trials are warranted before establishing its role in wound healing [68]. Other drugs which have been found beneficial for wound healing but not yet approved by FDA include Misoprostol(prostaglandin E-1) [72] and Nefidipine [73].

Zhang et al. found accelerated skin wound healing in skin donor site wounds in rabbits withlocal injection of long-acting insulin-zinc suspension [74]. Evidence suggests that topical insulin accelerates wound healing in humans [75-77]. Another underexplored option for chronic wound management in zinc. Lansdown et al. stated, "Zinc deficiency of hereditary or dietary cause can lead to pathological changes and delayed wound healing [78]."Further they suggested that topical application of zinc is probably better than oral supplementation. Zinc has an effect on fibroblast proliferation and collagen synthesis which are essential for wound strength and epithelization [79]. Few studies have suggested application of pure oxygen hastens wound healing [80,81]. Similarly natural products like curcumin (diferuloylmethane) [82], orange essential oil [83], virgin coconut oil [84], tea tree oil [85], Eucalyptus oil [86], dehydrozingerone, (a half analog of curcumin) [87] and Enamel matrix derivative [88] may promote wound healing. Animal-derived acellular biomateriallike the OASIS® Wound Matrix (Healthpoint Ltd, Texas, USA) have been extensively studied for chronic wound healing [89]. It is obtained from porcine small intestinal submucosa and used as a biological dressing. Further it has been found to increase the retention and bioactivity of 'fragile' growth factors [90]. The disadvantages include risk of infection transmission and immunological reaction [52].

Recent advances in wound healing

Low temperature plasma: Kramer et al. purposed the use of low temperature plasma (LTP) following surgical debridement [91]. The authors stated that following surgical debridement, the LTP could be used for "fine-tuning the debridement by detachment of the non-visible part of necrotic tissue". In comparison to antiseptics that are detrimental to regenerative granulation tissue, LTP acts superficially and enhances cell proliferation at the deeper layers. Plasma is form of matter (like solid, liquid and gas), which contains charged particles. Recently with the advent of technology of the low temprature plasma/ cold plasma their role in wound healing is being explored [92]. This cold plasma exhibits antimicrobial properties by virtue of agents such as heat, charged particles, reactive neutrals, and electromagnetic radiation [92]. Moreover there is no necrotic effect on the mammalian cells if optimal configuration is used. The wound healing effect is proposed to be due to fibroblast proliferation and Nitric oxide production. However, its role in the management of chronic wounds is not established as yet.

Extracorporeal Shock Wave Therapy (ESWT): ESWT is being studied as a modality to promote wound healing. These waves exert stress on the cells, which is postulated to increase angiogenesis by releasing vascular growth factors and pro-inflammatory factors to stimulate tissue healing [93]. One study comparing ESWT to HBOT showed that ESWT was more effective than HBOT in chronic diabetic foot ulcers, with an increase in blood perfusion rate and cell activity with better ulcer healing [94]. The effect of ESWT on diabetic ulcers has also been studied by Moretti et al. and found to be beneficial without any side effects [95].

Laser therapy: Low-intensity laser irradiation (LILI) is currently being tested for treatment possibilities in chronic, recalcitrant wounds [93]. Low intensity laser has been shown to promote wound healing in experimental studies by increasing collagen synthesis and angiogenesis [96]. In one RCT, healing of chronic leg ulcers was

Dressing	Use	Advantages	Disadvantages
Gauze (non-medicated or medicated)	Discharging wounds, wounds requiring debridement or packing	Readily available, cheap	Adherent, needs frequent change, permeable, may damage healing tissue on removal
Foams (hydrophilic polyurethane)	For discharging wounds, with vacuum assisted closure	Absorbent, non-adherent, occlusive, comfortable	Cost, wound desiccation
Films (polyurethane membrane dressings)	Superficial wounds with minimal exudate	Transparent (allows wound inspection), occlusive, promotes autolytic debridement	non absorbent fluid collection, skin maceration
Hydrogels (A three-dimensional network of hydrophilic polymers)	Necrotic or infected wounds, wounds covered with eschar, minimally exudative wounds	Cooling, non-adherent, easy application and removal	Requires a secondary dressing cover, cannot be used in heavy exudating wounds
Hydrocolloids (hydrophilic colloidal particles)	Wounds with minimal to moderate exudate	Adherent, absorbent, occlusive	Odor on removal, dislodged in heavy exudative wounds, can injure fragile skin
Alginates (from seaweed)	Wounds with moderate to heavy exudates	Biodegradable, non-adherent, absorbent, non-allergenic, moldable	Expensive, cannot be used in dry wounds
Composite dressings (Combination of 2 or more products manufactured as a single dressing)	Provides multiple functions, exudative wounds	Promote moist wound healing, provide autolytic debridement	Cannot modify to wound size, needs intact skin border for adhesion

Table 1: Commonly used wound care dressing materials.

compared between patients treated with non-healing placebo light and those treated with laser therapy. It was found that healing was better in the laser group. However, this study was small and needs further validation [97].

Platelet rich plasma (PRP): Villella in a meta-analysis showed that PRP promotes the healing process in chronic ulcers [98]. The PRP is rich in growth factors such as PDGF, Transforming growth factor-β, platelet factor 4, epidermal growth factor, epithelial cell growth factor etc., thus causing cellular proliferation, angiogenesis, reduced inflammation and epithelialization, thus stimulating wound healing [99]. Lacci and Dardik suggested the use of autologous PRP compared to allogenic preparation associated risk of transmissible diseases and immunological reaction with the use of allogenic preparations [99]. However the widespread use is limited as this technology entails significant cost and expertise [98].

Summary

Chronic wounds are a common problem faced by health care professionals, both in the community and in the hospital setting. They are a difficult condition to manage, and as the name implies, take a long time to heal. These wounds are a cause of distress to the patient and a conundrum to the treating professional. They cause a financial burden not only to the patient in terms of lost man hours of work and reduced productivity, but also to the health services in terms of the cost of caring for the patient. With a better understanding of the pathophysiology of wound healing, newer modalities of management of these wounds are being introduced to support the existing traditional methods of treatment. It is imperative for all health care workers involved in the management of these patients to remain abreast of the available technology and methods, so that they can offer the best possible treatment. It is hoped that this article will help in the better understanding of the treatment modalities for this difficult problem, with a resultant improvement in care of these patients.

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