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PRACA POGLĄDOWA
REVIEW

Wound healing – characteristics of the ideal dressing

Gojenie ran – charakterystyka idealnego opatrunku

Kinga Orlińska[1], Katarzyna Komosińska-Vassev[2], Krystyna Olczyk[2], Marcin Glaesel[3], Paweł Olczyk[1]

[1]Department of Community Pharmacy, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland
[2]Department of Clinical Chemistry and Laboratory Diagnostics, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland
[3]Students' Research Club at the Department of Community Pharmacy, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland

ABSTRACT

Wound healing is a dynamic process aimed at restoring homeostasis and functionality of damaged tissue. It is a highly complex, multi-stage process, the disruption of which leads to complications and health problems for the injured person. The discussed process takes place in the human system in two ways. The first of them is granulation and the second is healing per primary. Regardless of the method of wound healing, the individual phases of this process overlap each other, where before the end of the previous phase, the next begins. Demarcation of individual phases is purely practical. There are four phases of healing: the hemostasis phase, the inflammation phase, the proliferative phase – in other words the replication and synthesis phase – and the remodeling phase.

The process of wound healing is a natural, long-term, and complex process that occurs in the body when injured. Incorrect healing may result in chronic wounds, necrosis or excessive scarring. Wound treatment supports this naturally occurring process in the body. In cases that require such support dressings are used, which are an essential element applicable in health care. An ideal dressing should create a barrier against external factors, maintain an appropriate environment in the wound bed (appropriate temperature, optimal humidity, slightly acidic pH, gas exchange), absorb excess of blood and exudate, keep the wound clean – cleanse it of necrotic tissue and toxins – do not adhere to the wound to avoid wound damage during dressing replacement, do not show sensitizing or irritating effects.

KEYWORDS

healing, wound, dressing

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Address for correspondence: prof. dr hab. n. farm. Paweł Olczyk, Department of Community Pharmacy, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland, Kasztanowa 3, 41-200 Sosnowiec, tel. +48 32 269 98 39, e-mail: pawel.olczyk@sum.edu.pl

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STRESZCZENIE

Gojenie się ran to proces dynamiczny, którego celem jest przywrócenie homeostazy oraz funkcjonalności uszkodzonej tkanki. To wysoce złożony, wieloetapowy proces, którego zaburzenie prowadzi do powikłań i problemów zdrowotnych osoby poszkodowanej. Omawiany proces przebiega w ustroju ludzkim dwiema drogami. Pierwszą z nich jest ziarninowanie, drugą rychłozrost. Niezależnie od sposobu gojenia się rany, poszczególne fazy tego procesu wzajemnie nachodzą na siebie, gdzie przed zakończeniem fazy poprzedniej rozpoczyna się następna. Rozgraniczenie poszczególnych faz ma charakter czysto praktyczny. Wyróżnia się cztery fazy gojenia: fazę hemostazy, fazę zapalenia, fazę proliferacyjną – inaczej fazę replikacji i syntezy – oraz fazę remodelingu.
Proces gojenia się ran jest procesem naturalnie zachodzącym w organizmie, długotrwałym i złożonym, który zachodzi w przypadku zranienia. Nieprawidłowy przebieg gojenia może skutkować wystąpieniem ran przewlekłych, martwic czy nadmiernego bliznowacenia. Wspomaganiem tego naturalnie zachodzącego w organizmie procesu jest leczenie ran. W przypadkach wymagających takiego wsparcia stosuje się opatrunki, które są elementem niezbędnym, mającym zastosowanie w ochronie zdrowia. Idealny opatrunek powinien: tworzyć barierę przed czynnikami zewnętrznymi, utrzymywać odpowiednie środowisko w łożysku rany (odpowiednia temperatura, wysoka wilgotność, lekko kwaśne pH, umożliwienie wymiany gazowej), absorbować nadmiar krwi oraz wysięku, utrzymywać ranę w czystości – oczyszczać z tkanki martwiczej i toksyn – nie przywierać do rany, aby uniknąć jej uszkodzenia w trakcie wymiany opatrunku, nie wykazywać działania uczulającego, a także drażniącego.

SŁOWA KLUCZOWE

gojenie, rana, opatrunek

Wound healing

Wound healing is a dynamic process aimed at restoring homeostasis and functionality of damaged tissue. This process is highly complex, and multi-stage, and its disruption leads to complications and health problems of the injured person [1].

Types of wound healing

Wound healing takes place in the human body in two ways. The first of them is granulation, and the second is healing per primary. Both processes are aimed at healing the wound and scarring it [2].
Clean wounds, without infection, without tissue loss, resulting from a surgical incision and then suturing, heal per primary (per primam). The healing process is short and is accompanied by a weak biosynthesis of connective tissue and rapid epidermisation [1,3].
Through granulation (per secundam) secondary wounds heal, an example of which is the healing of burn wounds. As a result of these wounds, there is a loss of tissue and the inability to close the wound, which is accompanied by infection of the lesion site [3].

Healing phases

Regardless of the method of wound healing, the individual phases of this process overlap each other, where before the end of the previous phase, the next begins. Demarcation of individual phases is purely practical. There are four phases of healing (Figure 1):

- hemostasis phase,
- inflammation phase,
- proliferative phase – replication and synthesis phase,
- remodeling phase [4].

The components of the extracellular matrix (ECM) perform specific functions in each of these phases. They determine the formation of the basic components of the repair process – matrix, granulation tissue, and scar. Their role is also associated with signaling, stimulation of cell adhesion, and migration, as well as with the effect of mediating of interactions between cells, between cells and the matrix or proteins of the ECM. Therefore, ECM components have functional roles, regulating the healing process by constituting a reservoir and modulator for cytokines and growth factors; they also perform structural functions by filling tissue cavities during the repair process [4,5,6].
The main role in the wound healing mechanism is played by stem cells, which give rise to specialized cells responsible for specific functions during wound healing, as well as creating new tissue. The presence of many elements, such as components of the ECM, cytokines, growth factors, and other active peptides or proteins, determine the activity of both stem cells and other skin cells (e.g. keratinocytes, fibroblasts) [6,7,8].

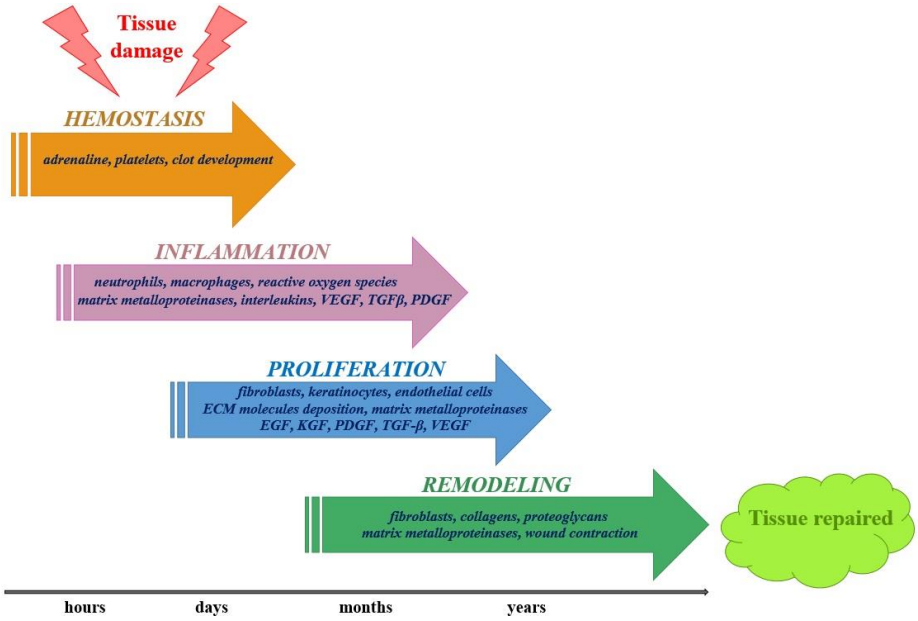

Fig. 1. Wound healing – consecutive phases (author's own study based on [1,2,3,4]).

Hemostasis phase

As a result of tissue damage, a coagulation cascade is triggered, the purpose of which is to close the wound. The triggered mechanisms of hemostasis include vasoconstriction, followed by thrombocyte aggregation, which in the next stage leads to the formation of a clot containing cross-linked fibrin, reinforced with ECM proteins such as fibronectin, thrombospondin, vitronectin or osteonectin (SPARC) [6,7,9,10].

Platelets play a key role in the initial stage of the wound healing process. They interact with the ECM components of the damaged vascular wall exposed to the flowing blood, including collagen, which initiates the intrinsic blood coagulation cascade. At the same time, an extrinsic coagulation cascade is initiated as a result of blood contact with tissue factor, exposed on the surface of the cells of the subendothelial layer of the blood vessel [11]. Platelets adhering to the damaged surface of the vessel are then activated and aggregated, forming a platelet plug, closing the defect site, and at the same time forming a temporary ECM. The process of platelet activation is associated with a change in their shape from discoidal to spherical, characterized by elongated pseudopodia, which facilitates the process of platelet aggregation. Activation of thrombocytes also increases the synthesis of thromboxane A2 (TXA2), which is a strong factor stimulating platelet aggregation, and the release of platelet granule components, such as adenosine diphosphate (ADP), serotonin (activating further thrombocytes and causing vasoconstriction), platelet factor 4 (PF4 – activating and enhancing leukocyte chemotaxis), growth factors such as platelet-derived growth factor (PDGF), transforming growth factor α (TGF-α), transforming growth factor β (TGF-β), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1), stromal origin factor 1 (SDF-1), stimulating angiogenesis and initiating the inflammatory reaction or stimulating the division of fibroblasts and the synthesis of ECM components by these cells, thus accelerating way of wound healing [4,7,9,10,12,13].

The above phenomena are accompanied by the influx of monocytes, neutrophils, and mast cells to the site of damage, whose main function is the elimination of microorganisms, and tissue debris and the stimulation of angiogenesis and tissue regeneration. The described phenomena constitute the phase of primary hemostasis, lasting 3–5 minutes, followed by the phase of secondary hemostasis. The essence of this second phase is the transition of soluble plasma protein–fibrinogen into the spatial network of insoluble fibrin to strengthen the primary platelet aggregate. The mechanisms of secondary hemostasis are closely related to primary hemostasis because it is on the activated platelets that the coagulation process takes place, resulting in the formation of a fibrin clot [7,12,14,15].

Inflammation phase

The course of the next phase of wound healing – the inflammatory phase – is largely dependent on the number of microorganisms in the bed of tissue damage, affecting the duration of this phase and the number and activity of neutrophils [7]. This phase begins during the first day of tissue damage. Its duration is usually a maximum of 48 hours. Patients who have entered this

phase of healing may experience redness, fever, swelling, or pain at the wound site. The early inflammatory phase of wound healing is characterized by the resolution of the initial vasoconstriction followed by dilatation of the lumen, which results in increased vascular permeability [4].

Neutrophils are the first cells to induce the inflammatory phase at the site of injury. Their presence depends on chemotactic factors – thrombin, fibrin breakdown products, histamine, leukotrienes, PDGF, TGF-β, bacteria, and components (C5a) of the complement system. The highest number of neutrophils is observed around the first day after injury, after which it decreases after about 48–72 hours (as a result of apoptosis). Next, monocytes appear, which are transformed into macrophages as a result of the action of TGF-β, fibrin breakdown products, and fibronectin, released from the temporary matrix formed in the hemostasis phase. Macrophages are responsible for the continuation of the activity of neutrophils – phagocytosis, degradation and digestion of pathogens, and elimination of tissue debris as a result of the secretion of enzymes (collagenase, elastase, cathepsin G). In addition, said cells degrade the remaining neutrophils [4,9,16]. Macrophages are also a valuable source of cytokines involved in the tissue healing process. These cytokines include interleukins (IL) – IL-1, IL-6, IL-8 – growth factors TGF-α, TGF-β, PDGF, FGF, VEGF, heparin-binding epidermal growth factor (HB-EGF), chemokines. They stimulate cell migration, angiogenesis, collagen accumulation as well as epithelization [4,9,16,17]. Released cytokines (mainly TGF-β) react to vascular endothelial cells, which results in increased expression of adhesion molecules, e.g. vascular cell adhesion molecule 1 (VCAM-1), endothelial-leukocyte adhesion molecule 1 (ELAM-1) and intercellular adhesion molecule 1 (ICAM-1) on the endothelial surface. These adhesion molecules enable interactions between the endothelium and leukocytes, via integrins or selectins. These cells participate in the phagocytosis of bacteria, cellular debris, and proteolysis of the ECM. Cytokines such as TGF-β, tumor necrosis factor α (TNF-α), and IL-1, released by the macrophages, regulate leukocyte protease activity [9,18].

About 72 hours after tissue damage (in the final course of the inflammation phase), the last cells participating in this healing phase, i.e. lymphocytes, flow into the wound [17,19]. They are attracted to IL-1, complement components, and immunoglobulin G (IgG) breakdown products; IL-1 affects the action of collagenase, which in later stages determines the remodeling of collagen, which is a component of the ECM. In this way, the damaged tissue is prepared to enter the next phase of the healing process – the proliferative phase. Its purpose is to close the wound and then create new tissue that will be resistant to infection [5,9,17].

It should be emphasized that an insufficient amount of monocytes/macrophages may contribute to impaired wound healing due to ineffective wound cleansing, and delay in angiogenesis, multiplication, and maturation of fibroblasts. The key goal of this phase of the tissue healing process is therefore to control infection [17,19]. Depending on the activity of macrophages, the transition from the inflammatory phase to the proliferative phase (wounds showing no signs of infection) takes place from 4 to 5 days after the tissue damage occurs [7].

Proliferation phase

The proliferation phase begins about 2–3 days after the start of the healing process and lasts about 14 days [4,7]. It is characterized by significant intensity – the number of cells, i.e. fibroblasts, keratinocytes, and endothelial cells – increases in the wound bed. Fibroblasts secrete IGF-1, PDGF, EGF, TGF-β and basic fibroblast growth factor (bFGF), while growth factors secreted by keratinocytes include TGF-α, TGF-β, and keratinocyte-derived autocrine factor (KDAF). Endothelial cells synthesize VEGF, bFGF, and PDGF. The task of these mediators is to modulate and stimulate the basic processes taking place in the proliferation phase, i.e. ECM biosynthesis, epithelialization, and angiogenesis. The production of mediators and growth factors by the above-mentioned cells during the inflammation phase contributes to their migration and then proliferation [4,9,17,20].

Fibroblasts play a key role in the biosynthesis stage of the ECM. They arise from undifferentiated mesenchymal cells of the dermis, which, through the influence of cytokines and growth factors produced by platelets, neutrophils, and macrophages, are transformed into fibroblasts. Within 48–72 hours of skin damage, these cells migrate to the wound site as a result of attraction by EGF, PDGF, TGF-β, and IGF-1, where the cells multiply, then the synthesis of ECM components and the formation of granulation tissue begins. The term "granulation tissue" is derived from the characteristic structure of this tissue, associated with the presence of newly formed capillaries [4,9].

During the process of granulation tissue formation, biosynthesis (mainly by fibroblasts) of collagens (type I and III), elastin, glycosaminoglycans, and proteoglycans takes place. The matrix of early "granulation tissue" (up to the third day after the skin damage occurs) is rich in hyaluronic acid (HA) and fibronectin. The role of HA, with highly hygroscopic properties, therefore characterized by the ability to swell strongly, is to create a woven structure that allows incoming cells to penetrate the surface of the healing wound. From the third day after the injury, the content of HA decreases, and collagen replaces it (the amount

of this protein in the granulation tissue increases until the third week after the injury). At this stage of wound healing, type III collagen dominates, it gives the tissue the desired biomechanical properties (tensile strength), determining its integrity and remodeling the primary ECM of the wound. Simultaneously with the increase in collagen content, the number of fibroblasts decreases. Fibronectin is involved in the binding of fibroblasts to the ECM and creates a scaffold for collagen fibers, and also mediates in closing the healing wound. The "granulation tissue" produced during this stage, temporarily replacing the dermis, turns into a scar during the next phase of the healing process – the remodeling phase [4,7,9,16,17,20,21].

Epithelization is a multi-stage process of rebuilding the damaged epidermis. It consists of such stages as the migration of keratinocytes into the wound, their proliferation, and differentiation, as well as restoration of the basement membrane, which connects the epidermis with the dermis. Epidermal cells involved in closing the wound surface come from both its edges and epithelial appendages (hair follicles, sweat, or sebaceous glands). To interact with the temporary matrix formed in the initial stage of healing, the migrating keratinocytes interact with surface integrin receptors. The binding of keratinocytes with integrin receptors, which are present on newly formed collagen molecules, affects the regulation of the direction of migration of the cells in question. An important role in the process of separating keratinocytes from basement membranes is also played by matrix metalloproteinases (MMPs), which disrupt the binding of keratinocytes with integrin receptors. Metalloproteinases, among others: MMP-1 (interstitial collagenase) and MMP-9 (gelatinase B), released by keratinocytes are involved in the type IV collagen as well as laminins associated with fibrillar collagen degradation. It further contributes to "leave" the basement membrane and keratinocytes to migrate directly into the wound. In the later stage of this healing phase, keratinocytes are involved in the final differentiation aimed at the formation of epidermal layers [4,9,17,20].

In the proliferation phase, angiogenesis also occurs, i.e. the process of creating new blood vessels. Restoration of blood circulation at the site of damage prevents the formation of necrosis as a result of ischemia but also stimulates the process of tissue repair at the same time. Environmental factors that stimulate angiogenesis include low oxygen concentration, low pH as well as high concentrations of lactic acid, and low molecular weight HA molecules. In addition, pro-angiogenic activity is shown by TNF-α, TGF-β, VEGF, and bFGF as well as angiogenin, and angiotropin. On the other hand, the factors inhibiting the discussed process are angiostatin, thrombospondin, and HA molecules characterized by high molecular weight [7,9,12,20, 22,23,24]. In the course of angiogenesis, endothelial cells migrate to the provisional wound matrix, then proliferate and form branching structures. The migration of these cells is dependent on the activity of MMPs, which break down basement membranes and release growth factors that are stored in the ECM. The merging of endothelial cells determines the formation of structures giving rise to new blood vessels [4,17].

Remodeling phase

Remodeling is the last phase of the healing process. It lasts from a one year to two years, sometimes even several years. During this healing phase, the ECM is rebuilt, and the granulation tissue matures into a scar, which leads to an increase in the mechanical strength of the newly formed tissue. During the process of granulation tissue maturation, the number of capillaries is reduced (as a result of their aggregation into larger blood vessels), as well as the content of glycosaminoglycans and proteoglycans is reduced; the cellular density and metabolic activity of the tissue are also reduced. Type III collagen present in the granulation tissue is replaced by type I collagen (it is characterized by greater strength compared to type III collagen), and the total content of this protein increases [22,25]. In the remodeling phase, the wound surface shrinks – TGF-β1 stimulates fibroblasts to differentiate into myofibroblasts, which are involved in this process. Myofibroblasts are responsible for the secretion of MMPs, which can degrade ECM and for the synthesis of inhibitors of these metalloproteinases (tissue inhibitors of metalloproteinases – TIMPs). As a result of an imbalance between MMP and TIMP expression, atypical modification of the ECM may take place, leading to the formation of chronic wounds. In the final stage of healing, myofibroblasts undergo apoptosis. If not, excessive scarring may occur. Macrophages involved in this stage of wound healing play an important role in the elimination of ECM residues as well as apoptotic cells. In this last phase of healing, the granulation tissue is replaced by a scar, which only reaches about 20–40% of its final strength in the first three weeks. Further increase in the strength of the scar is much slower, to finally reach a maximum of approx. 70–80% of the strength of normal skin [1,4,7,9,17, 20,21,22,25].

Topical wound treatment, requirements for ideal dressings

Wound healing is a naturally occurring, long-term, and complex process that occurs in the body when injured. Its incorrect course may result in chronic wounds, necrosis or excessive scarring. Wound treatment supports this natural process.

Local management of burn wounds is an early treatment option, which aims to clean and cover the wounds as early as possible, and consequently protect

against infection. This treatment depends on the depth and area of the burn. There are three ways to treat a burn wound: open (without a dressing), closed (with a dressing), early necrectomy, and covering the wounds with auto-, allografts, or other materials [26].

In cases that require such support, dressings are used, which are an essential element applicable in health care [27]. An ideal dressing should: create a barrier against external factors, maintain an appropriate environment in the wound bed (appropriate temperature, optimal humidity, slightly acidic pH, gas exchange), absorb blood and exudate excess, keep the wound clean – cleanse of necrotic tissue and toxins – do not adhere to the wound to avoid damage to the wound during dressing replacement and do not show sensitizing or irritating effects [3].

Properly performed local treatment of a burn wound should be based on a procedure that inhibits the action of the destructive factor, then on cleaning the wound bed of dead tissues, and finally the appropriate selection of specialist dressings to support the healing process [28]. When selecting a dressing for the type of burn wound, its size and depth should be taken into account, but treatment with the dressing should also achieve the following goals, i.e.: preventing infection, ensuring a moist environment in the wound bed, protecting tissues from further damage, reducing pain, enabling movement without feeling discomfort and reducing swelling [29].

The properties and structure of the dressing have a beneficial effect on the healing process of a burn wound. The appropriate selection of the dressing is based on taking into account such factors as wound characteristics, location of the injury, type of burn, depth and extent of the wound, severity of the injury, stage of the healing process, exudate intensity, presence of infection, general condition of the patient (immunological status, chronic diseases) as well as quality pre-medical assistance. Most of the available dressings and topical preparations are used in conservative local treatment of burns [30].

One of the proposals for the so-called ideal dressing, designed for the regeneration of hard-to-heal burn wounds, is a biodegradable, apitherapeutic nonwoven dressing. The developed dressing under the name biodegradable nonwoven dressing was patented by the authors of the publication (P.425636).

Obtained by electrospinning, using a biodegradable polymer, the unique nonwoven dressing nanofiber contains an apitherapeutic agent – propolis. The effect of the dressing in question is to protect the sensitive wound surface, but most importantly to interfere with the complex healing process, to accelerate it and minimize potential complications.

The dressing in question, with incorporated propolis, provides "hydration" of the wound, accelerates re--epithelialization, and stimulates angiogenesis and biosynthesis of ECM components, allowing gas exchange between the wound and the environment.

The beneficial effect of the dressing on the healing process of a burn wound, confirmed by experimental studies [31,32], is associated with the well-known antioxidant, anti-inflammatory, immunomodulatory, antiviral, antitumor, antimicrobial, and antifungal activities of propolis, also including the properties of stimulating re-epithelialization and reducing the repair time of tissue damage.

Dressings commonly used in medicine are primarily limited to physical protection of the wound, although they do not always meet the requirements for an ideal dressing. They do not provide an appropriate environment within the damaged tissue, which has a limited impact on the wound-healing process. In addition, some wounds – apart from physical isolation of the wound – require active treatment, i.e. the use of dressings with an active substance (e.g. antibiotics or silver). All these assumptions contributed to the emergence of modern dressings – characterized by biocompatibility, the ability to degrade, and better retention of moisture compared to traditional dressings. They contain active substances, often of plant origin [27,33]

Author's contribution

Study design – K. Orlińska, K. Komosińska-Vassev, K. Olczyk

Manuscript preparation – K. Orlińska, M. Glaesel, P. Olczyk

Literature research – K. Orlińska, K. Komosińska-Vassev, K. Olczyk, M. Glaesel, P. Olczyk

Final approval of the version to be published – K. Orlińska, K. Komosińska-Vassev, K. Olczyk, M. Glaesel, P. Olczyk

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