WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 15, 621-631. Review Article ISSN 2277– 7105

FACTORS INFLUENCING HEALING OF WOUND: A REVIEW

Dr. K. Rajeshwar Reddy[1] and Dr. Chetana Suresh Patil*[2]

[1]MS (Shalyatantra), Professor, Shalyatantra Dept., R. A. Podar (Ayu) Medical College, Worli, Mumbai.

[2]PG Student, Shalyatantra Dept., Shalyatantra Dept., R. A. Podar (Ayu) Medical College, Worli, Mumbai.

Article Received on
04 Oct. 2020,

Revised on 24 Oct. 2020,
Accepted on 14 Nov. 2020

DOI: 10.20959/wjpr202015-19281

***Corresponding Author**
Dr. Chetana Suresh Patil
PG Student, Shalyatantra Dept., Shalyatantra Dept., R. A. Podar (Ayu) Medical College, Worli, Mumbai.

ABSTRACT

Surgery as a science, quintessentially revolves around 'wound', may it is traumatic or pyogenic. Surgeon either has to create the wound during surgical procedure or treat the wound occurred by trauma, accidental conditions, vitiated doshas. The healing of these wounds has always been a central consideration in surgical practice because any break in continuity of skin exposes the deeper tissues to the danger of infections. Today wound healing abnormalities are among the greatest causes of disability and deformity. It is the amount and quality of scar tissue and ultimately its remodelling that is of greater importance. The understanding of this process of wound healing and factors affecting it forms the basis of any surgical procedure. Wounds may fail to heal or healing time may be greatly increased when unfavourable conditions are allowed to persist. The factors which affect wound healing can be broadly categorised into extrinsic and intrinsic factors. Extrinsic factors affecting wound healing include: smoking, mechanical stress, moisture, infection, and chemical stress. Intrinsic factor that directly affect the healing of wound are multiple comorbidities, increased age, obesity, nutritional status and health status.

KEYWORDS: wound, traumatic, pyogenic, infections, comorbidities.

INTRODUCTION

The science of Ayurveda has forever been treasure trove of knowledge which aims at maintaining health, curing and preventing various diseases thereby giving human being a healthy life. Shalyatantra is one of the eight branches of Ayurveda. Vrana i.e wound and its management has been dealt with since the beginning of vedas till date. Acharya Sushruta has

described the etiology, pathogenesis and types of vrana with its management with Shashti-upakrama.

A physiological wound healing is a highly organized process initiated by the tissue injury and resolved by the restoration of tissue integrity. It includes following phases: hemostasis, inflammation, proliferation, and remodeling.[1] Immediately after disruption of tissue integrity either by accidental trauma or surgeon's knife injury, the Haemostasis phase is triggered; platelets become adherent and with clotting factors form a haemostatic plug to stop bleeding from the small vessels, which altogether initiate the next phase, namely the Inflammatory one. During this phase, the platelets gets activated and the injured tissue releases a well-controlled panel of growth factors, cytokines, and chemoattractants which, in turn, do attract neutrophils, macrophages and lymphocytes to the wound site. The locally involved extracellular matrix (ECM) and the entire wound area get enriched by the recruited platelets, macrophages which altoghether release core of growth factors which promotes fibriblasts activation initiating the next phase- the Proliferative phase. It lasts from third day to the third week consisting mainly of fibroblasts activity with the production of collagen and ground substance, angiogenesis and re-epithelialization of wound surface. Final phase of wound healing is Remodelling phase. It is characterized by maturation of collagen. There is realignment of collagen fibres along the line of tension, decreased wound vascularity and wound contraction.

Whereas the physiologic wound healing successfully proceeds through the clearly defined sequence of the individual phases of wound healing, chronic non-healing wounds/ulcers fail to complete the individual stages and the entire healing process. Delayed healing may result in loss of function or poor cosmetic outcome.[2] There are many risk factors both modifiable such as stress, smoking, inappropriate alcohol consumption, malnutrition, obesity, diabetes, cardio-vascular disease, etc. And non-modifiable such as genetic disease and ageing.

Hence, it is very essential to understand the factors affecting wound healing. This article provides detail study of factors linked to impaired wound healing.

ACCORDING TO AYURVED[3,4]

- **Anatmavatam Rugna**: If the patient is not aatmavan i.e consumes the ahar and follows the vihar which is not good for his health (apathyakar ahar-vihar); affects the proper wound healing mechanism.

- **Adnyaschaupakranta**: Treatment taken from Adnya; maybe inappropriate surgical technique which can be rough handling of tissue and use of inappropriate instruments, impaires the wound healing procedure.

These factors causes doshaprakop making vrana to become dushta; ultimately affects proper wound healing process.

- According to sushrutacharya the vrana may precipitate immediately after its healing if is encountered with Doshaprakopa, Exercises, Trauma, Ajirna, and Mental factors like krodha & Bhaya. It causes reoccurrence of vrana leading to delayed wound healing.

❖ **ACCORDING TO MODERN**

1. **Local factors affecting wound healing** are discussed below.

1. Infection
2. Presence of necrotic tissue
3. Surgical Technique
4. Haematoma Formation
5. Foreign body reaction
6. Tissue hypoxia
7. Topical medications

1) Infection

The majority of surgical site wound infections are due to endogenous flora that is usually present on the mucous membranes, skin or hollow viscera. Acute and chronic wound infection exists when the microbial load is $>10^5$ CFU/g of tissue.[5] Due to infection, fibroblasts face tough time to persist as they have to compete with inflammatory cells and bacteria for oxygen and nutrients. So proper granulation tissue formation and collagen formation become affected. Formation of excessive devitalised tissue, increased tension in the wound, hematoma and seromas, foreign bodies in the wound, all these factors predispose for bacterial secondary infection.

2) Presence of necrotic tissue

The presence of necrotic tissue in a wound will delay healing and predispose it to infection as it act as a source of nutrients for bacteria.

3) Surgical Technique[6]

- The rough handling of tissue or the use of inappropriately bulky instrumentation can lead to crushed skin edges and subsequent devitalization of tissue, leading to increase in

inflammatory reaction and risk of secondary infection with increased scarring.

- Wound closed with inappropriately suture material may increase the chances of a foreign body reaction and subsequent infection.
- Skin sutures tied too tightly may lead to tissue ischaemia and predispose to infection.

4) Haematoma Formation

Excessive bleeding and the formation of a hematoma within the wound not only causes wound dehiscence but also can serve as an excellent culture medium for microorganisms.
If wound is in tension its healing will be jeopardized, and haematoma increases tension.

5) Foreign body reaction

A foreign body in the wound causes a prolonged inflammatory response, which interferes with the subsequent stages of wound repairs. Wounds containing foreign materials are characterised by low pH and low pO2. These factors significantly slow down wound repair.

6) Tissue hypoxia

Local factors such as foreign bodies, strangulating sutures or infection significantly slow down healing by promoting tissue ischemia. Limited supply of oxygen to the wound prevents production of collagen. Local hypoxia is detrimental to cellular proliferation, resistance to infection. The cumulative effect is delayed healing.

7) Topical medications

Local medicines applied to the wound may affect wound repairs. Even the bases in which these agents are compounded may accelerate or diminish the rates of epithelization.

Triamcinolone acetonide ointment (0.1%), Nitrofurazone, Benzoyl peroxidase cream, silver sulfadiazine are examples of the drugs that affect epidermal migration.

2. Regional factors affecting wound healing are discussed below:

1. Arterial insufficiency
2. Venous insufficiency
3. Neuropathy

1. Arterial insufficiency

It is the most common type of peripheral vascular disease. Arterial diseases, especially associated with diabetes, represents a major complicating factor in wound healing.

2. Venous insufficiency

Is another cause of most leg ulcers. Chronic venous insufficiency, characterized by the retrograde flow of blood in the lower extremity, is associated with changes in the venous wall and valves caused by inflammatory disorders induced by venous hypertension and associated fluid shear stress.

3. Neuropathy

Local paresthesias, or lack of sensation over pressure points on the foot leads to microtrauma, breakdown of overlying tissue, and eventually ulceration.

Peripheral neuropathy is often a result of:

- A primary neurological condition
- Diabetes
- Ranal failure
- Trauma

3. Systemic factors affecting wound healing are discussed below.

1) DIABETES[7]

Diabetes plays a detrimental role in wound healing. It does so by affecting the wound healing process at multiple steps.

- **Wound hypoxia**, through a combination of impaired angiogenesis, inadequate tissue perfusion, and pressure-related ischemia, is a major driver of chronic diabetic wounds.
- **Ischemia** can lead to prolonged inflammation, which increases the levels of oxygen radicals, leading to further tissue injury.
- **Elevated levels of matrix metalloproteases** in chronic diabetic wounds, sometimes up to 50-100 times higher than acute wounds, cause tissue destruction and prevent normal repair processes from taking place.
- Also, diabetes is associated with **impaired immunity,** with critical defects occurring at multiple points within the immune system cascade of the wound healing. For example, neutrophils show impaired chemotaxis and phagocytosis. As a result, diabetic wounds are prone to chronic infection due to inadequate bacterial clearance.
- These wounds have **defects** in **angiogenesis** and **neovascularization**.
- Normally, wound hypoxia stimulates mobilization of endothelial progenitor cells via vascular endothelial growth factor. In diabetic wounds, there are **aberrant levels of**

vascular endothelial growth factor (VEGF) and other angiogenic factors such as angiopoietin-1 and angiopoietin-2 that lead to dysangiogenesis.

- **Diabetic neuropathy** may also play a role in poor wound healing. Lower levels of neuropeptides, as well as reduced leukocyte infiltration as a result of sensory denervation, have been shown to impair wound healing.

When combined, all these factors play a role in the formation and propagation of chronic, debilitating wounds in patients with diabetes.

2) DEFICIENCY STATES/ MALNUTRITION[8]

Wounds require different micro and macronutrients to heal properly.

Regarding **macronutrients**, **proteins** are the key building blocks of our tissues, highlighting the importance of ample supply of protein/amino acid-rich nutrition to ensure adequate wound healing. **Amino acids** such as, **arginine**, and **glutamine** play a critical in the overall wound healing process.

Arginine improves immune function, supports collagen deposition, and plays a role in neovascularization. Arginine supplementation also has a positive effect on wound healing. **Glutamine** is a critical energy source in proliferating cells. This amino acid is thought to improve the overall wound strength by increasing levels of mature collagen. The 2 other major macronutrients, **fatty acids** and **carbohydrates**, are also critical to wound healing. Carbohydrates, primarily glucose, act as the primary fuel for cells as it becomes broken down to form adenosine triphosphate (ATP). Polyunsaturated fatty acids, such as omega-3 and omega-6 fatty acids, both of which are essential fatty acids, may enhance the wound healing by having an overall positive effect on host immune function.

Several **micronutrients** play a particularly important role in wound healing.

These include ascorbic acid or vitamin C, vitamin A, vitamin E, as well as magnesium, zinc, and iron.

Vitamin C supports the hydroxylation of proline to hydroxyproline, which is essential for proper collagen formation.

In scurvy (deficiency of vitamin c), the collagen formed is unhydroxylated, relatively unstable and subject to collagenolysis.

Vitamin A stimulates epidermal turnover, increases the rate of re-epithelialization, and restores epithelial structure. similarly supports collagen formation, as well as immune modulation, and decreased metalloprotease ECM degradation. It has been demonstrated to enhance production of extracellular matrix components such as collagen type I and fibronectin, increased proliferation of keratinocytes and fibroblasts, and decrease levels of degrading matrix metalloproteinases.

Vitamin A deficiency has been associated with slowed reepithelization, decreased collagen synthesis and stability and an increased susceptibility to infection.

As an antioxidant, **vitamin E** helps protect against oxidative tissue destruction, as well as may decrease excess scar formation. **Magnesium** is a cofactor in enzymes involved in collagen synthesis. **Zinc**, on the other hand, is a cofactor for DNA and RNA polymerase, playing a vital role in cell division.

Iron deficiency has been shown to result in impaired collagen synthesis.

Vitamin K deficiency results in a deficiency in the production of vitamin K dependent clotting factors (factors II, VII, IX and X) resulting in bleeding diathesis, hematoma formation and secondary detrimental effects on wound healing.

3) AGING

Disturbed microcirculation and hypoperfusion which are characteristic of ageing skin contributes to the impaired inflammatory response and hinders the physiologic angiogenic phase in the overall wound healing. Another characteristic of the ageing skin is a strongly reduced ECM(extracellular matrix) production and overexpressed MMPs (matrix metalloproteinase), especially MMP-2 that collectively leads to impairments in the remodelling phase.

4) DISEASE STATES

Some of the most important diseases leading to impaired wound healing are listed here. Disease states associated with impaired wound healing.

- Hereditary
- Ehlers-Danlos syndrome, Prolidase deficiency(hereditary disorder of collagen metabolism that leads to skin fragility and recurrent ulceration).

- Werner's syndrome
- Coagulation disorders like Hemophilia, Von Willebrand's disease, Factor XIII deficiency, Hypofibrinogenemia
- Congestive heart failure, Atherosclerosis, Vasculitis
- Vascular disorders
- Venous stasis
- Lymphoedema
- Metabolic
- Chronic renal failure
- Diabetes mellitus
- Malnutrition
- Cushing's syndrome
- Hyperthyroidism
- Immunologic deficiency states
- Chronic pulmonary disease
- Chronic liver disease (cirrhosis)
- Malignancy
- Myelofibrosis and other chronic hematologic disorders associated with thrombocytopenia
- Other chronic illness

The immunologic deficiency states may impair healing by predisposing the wound to infection and diminishing the inflammatory phase of wound healing.

- Immediate skin grafting prevents wound contraction.
- X-Irradiation, if applied on the wound, causes delay in wound contraction.

5) MEDICATION[9]

Some of the drugs causing impaired wound healing are:

- Glucocorticoids
- Anticoagulants
- Angiogenesis inhibitors
- Antineoplastic drugs
- Cyclosporine A
- Cholchicine

- Penicillamine
- Zinc sulfate(high doses)
- Beta amino proprionitrile

Better documented are the effects of anticoagulants and glucocorticosteroids.

Glucocorticosides cause dehiscence of surgical incisions, increased risk of wound infection and delayed healing of open wounds. Corticosteroids, directly inhibit wound healing. They diminish inflammation, decrease protein and collagen synthesis, decrease epidermal proliferation, interfere with host defense mechanisms and promote the hypercatabolism of existing collagen. In addition they may lead to relative tissue ischaemia by means of their vasoconstrictive properties.

Anticoagulants indirectly interfere with healing by increasing the chances of bleeding and hematoma formation.

6) OBESITY

Obesity is a significant factor in surgical wound healing.

Abdominal obesity is correlated with oxidative stress, and is associated with deficiency of adiponectin. Adiponectin-deficient state leads to impaired perfusion and reepithelialization of the wound.

Surgical site infections and fat necrosis are more common in obese patients.

Pressure ulcers are more common in obese patients through pressure-related ischemia as well as decreased mobility.

Systemic effects of obesity, such as hypertension, hyperglycemia, and upregulation of the stress hormones in response to the physiologic burden of surgery and acute illness, all are responsible for impairment of wound healing.

7) TOBACCO ABUSE

Cigarette smoking leads to numerous adverse health consequences, including various types of cancer, primary lung disease, and cardiovascular disease.

However, in addition to those, smoking has severe ill-effects on the wound healing process, inducing **wound ischemia**.

Nicotine in smoke acts as a **vasoconstrictor.**[9] Also, tobacco use stimulates the release of

catecholamines such as **epinephrine**, leading to further reductions in tissue blood flow and hypoxia.

Relative wound ischemia can also result from the development of chronic obstructive pulmonary disease, which can lead to the permanent lowering of oxygen tension in the blood.

Also, nicotine reduces fibrinolysis, causing blood to become more viscous, leading to decreased tissue blood flow. **Carbon monoxide** (CO) in cigarette smoke binds to hemoglobin with 200 times greater affinity than oxygen, so even small amounts of carbon monoxide can profoundly reduce the oxygen carrying capacity of hemoglobin. In addition to the induction of ischemia, smoking leads to immunopathy of the wound via impaired PMN migration into the wound. Fibroblast migration and proliferation are also hindered, leading to decreased production of ECM (extracellular matrix) and ultimately weaker scar formation.

CONCLUSION

The local factors like infection, tissue hypoxia, surgical technique etc. and systemic factors like vascular insufficiency, neuropathy, disease states, malnutrition etc. are the major causes influencing wound healing, which can affect one or more phases of wound healing. Single or multiple factors may play a role in delaying wound healing. So the detailed study of factors influencing wound healing can be helpful to clinician for successful treatment of wound.

REFERENCES

1. Norman S. Williams et al., Bailey & Love's shorts practice of surgery, CRC press Taylor & Francis Group, 27th edition, chapter 3, pg. no. 24.
2. Norman S. Williams et al., Bailey & Love's shorts practice of surgery, CRC press Taylor & Francis Group, 27th edition, chapter 3, pg. no. 25.
3. Dr.Sharma A.R., Sushrut Samhita, Chaukhambha surbharti prakashan, Varanasi, Reprint: 2017, Volume I, Chikitsasthana, Adhyay 22, page no. 191, Shlok no.6.
4. Dr.Sharma A.R., Sushrut Samhita, Chaukhambha surbharti prakashan, Varanasi, Reprint: 2017, Volume I, Sutrasthana, Adhyay 23, page no.200, Shlok no. 21.
5. Young PY, et al., Surgical site infections. Surg Clin North Am., 2014 Dec; 94(6): 1245-64.
6. AK Deodhar et al., Surgical physiology of wound healing: a review, year: 1997; 43(2): 52-6.
7. Wernick B et al., Impaired wound healing, sept. 7, 2020.

a. Seied Hadi Saghaleini et al., pressure ulcer and nutrition, Indian Journal of Critical Care Medicine, 2018 Apr; 22(4): 283-289.
8. Avishai E et al., Imapired wound healing: facts and hypothesis for multi-professional considerations in predictive, preventive and personalized medicine, EPMA Journal, 2017; 8: 23-33.