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Published Research Paper : Newer Aspects Of Wound Healing In Surgical Specialities

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Research Paper

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Newer Aspects Of Wound Healing In Surgical Specialities

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Declaration

The Declaration of the authors for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) We Nischal Gupta1, Pallav Agarwal2, and M.K. Agarwal3 the authors of the research paper entitled Newer Aspects Of Wound Healing In Surgical Specialities declare that , We take the responsibility of the content and material of our paper as We ourself have written it and also have read the manuscript of our paper carefully. Also, We hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.We authorise the Editorial Board of the Journal to modify and edit the manuscript. We also give our consent to the publisher of ajmams to own the copyright of our research paper.

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ABSTRACT Wound healing is a complex and dynamic process that passes through a highly regulated and sequential yet overlapping event. Any disturbance in its course at cellular or molecular level results in chronicity of wound and failure to heal. We are discussing in the article some of the recent advances and novel therapies in wound healing, which could be utilised for optimized wound care. We are also enlightening the future area of research potential as stem cell and gene therapies.

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WOUND-

"May be defined as a defect or break in the integrity of skin that results from physical , mechanical or thermal damage or that develops as a result of the presence of an underlying medical or physiological disorder" (Thomas, 1990).

ACUTE WOUND-

Results from trauma, which may be surgical or due to accidents caused by blunt force, projectiles, heat, electricity, chemical or friction.

CRONIC WOUND-

A wound that fails to progress or respond to treatment over the normal expected course of healing process and become stuck in inflammatory phase i.e. not adequately re-epithelised within 6-8 weeks period.

WOUND HEALING-

Wound healing is a complex & dynamic process that passes through a sequential, yet overlapping, regulated, cascade of events.

TYPES OF WOUND HEALING: - 4 types

1. **Primary wound healing**:-(**Healing by primary intention**)	-Occur in wounds such as clean surgical incisions. **-** When wound edges are brought together (reapproximated) directly by mechanical means like sutures, glue, tapes etc. **-** Minimal or no scarring
2. **Delayed primary wound healing**:- (**Healing by tertiary intention**)	-If the wound edges are not reapproximated immediately, but left open for few days& then closed later surgically. -Ideally in contaminated wounds. - Wound is initially cleaned, debrided & left open for 4-5 days before closure.
3. **Secondary wound healing:-** **(Healing by secondary intention)**	**-** Preferred in large cavity wound, where closure is not feasible. e.g. A full thickness wound or wound at difficult anatomical position. **-**Wound is allowed to close & left open and heal by granulation tissue & contraction. **-** Results in broader scar formation.
4. **Healing by epitheliazation**:-	- Scar in partial thickness wounds involving only epidermis and superficial dermis, e.g. superficial burns & abrasions, wounds caused by split thickness skin graft. - Epitheliazation is predominant method of healing. - Wound contraction is not a common component. -Minimal scarring.

PHASES OF WOUND HEALING - (Table-1)

4 overlapping & regulated phases are: 1-Hemostasis 2-Inflammatry phase 3- Proliferative phase 4- Phases of Maturation & Remodelling.

Table-1:

BRIEF DISCRIPTION OF PHASES OF WOUND HEALING

Phases	Duration from Injury	Predominant cell type & factors	Important events & Resultant effects
1-Hemostasis	Immediate	Clotting cascade -**Platelets** -Inflammatory mediators -ECM, protein, PDGF. -Cytokines, Growth factors. -Platelet factorIV, TGF-5. -Serotonin, bradykinin, Prostaglandins, Prostacyclins , Thromb-exane & Histamine.	●Loss of structural integrity ↓ ● Blood in contact with vessel wall collagen stimulates platelets ↓ →Platelets aggregation Fibrin-Fibronectin plug formation →Vasoconstriction (lasts for 5-10 min) **limits further blood** ● Major initial stimulation for inflammation.
2-Inflammatory	First 6-8 hrs to 72 hrs	-**PMNs** (Neutrophils) (predominant cells in first 2 days.) -**Macrophages** (replace PMNs after 2 days). -TGF-b , FGF ,TGF-a , PDGF, C3a and C5a, cytokines , IL-1, TNF	● Neutrophils phagocytise debris & bacteria also kills bacteria by releasing free radicals. ● **Macrophages' key role** is to: ▪ Phagocytise bacteria & damaged tissue ▪ Stimulate cells (fibroblasts) that re-epitheliaize the wound, create granulation tissue & lay down new extracellular matrix. ▪ Induce angiogenesis. ● Fight infection clears debris & induce proliferative phase.

3. Proliferative Sub phases- {Fibroplasia Matrix deposition Angiogenesis Re-epithelialisation	3 days to 2 weeks	- **Fibroblasts** -Endothelial cells - **Keratinocytes** - Myofibroblasts -Growth Factors(PDGF, TGF-β), Fibronectin, GM-CSF, Matrix metalloproteinase(MMPs) -FGF , vascular endothelial growth factor (VEGF) -Epidermal growth factors(EGF)	Fibroplasia ↓ Extracellular matrix deposition. (Fibronectin + Hyaluronan), as main component. ↓ Collagen deposition. (Type III Collagen) ↓ • **Granulation tissue formation.** •Angiogenesis (Neovascularisation) •**Re-epithelisation** by keratinocyte migration & prolife- ration •**Wound contraction** (Fibroblast differen-tiation into Myofib-roblasts) ↓ Form connection to ECM at wound edges. -Fibro nexus (Action in Myofibroblast is linked across cell membrane to fibronectin & collagen in ECM. ↓ Actin in myofibroblasts contracts. ↓ Wound contraction.
4. Maturation & Remodelling	3weeks to 1 yr or even longer.	- **Fibroblasts** (principal cells) - Myofibroblasts	→Degradation & deposition of collagen in an equilibrium producing fashion. →**Reorganization of collagen**. →Replacement of Type III collagen by Type I collagen. →On going wound contraction. →**Scar formation** →Increase in tensile strength of wound, ultimately up to 80% as strong as normal.

Table -2:

FACTORS AFFECTING HEALING PROCESS:-

LOCAL	SYSTEMIC FACTORS
-Mechanical factors	- General malnutrition
- Unrelieved pressure	- Deficiency of proteins, vitamins (A, C &B
- Inadequate blood supply	Complex) & or trace elements such as Zinc.
- Peripheral vascular disease and vasculitis	- Stress & lack of sleep.
- Poor venous drainage	- Systemic disease e.g. Diabetes mellitus
- Presence of foreign body	rheumatoid arthritis, Connective tissue and
- Presence of infection (microorganism)	metabolic disease.
- Excess local mobility	- Systemic malignancy & terminal illness.
- Underlying cause (e.g. Osteomylitis)	- Chemotherapy & whole body radiation.
- Malignant transformation	- Immunosuppressant drugs &corticosteroids.
(Marjolin's ulcer)	- Increasing age.
	- Dehydration.
	- Obesity.
	- Anticoagulant therapy.

Table-3:

GROWTH FACTORS INVOLVED IN WOUND HEALING:-

Growth Factors	Main source	Functions in wound healing
PDGF (Platelets derived Growth factor)	-Platelets -Macrophages -Fibroblasts -Endothelial cells	●Chemotaxis of Neutrophils, macrophages & fibroblasts. ●Fibroblasts, endothelial cell &smooth muscle cell proliferation. ●MMPs, Fibronectin & Hyalurona production 7 collagen metabolism.
TGF-α (Transformin growth factor)	-Activated macrophages -Platelets -Epithelial cells	●Stimulates epithelial cell & fibroblast proliferation. ●Granulation tissue formation.
TGF-β (Transformin growth factor)	-Platelets -Macrophages -Fibroblasts -Neutrophils -Keratinocytes.	●Fibroblasts 7 smooth muscle cells proliferation. ●Macrophages chemotaxis. ●Stimulates angiogenesis & collagen metabolism.
VEGF (Vascular endothelial growth factor)	-Platelets -Neutrophils	●Endothelial proliferation ●Stimulates angiogenesis in granulation tissue.
FGF-1&2 (Fibroblast Growth factor)	-Macrophages -Endothelial cells -Fibroblasts -Smooth muscle cells	●Fibroblast & Keratinocytes proliferation. ●Matrix deposition, angiogenesis & wound contraction. ●Accelerate granulation tissue formation
EGF (Epidermal growth Factor)	-Activated macrophages -Keratinocytes -Salivary glands	●Keratinocytes proliferation differentiation, migrations &adhesion. ●Fibroblast mitogen ●granulation tissue formation
KGF (Keratinocytes	-Fibroblast.	●Keratinocytes proliferation,

Growth factor)		migration & differentiation.
G-CSF (Granulocyte colony stimulating factor)	-Monocytes, fibroblasts , lymphocytes	•Stimulates Neutrophils production. •Enhance Neutrophils & monocytes function. •Promotes keratinocyte proliferation.
GM-CSF (Granulocyte macrophage colony stimulating factor)	-Macrophages -Lymphocyte -Keratinocytes -Fibroblasts	•Mediates epidermal cell proliferation
IL-1 (Interleukin)	-Macrophages -Lymphocytes -Many other cells& tissue	•Neutrophils chemo taxis •Fibroblast proliferation
HGF (Hepatocyte growth Factor)	-Fibroblast -Keratinocytes -Endothelial cells -Tumor cells.	•Endothelial & epithelial cell proliferation. •Re-epitheliazation •Neovascularisation •Granulation tissue formation

RECENT ADVANCES AND NOVEL THERAPIES IN WOUND HEALING:-

Successful wound care involves optimising patient's local & systemic conditions along with an ideal wound healing environment.
► Our goal is to find the most appropriate modality or combination of modalities to optimise healing which is given below.

Intermittent pneumatic compression (IPC):-

IPC is effective for managing chronic venous ulcers with severe oedema, that are resistant to simple compression therapy (Emoch et al, 200 ba) .A compression pressure of 20-120 mmhg is provided at present intervals to improve venous & lymphatic flow. It is generally used 2 hrs a day for up to 6 weeks. This method is ideal for patients with limited mobility and should be used as an additional therapy to simple compression, not as a substitute (Enoch et al, 200 ba).

Nanocrystalline Silver dressings:-

Use of silver in newer form of delivery system as Nanocrystalline silver dressings is one of the latest technologies in the reason of antimicrobial prophylaxis. Elemental silver requires ionization for antimicrobial efficacy. The highly reactive charged silver ion (Ag++) reacts by binding to negatively charged particles such as proteins, DNA, RNA & chloride ions.

Nanocrystalline silver dressings currently in use contain 2 layers of high density polyethylene net, sandwiching a layer of rayon/polyester gauge. The outer layer is coated with a Nanocrystalline (<20 mm), noncharged form of silver (Ag °), and the inner layer helps maintain a moist environment for

wound healing, because the noncharged silver is less reactive with negatively particle in the wound , it is deactivated much more slowely and provides an initial large bolus of silver followed by a sustained release into the wound. Silver has a very broad spectrum of microbial coverage, including yeast, fungi, mould and even antibiotic resistant bacteria, such as methicillin resistant staphaureus (MRSA) and vancomycin resistant enterococci (VRE). When used at appropriate concentration. Silver is a bactericidal material that kills on contact by inhibiting the respiratory chain at the cytochrome level, as well as interfering with electron transport, denaturing nucleic acids, inhibiting DNA replication and altering cell membrane permeability. Bacterial resistance to silver is exceedingly low.

TOPICAL NEGATIVE PRESSURE THERAPY (TNPT) :-

Acute wounds are now more frequently treated with TNPT. In patients with significant co-morbidities or other serious injuries, TNPT can be used in large soft tissue injuries, contaminated wounds & wound with compromised tissue. One discovery that the overall volume & dimensions of the wound tend to decrease with TNPT is possibly allowing a less complex reconstruction than would initially be required. TNPT improves local dermal perfusion, promotes angiogenesis , stimulates granulation tissue, decrease interstitial fluid , control wound exudates and bacterial load (Enoch et al, 200 ba) and thus clinically translated into faster healing rates of wound.

HYPERBARIC OXYGEN:-

Hyperbaric oxygen is a treatment modality used as an adjunct in management of nonhealing wounds. It involves placing the patient in a sealed chamber where 100% oxygen is pressurized to between 1.5 and 3 atmospheres absolute (Ata) for 60-120 minutes over a course of multiple treatments. Hyperbaric oxygen , increases arterial oxygen pressure (PaO_2) which causes vasoconstriction and thus reduces capillary pressure which reduces oedema; as well as causes an increase in hyper oxygenated plasma to the tissue, thus hastens tissue repair process such as collagen elongation and deposition and bacterial killing by macrophages, that are dependent on oxygen. Neovascularisation in wound is enhanced by hyperbaric oxygen as it is shown to stimulate EPCs (Endothelial progenital cells) and stem cell release from bone marrow both by increases cell proliferation within the marrow, as well as by rapid metabolism via matrix metalloprotease mechanisms.

ADVANCED DRESSINGS:-

New wound understanding and technology have produced advanced product that help the body to achieve ideal moist, warm, protected wound healing environment. These products range from occlusive films such as Tegaderm, which are permeable to air and water vapour but impermeable to fluid micro organisms, to hydrocolloids such as DuoDERM which are also occlusive but provide absorption of exudates in addition to maintaining a moist environment for autolysis. For heavily exudative wounds, there are a range of absorptive product including various hydrophilic foam dressings, hydrogels, hydro fibres and alginates.

TISSUE ENGINEERED SKIN SUBSTITUTES:-

The advances in technology of biomaterials and tissue engineering has resulted in changed with regard to temporary and permanent coverage of wounds especially burn wounds. Autograft is currently the preferred option but many times there is an insufficient amount of tissue available for grafting. Allograft and xenograft can provides a temporary coverage option but; there are problems regarding rejection, possible disease transfer (Prion related), availability and cultured and ethical considerations. Bioengineered skin substitutes, both biosynthetic skin substitute and cultured autologous engineered skins are available to provide temporary and permanent coverage with advantage of availability in large quantities and negligible risk of immunologic issues.

Biobrane, Transcyte, Dermograft, apligraf, Integra, Epicel, alloderm are some of these products.

GROWTH FACTORS AND BIOLOGIC WOUND PRODUCTS:-

Chronic wounds may be arrested in any of the four phages; commonly however this arrest occasions the inflammatory or the proliferative phases. Normal wound healing is dependent upon numerous cellular mediators, including eicosanoids, cytokines and various growth factors. Use of these biologic products and growth factors produced by recombinant DNA technology can modify the healing process and aims to accelerate it by augmenting or modulating the inflammatory mediators.

EICOSANOIDS are arachidonic acid metabolites including prostaglandins, Prostacyclins, thromboxane and leukotrienes. They primarily affect the early stages of wound healing. *CYTOKINES* regulate inflammation by influencing hematopoietic cells and include chemokines, lymphokines, monokines, interleukins, colony stimulating factors and interferon's. *GROWTH FACTORS* have been studied more than any other biologic wound supplement. They are divided into five super families, the most known being the platelets derived growth factors. Recombinant PDGF, (rh PDGF) which is now known as becaplermin (trade name-regranex) is the only current. FDA-approved product in growth factor family.

Products targeting at different phases of wound healing:-

• ***Products targeting inflammatory phases***:-
The production and activity of several proteases e.g. Metalloproteases, serine proteases and Neutrophils elastases, may be altered in chronic wounds. Raised level of such proteases can be detrimental to healing and products aimed at counteracting their effect have been developed.
Promogen; - designed to inactivate proteases and also protect the host's naturally produced growth factor i it may be useful in treatment of chronic wounds refractory to conventional treatments.

• ***Products targeting proliferative phase***:-
Growth factors, including *granulocyte colony stimulating factor* (G-CSF) and *Transformin growth factor-β* (TGF-β) have also been used to target this phase of healing.
-*Recombinant human G-CSF*, injected subcutaneously has been shown to enhance healing in infected diabetic foot ulcers.
-*TGF-β_2* topical application has been shown to be effective in the healing of diabetic foot ulcers.
-*Recombinant PDGF (Becaplermin)* is being used topically in chronic diabetic foot ulcer.
-*Fibroblast growth factor (FGF*) and *vascular endothelial growth factor (VEGF)* are active in this phase of repair.

•***Product targeting epithelialisation and remodelling:-***
-*Recombinant human KGF-2* induces proliferation of epithelial cells and has been shown to enhance healing of venous leg ulcers.
-*Topical recombinant human GM-CSF* is effective in the healing of venous leg ulcers. -*TGF-β_3* causes reduced deposition of collagen during the proliferative and remodelling phases, thus reducing scar formation .trails into the efficacy of *TGF-β_3* in the treatment of hypertrophic scars are under way; the role of *TGF-β_3* in the treatment of keloid scars is unclear.

FUTURE ADVANCES & RESEARCH POTENTIAL:-

Recently the combination of stem cell and gene therapy has emerged as a promising approach for treatment of chronic and acute wounds.

STEM CELL THERAPY:-

Current areas of research include use of *adult pluripotent stem cells*, which have capability to renew themselves and to differentiate into various types of specialised cells such as fibroblasts, endothelial cells and Keratinocytes essential for wound healing. It is thought that the epidermis

and dermis are reconstituted by mitotically active stem cells that reside at the apex of rete ridges (*basal stem cell)* , the bulge of hair follicles (*hair follicular stem cells*), and the papillary dermis (*dermal stem cells*). Recent reports however, have indicated that bone marrow might also contain early stem cells that can differentiate into other organ tissue such as skin and thus play a major role in wound healing .Thus a variety of sources such as bone marrow, peripheral blood, umbilical cord blood, adipose tissue , skin and hair follicles have been utilised to isolate stem cells to accelerate the healing response of acute and chronic wounds. Recent studies have looked at the potential of *skeletal muscle* and *adipose derived stem cells*. Since fat can be obtained relatively easily in most people, adipose derived stem cells have become the ideal large scale source in practical regenerative medicine. They have an advantage over other stem cell sources as they have neither ethical nor immunoreactive consideration as long as they are of autologous origin. *Adipose derived stem cells* have found to accelerate wound healing and exhibit antioxidant effects under various experimental conditions.

GENE THERAPY:-

Gene therapy initially developed for treatment of congenital defects, is a new option for enhancing wound repair. In gene therapy, specific genes encoding for a particular product (e.g. *growth factors, cytokines, receptors, adhesions molecules and inhibitors of proteases*) are delivered to the target cell (s) to enhance, amend or negate the biological function of the cell (s) and its inherent genetic coding. Genes once incorporated in the cell; affect the cell and its environment by changing the way their products are expressed. The majority of gene delivering systems are based on *viral transfection, naked DNA application, high pressure microinjection or liposomal vectors (cationic liposomes)*. Genes may be employed to augment an affect (e.g. promote healing) such as genes for growth factors and its receptors, or to inhibit an affect (e.g. suppress excessive scaring) such as genes for antibodies against specific growth factors.

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