"A COMPARATIVE STUDY ON WOUND HEALING WITH TOPICAL APPLICATION OF HUMAN EPIDERMAL GROWTH FACTOR VERSES APPLICATION OF POVIDONE-IODINE IN DIABETIC WOUNDS"

A DISSERTATION SUBMITTED TO

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the regulations for the award of the degree of

MASTER OF SURGERY (GENERAL SURGERY)

BRANCH I: M.S (General Surgery)

DEPARTMENT OF GENERAL SURGERY

GOVERNMENT STANLEY MEDICAL COLLEGE AND HOSPITAL

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATE

This is to certify that the dissertation titled "**A COMPARITIVE STUDY ON WOUND HEALING WITH TOPICAL APPLICATION OF HUMAN EPIDERMAL GROWTH FACTOR VERSES APPLICATION OF POVIDINE IODINE IN DIABETIC WOUNDS**" the bonafide work done by **DR.MRUDHUL MATHEW** post graduate student (2013-2016) in the department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfilment of regulations of The Tamil Nadu Dr.M.G.R Medical University, Chennai for M.S. degree (General Surgery) Branch-1, Examination to be held in April 2016

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I, **DR. MRUDHUL MATHEW** solemnly declare that this dissertation titled "**A COMPARATIVE STUDY ON WOUND HEALING WITH TOPICAL APPLICATION OF HUMAN EPIDERMAL GROWTH FACTOR VERSES APPLICATION OF POVIDONE-IODINE IN DIABETIC WOUNDS"** is a bonafide work done by me in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of my unit chief.

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Place: Chennai.

Date : .09.2015 DR. MRUDHUL MATHEW

ACKNOWLEDGEMENT

It gives me immense pleasure for me to thank everyone who has helped me during the course of my study and in preparing this dissertation.

My sincere thanks to **Dr. ISAAC CHRISTIAN MOSES, M.D,FICP,FACP.,** the Dean, Govt. Stanley Medical College for permitting me to conduct the study and use the resources of the College.

I am very thankful to the chairman of Ethical Committee and members of Ethical Committee, Government Stanley Medical College and hospital for their guidance and help in getting the ethical clearance for this work.

I consider it a privilege to have done this study under the supervision of my beloved Professor and Head of the Department **Prof.Dr.S.VISWANATHAN, M.S,** who has been a source of constant inspiration and encouragement to accomplish this work.

I express my special thanks to **Prof. Dr. G.V.MANOHARAN.M.S** who encouraged me to accomplish this work

I express my deepest sense of thankfulness to my Assistant Professors **Dr. T. BABU ANTOMY, M.S, Dr. S. THIRUMURUGANAND, M.S, Dr. D.S. KUMARESAN, M.S, MRCS, Dr.KRISHNA BHARATH.M.S,** for their valuable inputs and constant encouragement without which this dissertation could not have been completed.

I am particularly thankful to my fellow postgraduate colleagues **Dr.Chelladurai** and **Dr. Jayalakshmi** and other fellow postgraduates for their valuable support in the time of need throughout the study.

I thank my Seniors **Dr.Venkatesh, Dr.Murugan, Dr. Robin Prabhu**, **Dr.Pandiaraja, Dr.Sanker** my junior PG's **Dr. S.Vijaya sarathy**, **Dr. S. Mathan shanker, Dr.N.Fazil Navabjan, Dr.K.Anbarasan, Dr.Deepak David, Dr.Sanjeev, Dr.Kokila, Dr.Manarmannan** who supported me in completing the dissertation.

It is my earnest duty to thank my dear parents **Mr. Mathew** and **Mrs.Rosamma** and my dear wife **Dr. Alpha Maria**, my dear sister **Dr.Misha Rose Mathew,** without whom accomplishing this task would have been impossible.

I am extremely thankful to my patients who consented and participated to make this study possible.

TABLE OF CONTENTS

LIST OF ABREVIATIONS USED

ECM	Extra cellular matrix
DNA	Deoxy ribo nucleic acid
DM	Diabetes mellitus
HB-EGF	Heparin binding EGF
MMP	Matrix Metalloproteinase
CDK	Cyclin dependent kinase
TNF	Tumour necrosis factor
EGF	Epidermal growth factor
HGF	Hepatocyte growth factor
PDGF	Platelet derived growth factor
VEGF	Vascular endothelial growth factor
CEA	Culture epithelial autograft

INTRODUCTION

- Diabetic wounds or ulcers are major complication of diabetes mellitus
- Diabetes is a metabolic disorder that impedes the normal steps of wound healing process
- Major increase in morbidity in diabetic patients is due to macro and micro vascular complications including failure of wound healing process
- Diabetes is the cause for more than 3/4th lower limb amputation
- Increased glucose in the tissue precipitates infection
- Increased glycosylated tissue protein decreases the oxygen utilization
- Epidermal growth factor will stimulates cell growth,proliferation and differentiation by binding to its receptor EGFR
- It acts on epithelial cells and fibroblasts promoting restoration of damaged epithelium
- Current evidence suggests that application of human recombinant EGF in addition to standard treatment is able to achieve both partial and complete healing and to prevent foot amputations.
- It also enhances the wound healing in diabetic wounds
- Its efficacy has been tested at various concentrations and by various administration routes (topical application and intralesional injection).

AIMS AND OBJECTIVE OF STUDY

The aim of this study is to establish whether topical application of human epidermal growth factor enhance wound healing better than conventional povidone-iodine dressing in diabetic wounds in Government Stanley Hospital, Chennai -1

REVIEW OF LITERATURE

History of Wound Healing

The earliest accounts of wound healing date back to about 2000 B.C., when the Sumerians employed two modes of treatment: a spiritual method consisting of incantations and a physical method of applying poultice-like materials to the wound.

The Egyptians were the first to differentiate between infected and diseased wounds compared to noninfected wounds.

The 1650 B.C. Edwin Smith Surgical Papyrus, a copy of a much older document, describes at least 48 different types of wounds.

A later document (Ebers Papyrus, 1550 B.C.) relates the use of concoctions containing honey (antibacterial properties), lint (absorbent properties), and grease (barrier) for treating wounds. These same properties are still considered essential in contemporary daily wound management.

The Greeks, equipped with the knowledge bequeathed by the Egyptians, went even further and classified wounds as acute or chronic in nature.

Galen of Pergamum (120–201 A.D.), appointed as the doctor to the Roman gladiators, had an enormous number of wounds to deal with after gladiatorial combats. He emphasized the importance of maintaining a moist environment to ensure adequate healing.

It took almost 19 centuries for this important concept to be proven scientifically, when it was shown that the epithelialization rate increases by 50% in a moist wound environment when compared to a dry wound environment.

The next major stride in the history of wound healing was the discovery of antiseptics and their importance in reducing wound infections.

Ignaz Philipp Semmelweis, a Hungarian obstetrician (1818–1865), noted that the incidence of puerperal fever was much lower if medical students, after cadaver-dissection class and before attending childbirth, washed their hands with soap and hypochlorite.

Louis Pasteur (1822–1895) was instrumental in dispelling the theory of spontaneous generation of germs and proving that germs were always introduced into the wound from the environment.

Joseph Lister probably made one of the most significant contributions to wound healing. On a visit to Glasgow, Scotland, Lister noted that some areas of the city's sewer system were less murky than the rest. He discovered that the water from pipes that were dumping waste containing carbolic acid (phenol) was clear. In 1865, Lister began soaking his instruments in phenol and spraying the operating rooms, reducing the mortality rates from 50 to 15%. This practice led to the suspension of Lister, although subsequent confirmation of his results paved the way for his triumphant return to Edinburgh.

After attending an impressive lecture by Lister in 1876, Robert Wood Johnson left the meeting and began 10 years of research that would ultimately result in the production of an antiseptic dressing in the form of cotton gauze impregnated with iodoform. Since then, several other materials have been used to impregnate cotton gauze to achieve antisepsis.

Polymeric dressings were developed in the 1960s and 1970s. These polymeric dressings can be custom made to specific parameters, such as permeability to gases (occlusive vs. semiocclusive), varying degrees of absorbency, and different physical forms. Due to the ability to customize, the available range of materials that aid in wound care has grown exponentially to include an ever-expanding variety. Currently, the practice of wound healing encompasses manipulation and/or use of, among others, inflammatory cytokines, growth factors, and bioengineered tissue. It is the combination of all these modalities that enables optimal wound healing.

Classification of Wounds

Wounds are classified as either **acute or chronic**. Acute wounds heal in a predictable manner and time frame. The process occurs with few, if any, complications, and the end result is a well-healed wound.

Surgical wounds can heal in several ways. An incised wound that is clean and closed by sutures is said to heal by primary intention. Often, because of bacterial contamination or tissue loss, a wound will be left open to heal by

granulation tissue formation and contraction; this constitutes healing by secondary intention.

Delayed primary closure, or healing by tertiary intention, represents a combination of the first two, consisting of the placement of sutures, allowing the wound to stay open for a few days, and the subsequent closure of the sutures.

Acute Wounds

The healing spectrum of acute wounds is broad . In examining the acquisition of mechanical integrity and strength during healing, the normal process is characterized by a constant and continual increase that reaches a plateau at some point postinjury.

Wounds with delayed healing are characterized by decreased wound-breaking strength in comparison to wounds that heal at a normal rate; however, they eventually achieve the same integrity and strength as wounds that heal normally. Conditions such as nutritional deficiencies, infections, or severe trauma cause delayed healing, which reverts to normal with correction of the underlying pathophysiology.

Impaired healing is characterized by a failure to achieve mechanical strength equivalent to normally healed wounds. Patients with compromised immune systems, such as those with **diabetes**, chronic steroid usage, or tissues damaged by radiotherapy, are prone to this type of impaired healing

Chronic Wounds

Chronic wounds are defined as wounds that have failed to proceed through the orderly process that produces satisfactory anatomic and functional integrity or that have proceeded through the repair process without producing an adequate anatomic and functional result. The majority of wounds that have not healed in 3 months are considered chronic.

Skin ulcers, which usually occur in traumatized or vascularly compromised soft tissue, are also considered chronic in nature, and proportionately are the major component of chronic wounds.

Repeated trauma, poor perfusion or oxygenation, and/or excessive inflammation contribute to the causation and the perpetuation of the chronicity of wounds.

Unresponsiveness to normal regulatory signals also has been implicated as a predictive factor of chronic wounds. This may come about as a failure of normal growth factor synthesis, and thus an increased breakdown of growth factors within a wound environment that is markedly proteolytic because of overexpression of protease activity or a failure of the normal antiprotease inhibitor mechanisms.

Fibroblasts from chronic wounds also have been found to have decreased proliferative potential, perhaps because of senescence or decreased expression of growth factor receptors.

Chronic wounds occur due to various etiologic factors, and several of the most common are discussed in the following sections.

Malignant transformation of chronic ulcers can occur in any long-standing wound (Marjolin ulcer). Any wound that does not heal for a prolonged period of time is prone to malignant transformation.

Malignant wounds are differentiated clinically from non-malignant wounds by the presence of overturned wound edges. In patients with suspected malignant transformations, biopsy of the wound edges must be performed to rule out malignancy. Cancers arising de novo in chronic wounds include both squamous and basal cell carcinomas

Pathology of Wound Healing

Tissue Renewal, Regeneration and Repair

Injury to cells and tissues sets in motion a series of events that contain the damage and initiate the healing process.

This process can be broadly separated into regeneration and repair . Regeneration results in the complete restitution of lost or damaged tissue; repair may restore some original structures but can cause structural derangements.

In healthy tissues, healing, in the form of regeneration or repair, occurs after practically any insult that causes tissue destruction, and is essential for the survival of the organism.

Tissues with high proliferative capacity, such as the hematopoietic system and the epithelia of the skin and gastrointestinal (GI) tract, renew themselves continuously and can regenerate after injury, as long as the stem cells of these tissues are not destroyed.

Repair most often consists of a combination of regeneration and scar formation by the deposition of collagen.

The relative contribution of regeneration and scarring in tissue repair depends on the ability of the tissue to regenerate and the extent of the injury. For instance, a superficial skin wound heals through the regeneration of the surface

epithelium. However, scar formation is the predominant healing process that occurs when the extracellular matrix (ECM) framework is damaged by severe injury .

Chronic inflammation that accompanies persistent injury also stimulates scar formation because of local production of growth factors and cytokines that promote fibroblast proliferation and collagen synthesis.

The term fibrosis is used to describe the extensive deposition of collagen that occurs under these situations.

ECM components are essential for wound healing, because they provide the framework for cell migration, maintain the correct cell polarity for the re-assembly of multilayer structures, and participate in the formation of new blood vessels (angiogenesis). Cells in the ECM (fibroblasts, macrophages, and other cell types) produce growth factors, cytokines, and chemokines that are critical for regeneration and repair.

Although repair is a healing process, it may itself cause tissue dysfunction, as, for instance, in the development of atherosclerosis.

Cell Cycle and the Regulation of Cell Replication

Cell proliferation is a tightly regulated process that involves a large number of molecules and interrelated pathways.

These are some salient features of the process of cellular proliferation.

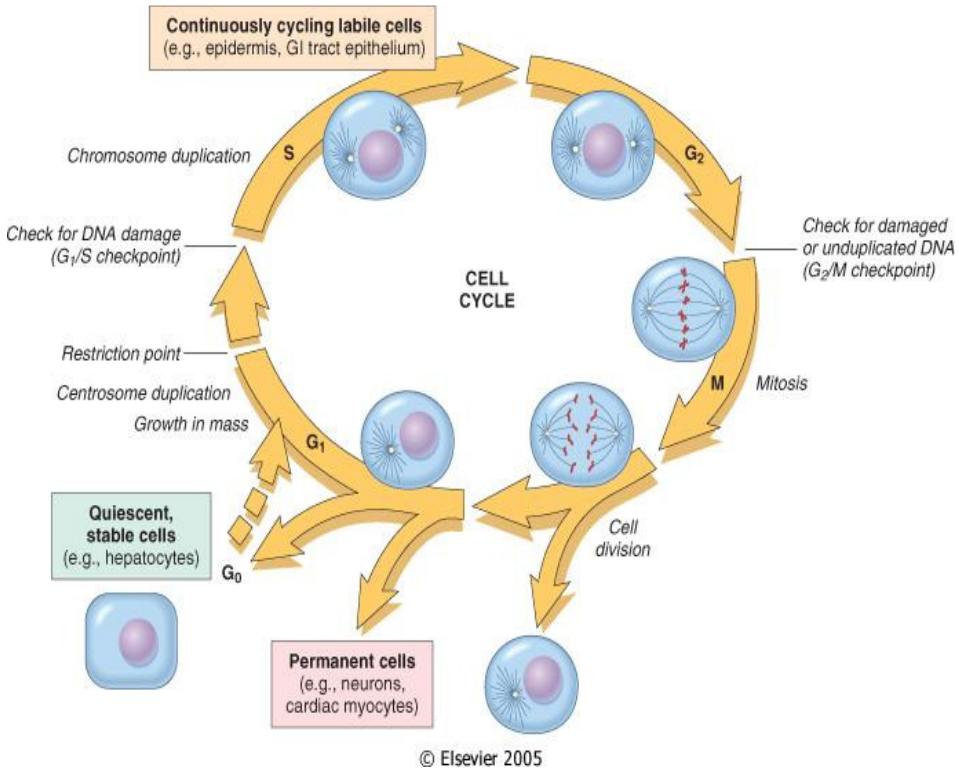
The replication of cells is stimulated by growth factors or by signaling from ECM components through integrins.

To achieve DNA replication and division, the cell goes through a tightly controlled sequence of events known as the cell cycle.

The cell cycle consists of G_1 (presynthetic), S (DNA synthesis), G_2 (premitotic), and M (mitotic) phases.

Quiescent cells which have not entered the cell cycle are in the G_0 state.

Each cell cycle phase is dependent on the proper activation and completion of the previous one, and the cycle stops at a place at which an essential gene function is deficient. Because of its central role in maintaining tissue homeostasis and regulating physiologic growth processes such as regeneration and repair, the cell cycle has multiple controls and redundancies, particularly during the transition between the G_1 and S phases. These controls include activators and inhibitors, as well as sensors that are responsible for checkpoints.



Cells enter G_1 either from G_0 (quiescent cells) or after completing mitosis (continuously replicating cells).

Quiescent cells first must go through the transition from G_0 to G_1, that functions as a gateway to the cell cycle. This transition involves the transcriptional activation of a large set of genes, including different proto-oncogenes and genes required for ribosome synthesis and protein translation.

Cells in G_1 progress through the cycle and reach a critical stage at the G_1/S transition, known as a restriction point, a ratelimiting step for replication . After

passing this restriction point, normal cells become irreversibly committed to DNA replication.

Progression through the cell cycle, particularly at the G_1/S transition, is tightly regulated by proteins called cyclins and associated enzymes called cyclin-dependent kinases (CDKs). CDKs acquire catalytic activity by binding to and forming complexes with the cyclins. Activated CDKs in these complexes drive the cell cycle by phosphorylating proteins that are critical for cell cycle transitions.

The activity of cyclin-CDK complexes is tightly regulated by CDK inhibitors. Some growth factors shut off production of these inhibitors.

Embedded in the cell cycle are surveillance mechanisms that are geared primarily at sensing damage to DNA and chromosomes. These quality control checks are called checkpoints; they ensure that cells with damaged DNA or chromosomes do not complete replication.

The G_1/S checkpoint monitors the integrity of DNA before replication, whereas the G_2/M checkpoint checks DNA after replication and monitors whether the cell can safely enter mitosis.

When cells sense DNA damage, checkpoint activation delays the cell cycle and triggers DNA repair mechanisms. If DNA damage is too severe to be repaired, the cells are eliminated by apoptosis, or enter a non-replicative state called senescence, primarily through p53-dependent mechanisms.

GROWTH FACTORS

The proliferation of many cell types is driven by polypeptides known as growth factors. These factors, which can have restricted or multiple cell targets, may also promote cell survival, locomotion, contractility, differentiation, and angiogenesis, activities that may be as important as their growth-promoting effects.

All growth factors function as ligands that bind to specific receptors, which deliver signals to the target cells. These signals stimulate the transcription of genes that may be silent in resting cells, including genes that control cell cycle entry and progression

Factors and Cytokines Involved in Regeneration and Wound Healing

Growth Factor	Symbol	Source	Functions
Epidermal growth factor	**EGF**	**Platelets, macrophages, saliva, urine, milk, plasma**	**Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation**
Transforming growth factor α	TGF-α	Macrophages, T lymphocytes, keratinocytes, and many tissues	Similar to EGF; stimulates replication of hepatocytes and most epithelial cells
Heparin-binding EGF	HB-EGF	Macrophages, mesenchymal cells	Keratinocyte replication
Hepatocyte growth factor/scatter factor	HGF	Mesenchymal cells	Enhances proliferation of hepatocytes, epithelial cells, and endothelial cells; increases cell motility, keratinocyte replication
Vascular endothelial cell growth factor	VEGF	Many types of cells	Increases vascular permeability; mitogenic for endothelial cells (see Table

Growth Factor	Symbol	Source	Functions
(isoforms A, B, C, D)			3-3); angiogenesis
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction
Fibroblast growth factor 1 (acidic), 2 (basic), and family	FGF	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition

Growth Factor	Symbol	Source	Functions
Transforming growth factor β (isoforms 1, 2, 3); other members of the family are BMPs and activin	TGF-β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth muscle cells; stimulates TIMP synthesis, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation
Keratinocyte growth factor (also called FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Tumor necrosis factor	TNF	Macrophages, mast cells, T lymphocytes	Activates macrophages; regulates other cytokines; multiple functions

Epidermal Growth Factor (EGF)

EGF has receptor called epidermal growth factor receptor (EGFR).

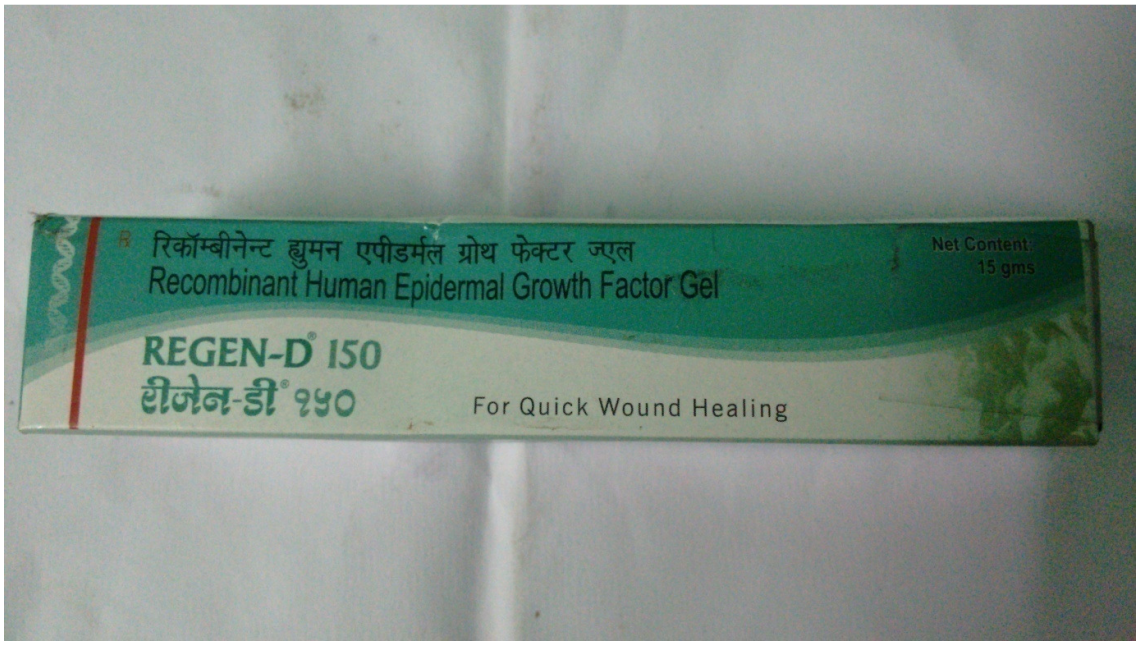
EGF is mitogenic for a variety of epithelial cells, hepatocytes, and fibroblasts, and is widely distributed in tissue secretions and fluids.

In healing wounds of the skin, EGF is produced by keratinocytes, macrophages, and other inflammatory cells that migrate into the area.

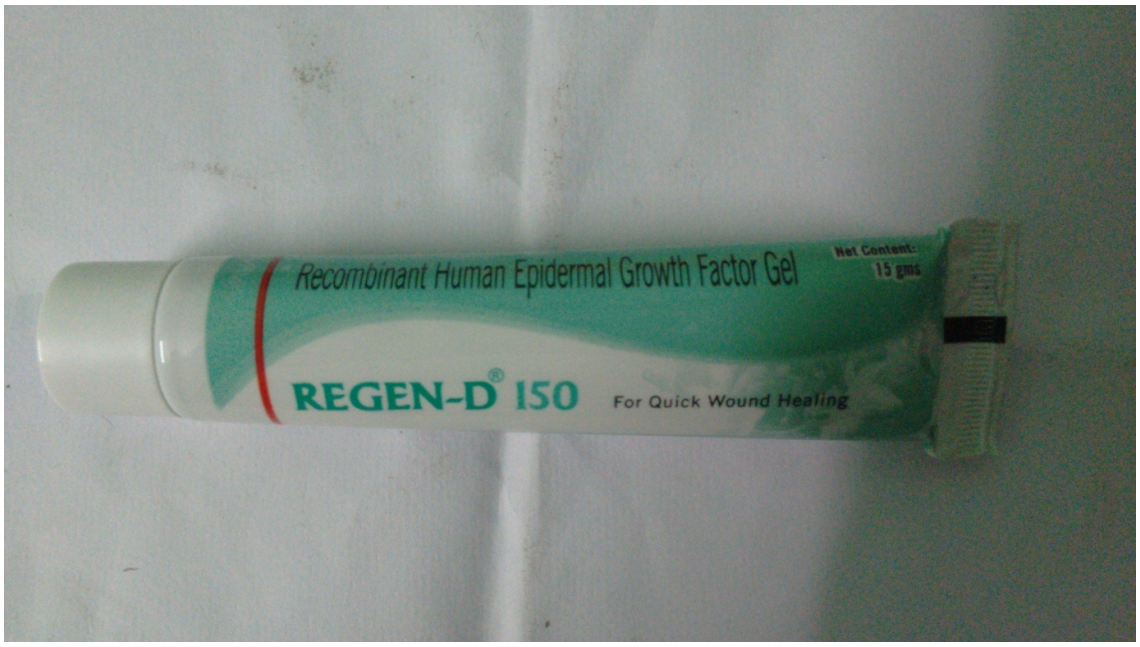
The "EGF receptor" is actually a family of four membrane receptors with intrinsic tyrosine kinase activity. The best-characterized EGFR is referred to as EGFR1, ERB B1, or simply EGFR. It responds to EGF, TGF-α, and other ligands of the EGF family, such as HB-EGF (heparin-binding EGF) and amphiregulin.

EGFR1 mutations and amplification have been detected in cancers of the lung, head and neck, and breast, glioblastomas, and other cancers, leading to the development of new types of treatments for these conditions.

The ERB B2 receptor (also known as HER-2 or HER2/Neu), whose main ligand has not been identified, has received great attention because it is overexpressed in a subset of breast cancers and is an important therapeutic target



Human epidermal growth factor gel



Healing by Repair, Scar Formation and Fibrosis

If tissue injury is severe or chronic, and results in damage of both parenchymal cells and the stromal framework of the tissue, healing can not be accomplished by regeneration. Under these conditions, the main healing process is repair by deposition of collagen and other ECM components, causing the formation of a scar.

In contrast to regeneration which involves the restitution of tissue components, repair is a fibroproliferative response that “patches” rather than restores the tissue.

The term scar is most often used in connection to wound healing in the skin, but is also used to describe the replacement of parenchymal cells in any tissue by collagen, as in the heart after myocardial infarction. Repair by connective tissue deposition includes the following basic features:

- Inflammation
- angiogenesis,
- migration and proliferation of fibroblasts,
- scar formation
- connective tissue remodeling.

The inflammatory reaction elicited by the injury contains the damage, removes injured tissue, and promotes the deposition of ECM components in the area of injury, at the same time that angiogenesis is stimulated. However, if the

damage persists, inflammation becomes chronic, leading to an excess deposition of connective tissue known as fibrosis. In most healing processes, a combination of repair and regeneration occurs. The relative contributions of repair and regeneration are influenced by:

(1) the proliferative capacity of the cells of the tissue;

(2) the integrity of the extracellular matrix; and

(3) the resolution or chronicity of the injury and inflammation.

CUTANEOUS WOUND HEALING

Cutaneous wound healing is divided into three phases:

1. inflammation,
2. proliferation, and
3. maturation.

These phases overlap, and their separation is somewhat arbitrary, but they help to understand the sequence of events that take place in the healing of skin wounds.

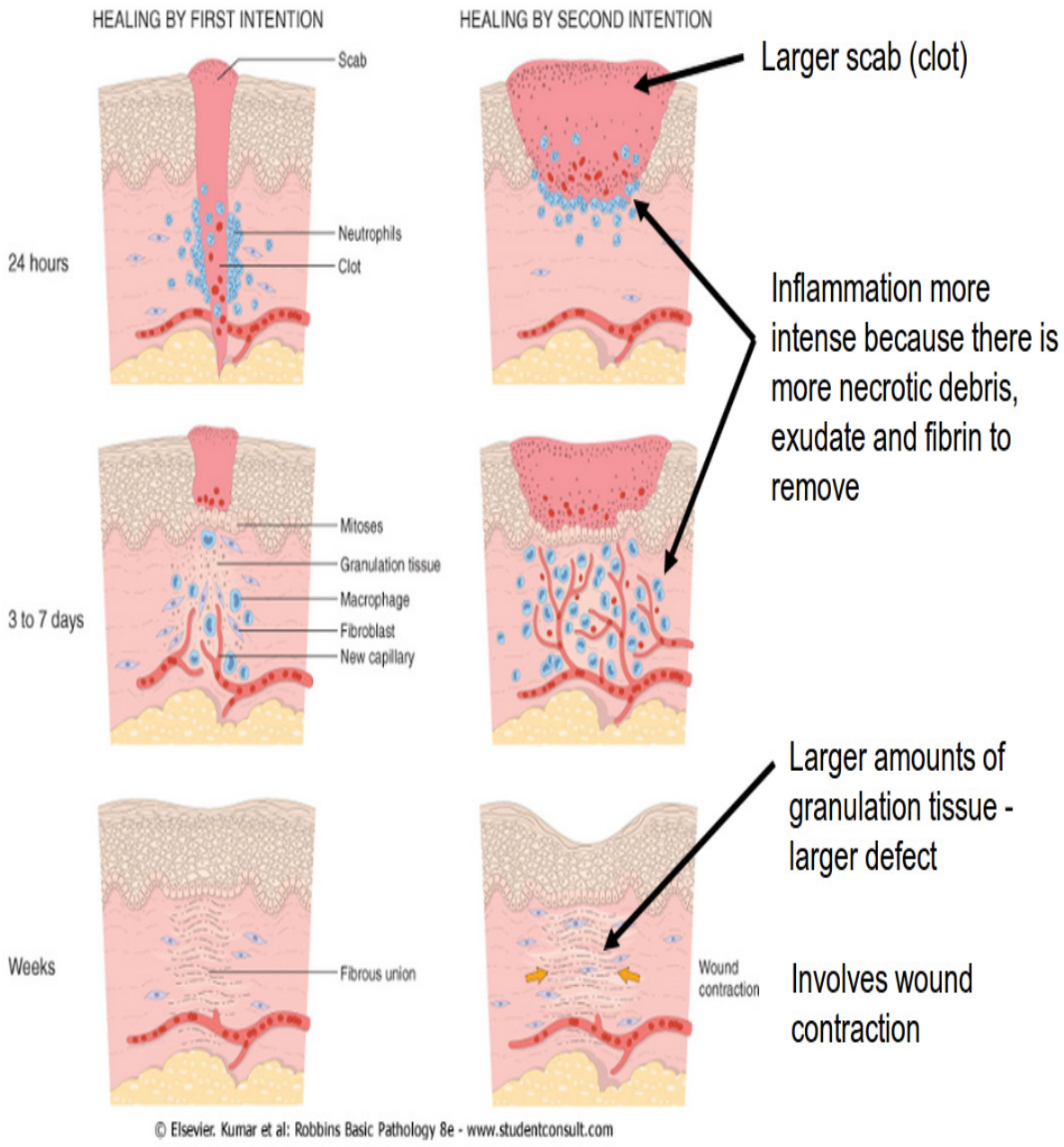
The initial injury causes platelet adhesion and aggregation and the formation of a clot in the surface of the wound, leading to inflammation.

In the proliferative phase there is formation of granulation tissue, proliferation and migration of connective tissue cells, and re-epithelialization of the wound surface. Maturation involves ECM deposition, tissue remodeling, and wound contraction.

The simplest type of cutaneous wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures. Such healing is referred to as **healing by primary union or by first intention.**.

Re-epithelialization to close the wound occurs with formation of a relatively thin scar. The repair process is more complicated in excisional wounds that create large defects on the skin surface, causing extensive loss of cells and tissue. The healing of these wounds involves a more intense inflammatory reaction, the formation of abundant granulation tissue, and extensive collagen deposition, leading to the formation of a substantial scar, which generally contracts. This form of healing is referred to as **healing by secondary union or by second intention.**

Despite these differences, the basic mechanisms of healing by primary (first intention) and secondary (second intention) union are similar.



Wound healing by first intension and second intension

Growth Factors and Cytokines Affecting Various Steps in Wound Healing

Monocyte chemotaxis	Chemokines, TNF, PDGF, FGF, TGF-β
Fibroblast migration/replication	PDGF, **EGF**, FGF, TGF-β, TNF, IL-1
Keratinocyte replication	HB-EGF, FGF-7, HGF
Angiogenesis	VEGF, angiopoietins, FGF
Collagen synthesis	TGF-β, PDGF
Collagenase secretion	PDGF, FGF, TNF; TGF-β inhibits

HB-EGF, heparin-binding EGF; IL-1, interleukin 1; TNF, tumor necrosis factor;.

Formation of Granulation Tissue.

Fibroblasts and vascular endothelial cells proliferate in the first 24 to 72 hours of the repair process to form a specialized type of tissue called granulation tissue, which is a hallmark of tissue repair.

Its characteristic histologic feature is the presence of new small blood vessels (angiogenesis) and the proliferation of fibroblasts.

These new vessels are leaky, allowing the passage of plasma proteins and fluid into the extravascular space. Thus, new granulation tissue is often edematous.

Granulation tissue progressively invades the incision space; the amount of granulation tissue that is formed depends on the size of the tissue deficit created by the wound and the intensity of inflammation.

Hence, it is much more prominent in healing by secondary union. By 5 to 7 days, granulation tissue fills the wound area and neovascularization is maximal.

Cell Proliferation and Collagen Deposition.

Neutrophils are largely replaced by macrophages by 48 to 96 hours.

Macrophages are key cellular constituents of tissue repair, clearing extracellular debris, fibrin, and other foreign material at the site of repair, and promoting angiogenesis and ECM deposition.

Full epithelialization of the wound surface is much slower in healing by secondary union because the gap to be bridged is much greater. Subsequent epithelial cell proliferation thickens the epidermal layer. ..

Scar Formation.

The leukocytic infiltrate, edema, and increased vascularity largely disappear during the second week.

Blanching begins, accomplished by the increased accumulation of collagen within the wound area and regression of vascular channels.

Mainly, the original granulation tissue scaffolding is converted into a pale, avascular scar, composed of spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components.

The dermal appendages that have been destroyed in the line of the incision are permanently lost, although in rats new hair follicles may develop in large healing wounds under Wnt stimulation. This result suggests that, with appropriate treatment procedures, regrowth of skin appendages during wound healing might be achieved in humans.

By the end of the first month, the scar is made up of acellular connective tissue devoid of inflammatory infiltrate, covered by intact epidermis.

Wound Contraction.

Wound contraction generally occurs in large surface wounds.

The contraction helps to close the wound by decreasing the gap between its dermal edges and by reducing the wound surface area. Hence, it is an important feature in healing by secondary union.

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Connective Tissue Remodeling.

The replacement of granulation tissue with a scar involves changes in the composition of the ECM. The balance between ECM synthesis and degradation results in remodeling of the connective tissue framework – an important feature of tissue repair. Some of the growth factors that stimulate synthesis of collagen and other connective tissue molecules also modulate the synthesis and activation of metalloproteinases, enzymes that degrade these ECM components.

.**Recovery of Tensile Strength**.

Fibrillar collagens (mostly type I collagen) form a major portion of the connective tissue in repair sites and are essential for the development of strength in healing wounds.

Net collagen accumulation, however, depends not only on increased collagen synthesis but also on decreased degradation.

When sutures are removed from an incisional surgical wound, usually at the end of the first week, wound strength is approximately 10% that of unwounded skin.

Wound strength increases rapidly over the next 4 weeks, slows down at approximately the third month after the original incision, and reaches a plateau at about 70% to 80% of the tensile strength of unwounded skin.

Lower tensile strength in the healed wound area may persist for life. The recovery of tensile strength results from the excess of collagen synthesis over collagen degradation during the first 2 months of healing, and, at later times, from structural modifications of collagen fibers (cross-linking, increased fiber size) after collagen synthesis ceases.

LOCAL AND SYSTEMIC FACTORS THAT INFLUENCE WOUND HEALING

Factors Affecting Wound Healing
Systemic factors
Age
Nutrition
Trauma
Metabolic diseases
Immunosuppression
Connective tissue disorders
Smoking
Local factors
Mechanical injury
Infection
Edema
Ischemia/necrotic tissue
Topical agents
Ionizing radiation
Low oxygen tension
Foreign bodies

Factors Affecting Wound Healing

Advanced Age

Aging produces intrinsic physiologic changes that result in delayed or impaired wound healing. The increased incidence of cardiovascular disease**,** metabolic diseases (diabetes mellitus, malnutrition, and vitamin deficiencies), cancer, and the widespread use of drugs that impair wound healing may all contribute to the higher incidence of wound problems in the elderly.

Hypoxia, Anemia, and Hypoperfusion

Low oxygen tension has a profoundly deleterious effect on all aspects of wound healing. Fibroplasia, although stimulated initially by the hypoxic wound environment, is significantly impaired by local hypoxia. Optimal collagen synthesis requires oxygen as a cofactor, particularly for the hydroxylation steps. Increasing subcutaneous oxygen tension levels by increasing the fraction of inspired oxygen (FiO_2) of inspired air for brief periods during and immediately after surgery results in enhanced collagen deposition and in decreased rates of wound infection after elective surgery.

Major factors affecting local oxygen delivery include hypoperfusion either for systemic reasons (low volume or cardiac failure) or due to local causes (arterial insufficiency, local vasoconstriction, or excessive tension on tissues).

The level of vasoconstriction of the subcutaneous capillary bed is exquisitely responsive to fluid status, temperature, and hyperactive sympathetic tone as is often induced by postoperative pain. Correction of these factors can have a remarkable influence on wound outcome, particularly on decreasing wound infection rates. Mild to moderate normovolemic anemia does not appear to adversely affect wound oxygen tension and collagen synthesis, unless the hematocrit falls below 15%.

Steroids and Chemotherapeutic Drugs

Large doses or chronic usage of glucocorticoids reduce collagen synthesis and wound strength.The major effect of steroids is to inhibit the inflammatory phase of wound healing (angiogenesis, neutrophil and macrophage migration, and fibroblast proliferation) and the release of lysosomal enzymes.It inhibit epithelialization and contraction and contribute to increased rates of wound infection, regardless of the time of administration. Steroid-delayed healing of cutaneous wounds can be stimulated to epithelialize by topical application of vitamin A. Collagen synthesis of steroid-treated wounds also can be stimulated by vitamin A.

Metabolic Disorders

Diabetes mellitus is the best known of the metabolic disorders contributing to increased rates of wound infection and failure.

Uremia also has been associated with disordered wound healing.

Nutrition

Poor nutritional intake or lack of individual nutrients significantly alters many aspects of wound healing.

The clinician must pay close attention to the nutritional status of patients with wounds, as wound failure or wound infections may be no more than a reflection of poor nutrition..

Clinically, it is extremely rare to encounter pure energy or protein malnutrition, and the vast majority of patients exhibit combined protein-energy malnutrition. Such patients have diminished hydroxyproline accumulation (an index of collagen deposition) into subcutaneously implanted polytetrafluoroethylene tubes when compared to normally nourished patients.

The possible role of single amino acids in enhanced wound healing has been studied for the last several decades. Arginine appears most active in terms of enhancing wound fibroplasia. Arginine deficiency results in decreased wound-breaking strength and wound collagen accumulation. The main effect of arginine on wound healing is to enhance wound collagen deposition.

As increases in breaking strength during the first weeks of healing are directly related to new collagen synthesis, arginine supplementation may result in an improvement in wound strength as a consequence of enhanced collagen deposition.

The **vitamins** most closely involved with wound healing are **vitamin C and vitamin A**. Scurvy, or vitamin C deficiency, leads to a defect in wound healing, particularly via a failure in collagen synthesis and cross-linking. Biochemically, vitamin C is required for the conversion of proline and lysine to hydroxyproline and hydroxylysine, respectively.

Vitamin C deficiency has also been associated with an increased incidence of wound infection, and if wound infection does occur, it tends to be more severe. These effects are believed to be due to an associated impairment in neutrophil function, decreased complement activity, and decreased walling-off of bacteria secondary to insufficient collagen deposition.

Vitamin A deficiency impairs wound healing, whereas supplemental vitamin A benefits wound healing in nondeficient humans and animals.

Vitamin A increases the inflammatory response in wound healing, probably by increasing the lability of lysosomal membranes. There is an increased influx of macrophages, with an increase in their activation and increased collagen synthesis. Vitamin A directly increases collagen production and epidermal growth factor receptors when it is added in vitro to cultured fibroblasts. Vitamin A also can restore wound healing that has been impaired by diabetes, tumor formation, cyclophosphamide, and radiation

The connections between **specific minerals and trace elements** and deficits in wound healing are complex. Frequently, deficiencies are multiple and include

macronutrient deficiencies. The specific trace element may function as a cofactor or part of an enzyme that is essential for homeostasis and wound healing.

Zinc is the most well-known element in wound healing and has been used empirically in dermatologic conditions for centuries. It is essential for wound healing in animals and humans. There are more than 150 known enzymes for which zinc is either an integral part or an essential cofactor, and many of these enzymes are critical to wound healing. With zinc deficiency there is decreased fibroblast proliferation, decreased collagen synthesis, impaired overall wound strength, and delayed epithelialization. These defects are reversed by zinc supplementation. To date, no study has shown improved wound healing with zinc supplementation in patients who are not zinc deficient.

Infections

Wound infections continue to represent a major medical problem, both in terms of how they affect the outcome of surgical procedures (surgical site infections), and for their impact on the length of hospital stay and medical costs.

Many otherwise successful surgical operations fail because of the development of wound infections. Cosmetically, infections can lead to disfiguring, unsightly, or delayed closures.

Antibiotic prophylaxis is most effective when adequate concentrations of antibiotic are present in the tissues at the time of incision, and assurance of

adequate preoperative antibiotic dosing and timing has become a significant hospital performance measure. Addition of antibiotics after operative contamination has occurred is clearly ineffective in preventing postoperative wound infections.

PATHOLOGIC ASPECTS OF REPAIR

Complications in wound healing can arise from abnormalities in any of the basic components of the repair process. These aberrations can be grouped into three general categories:

(1) deficient scar formation,

(2) excessive formation of the repair components, and

(3) formation of contractures.

- Inadequate formation of granulation tissue or assembly of a scar can lead to two types of complications: wound dehiscence and ulceration..
- Excessive formation of the components of the repair process can give rise to hypertrophic scars and keloids. The accumulation of excessive amounts of collagen may give rise to a raised scar known as a **hypertrophic scar**; if the scar tissue grows beyond the boundaries of the original wound and does not regress, it is called a **keloid**. Keloid formation seems to be an individual predisposition, and for unknown

reasons this aberration is somewhat more common in African Americans. Hyperthrophic scars generally develop after thermal or traumatic injury that involves the deep layers of the dermis.

- Contraction in the size of a wound is an important part of the normal healing process. An exaggeration of this process gives rise to contracture and results in deformities of the wound and the surrounding tissues. Contractures are particularly prone to develop on the palms, the soles, and the anterior aspect of the thorax. Contractures are commonly seen after serious burns and can compromise the movement of joints.

Fibrosis

Deposition of collagen is part of normal wound healing. However, the term fibrosis is used more broadly to denote the excessive deposition of collagen and other ECM components in a tissue.

The terms scar and fibrosis are used interchangeably, but fibrosis most often indicates the deposition of collagen in chronic diseases. The basic mechanisms that occur in the development of fibrosis associated with chronic inflammatory diseases are generally similar to the mechanisms of skin wound healing..

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DIABETES MELLITUS (DM)

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

DIAGNOSIS

Blood glucose values are normally maintained in a very narrow range, usually 70 to 120 mg/dL. The diagnosis of diabetes is established by noting elevation of blood glucose by any one of three criteria:

1. A random glucose concentration greater than 200 mg/dL, with classical signs and symptoms
2. A fasting glucose concentration greater than 126 mg/dL on more than one occasion

3. An abnormal oral glucose tolerance test (OGTT), in which the glucose concentration is greater than 200 mg/dL 2 hours after a standard carbohydrate load

.PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Type 2 diabetes is a prototypic multifactorial complex disease.

Environmental factors, such as a sedentary life style and dietary habits, unequivocally play a role, as will become evident when the association with obesity is considered.

The two metabolic defects that characterize type 2 diabetes are

1. a decreased response of peripheral tissues to insulin (insulin resistance) and
2. β-cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia.

Gangrene of the lower extremities, as a result of advanced vascular disease, is about 100 times more common in diabetics than in the general population.

The larger renal arteries are also subject to severe atherosclerosis, but the most damaging effect of diabetes on the kidneys is exerted at the level of the glomeruli and the microcirculation

Diabetic Microangiopathy:

One of the most consistent morphologic features of diabetes is diffuse thickening of basement membranes. The thickening is most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla. However, it may also be seen in such nonvascular structures as renal tubules, the Bowman capsule, peripheral nerves, and placenta. It should be noted that despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins. The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of neuropathy. An indistinguishable microangiopathy can be found in aged nondiabetic patients but rarely to the extent seen in patients with long-standing diabetes.

Diabetic Wounds

Diabetes mellitus impairs wound healing at all stages of the process. 10 to 15% of diabetic patients run the risk of developing ulcers. The major contributors to the formation of diabetic ulcers include neuropathy, foot deformity, and ischemia.

It is estimated that 60 to 70% of diabetic ulcers are due to neuropathy, 15 to 20% are due to ischemia, and another 15 to 20% are due to a combination of both. The neuropathy is both sensory and motor, and is secondary to persistently elevated glucose levels. The loss of sensory function allows

unrecognized injury to occur from ill-fitting shoes, foreign bodies, or other trauma.

The motor neuropathy or **Charcot foot** leads to collapse or dislocation of the interphalangeal or metatarsophalangeal joints, causing pressure on areas with little protection. There is also severe micro- and macrovascular circulatory impairment.

Tissue hypoxia, as indicated by reduced dorsal foot transcutaneous oxygen tension, is a consequence of vascular disease and has been well demonstrated in diabetic patients.

Diabetic patients are prone to repeated trauma as a result of the diabetic neuropathy that affects both sensory and motor function in both the somatic and autonomic pathways.

Furthermore, diabetics are susceptible to infection because of an attenuated inflammatory response, impaired chemotaxis, and inefficient bacterial killing. Infection also increases local tissue metabolism, thus further imposing a burden on an already tenuous blood supply and thereby amplifying the risk for tissue necrosis.

Lymphocyte and leukocyte function is impaired, and there is increased collagen degradation and decreased collagen deposition. The collagen that is formed is more brittle than normal collagen, probably because of glycosylation from the increased levels of glucose present in the ECM

Once ulceration occurs, the chances of healing are poor. The treatment of diabetic wounds involves local and systemic measures. Achievement of adequate blood sugar levels is very important. Most diabetic wounds are infected, and eradication of the infectious source is paramount to the success of healing. Treatment should address the possible presence of osteomyelitis, and should employ antibiotics that achieve adequate levels both in soft tissue and bone. Wide débridement of all necrotic or infected tissue is another cornerstone of treatment. Topical application of **Human epidermal growth factor** has met with significant success in achieving closure or allograft.

The application of engineered skin allograft substitutes, although expensive, has also shown some significant success. Prevention and, specifically, foot care play an important role in the management of diabetics.

Treatment of Diabetic Wounds

Local Care

Management of acute wounds begins with obtaining a careful history of the events surrounding the injury. The history is followed by a meticulous examination of the wound. Examination should assess the depth and configuration of the wound, the extent of nonviable tissue, and the presence of foreign bodies and other contaminants. Examination of the wound may require irrigation and débridement of the edges of the wound, and is facilitated by use

of local anesthesia. Antibiotic administration and tetanus prophylaxis may be needed, and planning the type and timing of wound repair should take place.

After completion of the history, examination, and administration of tetanus prophylaxis, the wound should be meticulously anesthetized..

Irrigation to visualize all areas of the wound and remove foreign material is best accomplished with normal saline. High-pressure wound irrigation is more effective in achieving complete débridement of foreign material and nonviable tissues.

Having ensured hemostasis and adequate débridement of nonviable tissues and removal of any remaining foreign bodies, irregular, macerated, or beveled wound edges should be débrided in order to provide a fresh edge for reapproximation..

After wound healing in areas of significant tissue loss, rotation of adjacent **musculocutaneous flaps** may be required to provide sufficient tissue mass for closure. These musculocutaneous flaps may be based on intrinsic blood supply, or may be moved from distant sites as free flaps and anastomosed into the local vascular bed. In areas with significant superficial tissue loss, split-thickness skin grafting (placed in a delayed manner to assure an adequate tissue bed) may be required and will speed formation of an intact epithelial barrier to fluid loss and infection.

Split-thickness skin grafts are readily obtained using manual or mechanical dermatomes, and the grafts may be **"meshed"** in order to increase the surface area of their coverage. It is essential to ensure hemostasis of the underlying tissue bed before placement of split-thickness skin grafts, as the presence of a hematoma below the graft will prevent the graft from taking, resulting in sloughing of the graft.

Antibiotics

Antibiotics should be used only when there is an obvious wound infection. Most wounds are contaminated or colonized with bacteria. The presence of a host response constitutes an infection and justifies the use of antibiotics. Signs of infection to look for include erythema, cellulitis, swelling, and purulent discharge. Indiscriminate use of antibiotics should be avoided to prevent emergence of multidrug-resistant bacteria. Antibiotic treatment of wounds must be based on organisms suspected to be found within the infected wound and the patient's overall immune status. Patient should be treated with antibiotics according to culture and sensitivity from wound.

Dressings

The main purpose of wound dressings is to provide the ideal environment for wound healing. The dressing should facilitate the major changes taking place during healing to produce an optimally healed wound. Although the ideal dressing is still not a clinical reality, technological advances are promising .

Desired Characteristics of Wound Dressings
Promote wound healing (maintain moist environment)
Conformability
Pain control
Odour control
Nonallergenic and nonirritating
Permeability to gas
Safety
Non traumatic removal
Cost-effectiveness
Convenience

Covering a wound with a dressing mimics the barrier role of epithelium and prevents further damage. In addition, application of compression provides hemostasis and limits edema.

Occlusion of a wound with dressing material helps healing by controlling the level of hydration and oxygen tension within the wound. It also allows transfer of gases and water vapor from the wound surface to the atmosphere.

Occlusion affects both the dermis and epidermis, and it has been shown that exposed wounds are more inflamed and develop more necrosis than covered wounds. Occlusion also helps in dermal collagen synthesis and epithelial cell migration and limits tissue desiccation. As it may enhance bacterial growth, occlusion is contraindicated in infected and highly exudative wounds.

Dressings can be classified as primary or secondary.

A primary dressing is placed directly on the wound and may provide absorption of fluids and prevent desiccation, infection, and adhesion of a secondary dressing.

A secondary dressing is one that is placed on the primary dressing for further protection, absorption, compression, and occlusion.

Many types of dressings exist and are designed to achieve certain clinically desired endpoints.

Absorbent Dressings

Accumulation of wound fluid can lead to maceration and bacterial overgrowth. Ideally, the dressing should absorb without getting soaked through, as this would permit bacteria from the outside to enter the wound.

The dressing must be designed to match the exudative properties of the wound and may include cotton, wool, and sponge.

Nonadherent Dressings

Nonadherent dressings are impregnated with paraffin, petroleum jelly, or water-soluble jelly for use as nonadherent coverage. A secondary dressing must be placed on top to seal the edges and prevent desiccation and infection.

Occlusive and Semiocclusive Dressings

Occlusive and semiocclusive dressings provide a good environment for clean, minimally exudative wounds. These film dressings are waterproof and impervious to microbes, but permeable to water vapor and oxygen.

Hydrophilic and Hydrophobic Dressings

Hydrophilic and hydrophobic dressings are components of a composite dressing. Hydrophilic dressing aids in absorption, whereas a hydrophobic dressing is waterproof and prevents absorption.

Hydrocolloid and Hydrogel Dressings

Hydrocolloid and hydrogel dressings attempt to combine the benefits of occlusion and absorbency.

Hydrocolloids and hydrogels form complex structures with water, and fluid absorption occurs with particle swelling, which aids in atraumatic removal of the dressing.

Absorption of exudates by the hydrocolloid dressing leaves a yellowish-brown gelatinous mass after dressing removal that can be washed off. Hydrogel is a cross-linked polymer that has high water content. Hydrogels allow a high rate of evaporation without compromising wound hydration, which makes them useful in burn treatment.

Alginates

Alginates are derived from brown algae and contain long chains of polysaccharides containing mannuronic and glucuronic acid. The ratios of these sugars vary with the species of algae used, as well as the season of harvest. Processed as the calcium form, alginates turn into soluble sodium alginate through ion exchange in the presence of wound exudates. The polymers gel, swell, and absorb a great deal of fluid. Alginates are being used when there is skin loss, in open surgical wounds with medium exudation, and on full-thickness chronic wounds.

Absorbable Materials

Absorbable materials are mainly used within wounds as hemostats and include collagen, gelatin, oxidized cellulose, and oxidized regenerated cellulose.

Medicated Dressings

Medicated dressings have long been used as a drug-delivery system. Agents delivered in the dressings include benzoyl peroxide, zinc oxide, neomycin, and

bacitracin-zinc. These agents have been shown to increase epithelialization by 28%.

The type of dressing to be used depends on the amount of wound drainage.

A nondraining wound can be covered with a semiocclusive dressing. Drainage of less than 1 to 2 mL/d may require a semiocclusive or absorbent nonadherent dressing. Moderately draining wounds (3 to 5 mL/d) can be dressed with a nonadherent primary layer plus an absorbent secondary layer plus an occlusive dressing to protect normal tissue. Heavily draining wounds (>5 mL/d) require a similar dressing to moderately draining wounds, but with the addition of a highly absorbent secondary layer.

Mechanical Devices

Mechanical therapy augments and improves on certain functions of dressings, in particular the absorption of exudates and control of odor. The vacuum-assisted closure system assists in wound closure by applying localized negative pressure to the surface and margins of the wound. The negative pressure therapy is applied to a special foam dressing cut to the dimensions of the wound and positioned in the wound cavity or over a flap or graft. The continuous negative pressure is very effective in removing exudates from the wound. This form of therapy has been found to be effective for chronic open wounds (diabetic ulcers and stages 3 and 4 pressure ulcers), acute and traumatic wounds, flaps and grafts, and subacute wounds (i.e., dehisced

incisions), although more randomized trials need to be carried out to confirm efficacy.

Skin Replacements

All wounds require coverage in order to prevent evaporative losses and infection and to provide an environment that promotes healing. Both acute and chronic wounds may demand use of skin replacement, and several options are available.

Skin Grafts

Skin grafts have long been used to treat both acute and chronic wounds. Split- or partial-thickness grafts consist of the epidermis plus part of the dermis, whereas full-thickness grafts retain the entire epidermis and dermis.

Autologous grafts (autografts) are transplants from one site on the body to another.

Allogeneic grafts (allografts, homografts) are transplants from a living nonidentical donor or cadaver to the host; and

xenogeneic grafts (heterografts) are taken from another species (e.g., porcine).

Split-thickness grafts require less blood supply to restore skin function. The dermal component of full-thickness grafts lends mechanical strength and resists wound contraction better, resulting in improved cosmesis.

Allogeneic and xenogeneic grafts require the availability of tissue, are subject to rejection, and may contain pathogens.

The use of skin grafts or bioengineered skin substitutes and other innovative treatments (e.g., topically applied growth factors, systemic agents, and gene therapy) cannot be effective unless the wound bed is adequately prepared. This may include débridement to remove necrotic or fibrinous tissue, control of edema, revascularization of the wound bed, decreasing the bacterial burden, and minimizing or eliminating exudate. Temporary placement of allografts or xenografts may be used to prepare the wound bed.

Skin Substitutes

Originally devised to provide coverage of extensive wounds with limited availability of autografts, skin substitutes also have gained acceptance as natural dressings. Manufactured by tissue engineering, they combine novel materials with living cells to provide functional skin substitutes, providing a bridge between dressings and skin grafts.

Skin substitutes have theoretical advantages of being readily available, not requiring painful harvest, and they may be applied freely or with surgical suturing. In addition, they promote healing, either by stimulating host cytokine generation or by providing cells that may also produce growth factors locally.

Their disadvantages include limited survival, high cost, and the need for multiple applications Allografting, albeit with a very thin graft, may at times be required to accomplish complete coverage.

Desired Features of Tissue-Engineered Skin
Rapid re-establishment of functional skin (epidermis/dermis)
Receptive to body's own cells (e.g., rapid "take" and integration)
Graftable by a single, simple procedure
Graftable on chronic or acute wounds
Engraftment without use of extraordinary clinical intervention (i.e., immunosuppression)

A variety of skin substitutes are available, each with its own set of advantages and disadvantages; however, the ideal skin substitute has yet to be developed. The development of newer composite substitutes, which provide both the dermal and epidermal components essential for permanent skin replacement, may represent an advance toward that goal.

The acellular (e.g., native collagen or synthetic material) component acts as a scaffold, promotes cell migration and growth, and activates tissue regeneration

and remodeling. The cellular elements re-establish lost tissue and associated function, synthesize extracellular matrix components, produce essential mediators such as cytokines and growth factors, and promote proliferation and migration.

Advantages and Disadvantages of Various Bioengineered Skin Substitutes		
Skin Substitute	Advantages	Disadvantages
Cultured allogeneic keratinocyte graft	No biopsy needed	Unstable
	"Off the shelf" availability	Does not prevent wound contracture
	Provides wound coverage	Inadequate cosmesis
	Promotes healing	Possibility of disease transmission
		Fragile
Bioengineered dermal replacement	Prevents contracture	Limited ability to drive re-epithelialization
	Good prep for graft application	Largely serves as temporary dressing
Cultured bilayer skin equivalent	More closely mimics normal anatomy	Cost
	Does not need secondary procedure	Short shelf life
	Easily handled	True engraftment questionable
	Can be sutured, meshed, etc.	

Cultured epithelial autografts (CEAs) represent expanded autologous or homologous keratinocytes. CEAs are expanded from a biopsy of the patient's own skin, will not be rejected, and can stimulate re-epithelialization as well as the growth of underlying connective tissue.

Keratinocytes harvested from a biopsy roughly the size of a postage stamp are cultured with fibroblasts and growth factors and grown into sheets that can cover large areas and give the appearance of normal skin. Until the epithelial sheets are sufficiently expanded, the wound must be covered with an occlusive dressing or a temporary allograft or xenograft.

The dermis regenerates very slowly, if at all, for full-thickness wounds, because the sheets are very fragile, difficult to work with, are susceptible to infection, and do not resist contracture well, leading to poor cosmetic results.

CEAs are available from cadavers, unrelated adult donors, or from neonatal foreskins. Fresh or cryopreserved cultured allogeneic keratinocytes can be left in place long enough to be superseded by multiplying endogenous skin cells because, unlike allografts containing epidermal Langerhans cells, they do not express major histocompatibility antigens. Cryopreserved CEAs are readily available "off the shelf," and provide growth factors that may aid healing. However, like autologous keratinocyte sheets, the grafts lack the strength provided by a dermal component and pose a risk of disease transmission.

Viable fibroblasts can be grown on bioabsorbable or nonbioabsorbable meshes to yield living dermal tissue that can act as a scaffold for epidermal growth. Fibroblasts stimulated by growth factors can produce type I collagen and glycosaminoglycans (e.g., chondroitin sulfates), which adhere to the wound surface to permit epithelial cell migration, as well as adhesive ligands (e.g., the matrix protein fibronectin), which promote cell adhesion. This approach has the virtue of being less time-consuming and expensive than culturing keratinocyte sheets. There are a number of commercially available, bioengineered dermal replacements approved for use in burn treatment as well as other indications.

Bioengineered skin substitutes have evolved from keratinocyte monolayers to dermal equivalents to split-thickness products with a pseudoepidermis and, most recently, to products containing both epidermal and dermal components that resemble the three-dimensional structure and function of normal skin Indicated for use with standard compression therapy in the treatment of venous insufficiency ulcers and for the treatment of neuropathic diabetic foot ulcers, these bilayered skin equivalents also are being used in a variety of wound care settings.

Growth Factor Therapy

It is believed that nonhealing wounds result from insufficient or inadequate growth factors in the wound environment. A simplistic solution would be to

flood the wound with single or multiple growth factors in order to "jump-start" healing and re-epithelialization.

Although there is a large body of work demonstrating the effects of growth factors in animals, translation of these data into clinical practice has met with limited success. Growth factors for clinical use may be either recombinant or homologous/autologous.

Autologous growth factors are harvested from the patient's own platelets, yielding an unpredictable combination and concentration of factors, which are then applied to the wound. This approach allows treatment with patient-specific factors at an apparently physiologic ratio of growth factor concentrations. Recombinant molecular biologic means permit the purification of high concentrations of individual growth factors. Current Food and Drug Administration–approved formulations, as well as those used experimentally, deliver concentrations approximately 10^3 times higher than those observed physiologically.

At present, studies have shown that Epidermal growth factor will enhance the wound healing process of diabetic wounds.

Application of recombinant human EGF in a gel suspension to these wounds increases the incidence of total healing, decreases healing time and reduction of non-healing ulcers.

MATERIALS AND METHODS:

Place of study:

All units in general surgery in Government Stanley Medical College and Hospital, Chennai-1.

Study Design:

Prospective, Non-randomized control trial

Study Duration:

July 2014 to June 2015

Sample Size: 50

Each Arm 25

Study tool:

Data was collected from all patients who was admitted in Government Stanley medical college and patients was included those who come under the inclusion criteria

METHOD

- For one group of patients, topical application of recombinant human epidermal growth factor gel over the wound and wound dressing was done twice daily

- For other group of patients, topical application of povidone-iodine over the wound and wound dressing done twice daily.
- The study end point was the complete closure of the wound.
- Failure to heal was arbitrarily defined as incomplete healing after 12 weeks.
- Results are tabulated and analyzed.

INCLUSION CRITERIA:

- All patients who are diagnosed as type 2 diabetes mellitus with a non-healing ulcer
- Both males and females
- Age between 35 to 75 years
- Size of the wound - 5cm to 15cm

EXCLUSION CRITERIA:

- Recurrent ulcers
- Non-diabetic wounds
- Malignant ulcers

Statistical method:

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test.

Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007

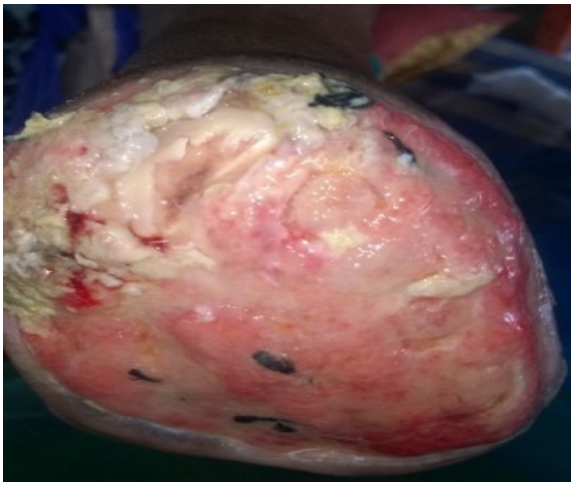
INVESTIGATIONS:

A. Routine investigations:

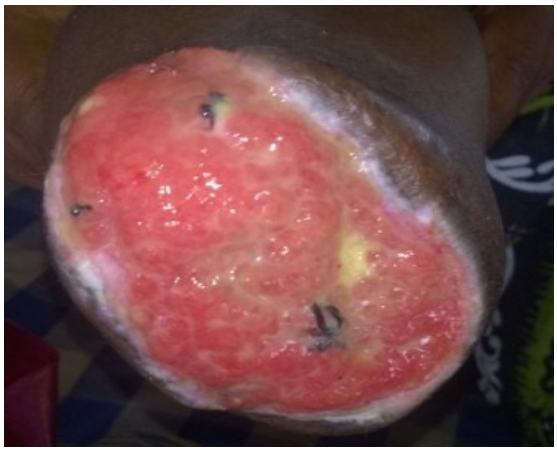
- Complete blood count
- Renal function test
- Random Blood Sugar
- Liver function test
- Serum electrolytes
- X-ray Chest

B. Special investigations

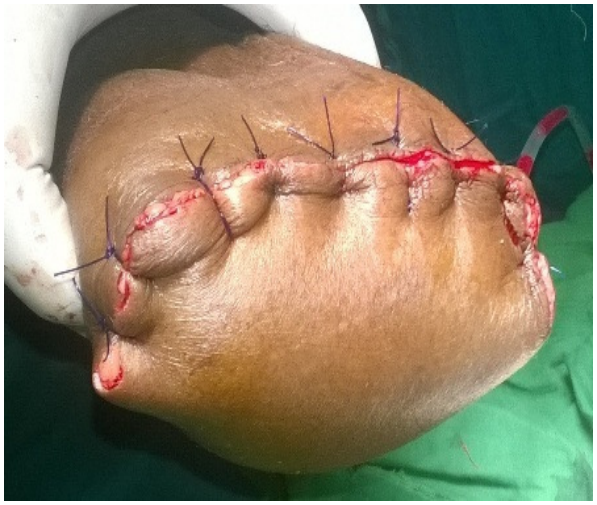
- Pus Culture and sensitivity
- Fasting Blood Sugar
- Post-Prandial Blood sugar
- Doppler scan (if needed)
- X-ray local area (if needed)



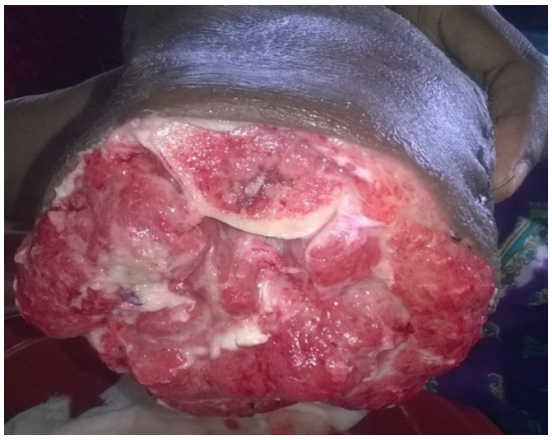
Initial unhealthy wound



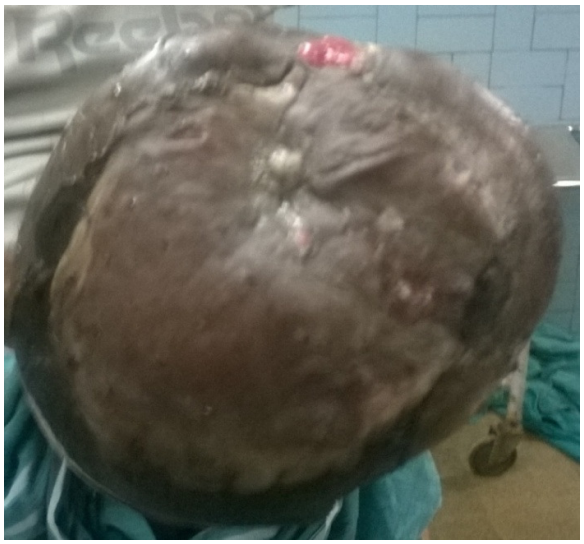
Wound healed with topical application of Human Epidermal growth factor



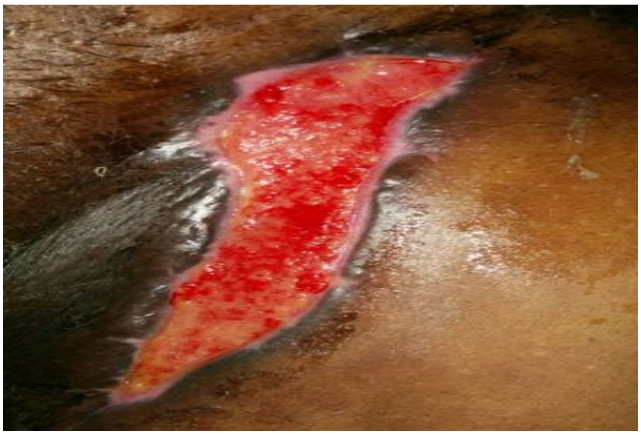
Wound after stump closure



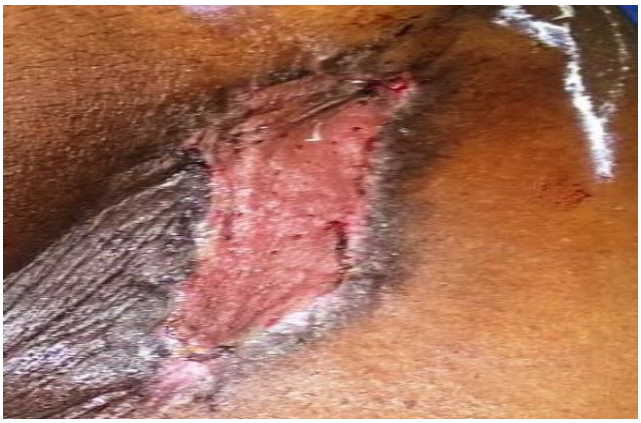
Initial unhealthy wound



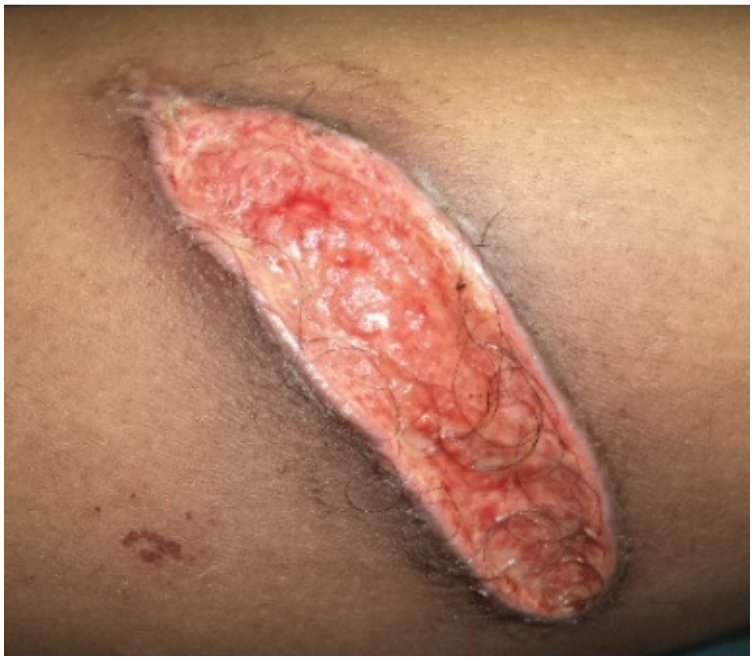
Wound healed after topical application of human epidermal growth factor and later stump closure was done



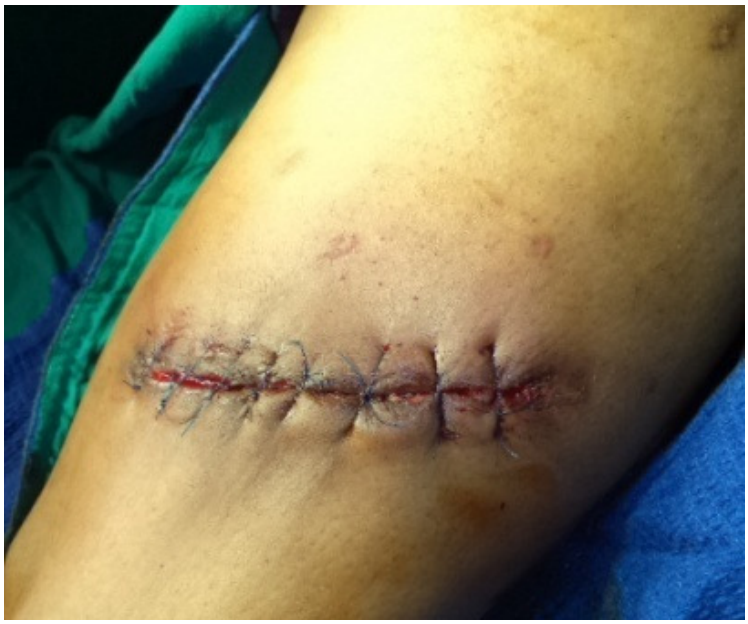
Initial wound



Wound healed after topical application of human epidermal growth factor and skin graft of the raw area was done



Initial wound



Wound healed After topical application of human epidermal growth factor and secondary suturing done.

RESULTS AND OBSERVATIONS

This is study consisted of total 50 patients who were admitted with diabetic wounds satisfying all inclusion and exclusion criteria, to all units of Department of General Surgery in Government Stanley medical college, Chennai during july 2014 to june 2015.

Total 50 patients with diabetic wounds were studied, each study group with 25 patients.

For first study group of patients, topical application of recombinant human epidermal growth factor gel over the wound and wound dressing was done twice daily

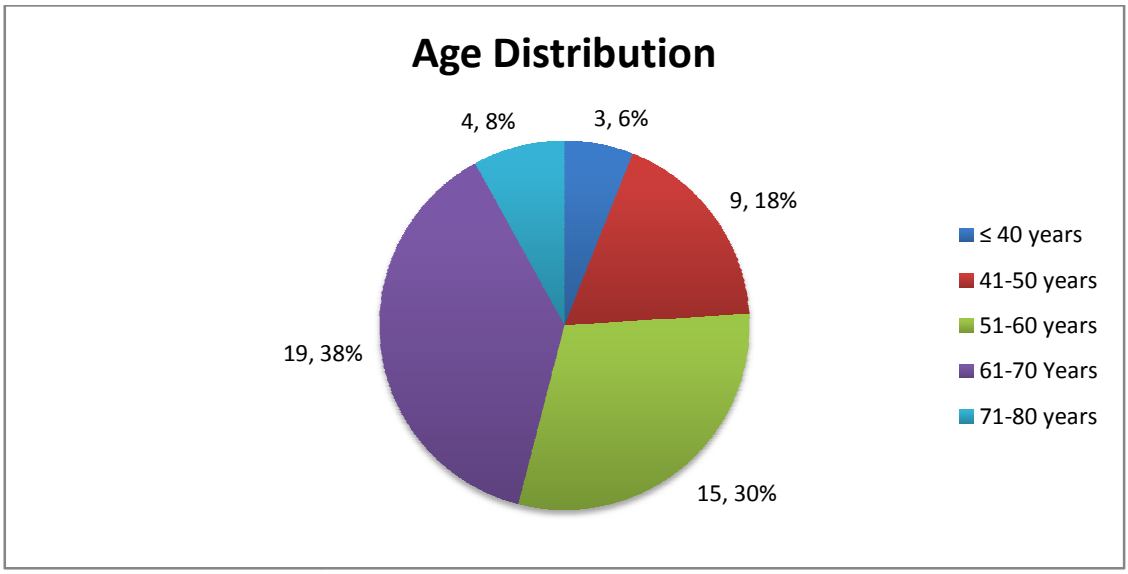
For second study group of patients, topical application of povidone-iodine over the wound and wound dressing was done twice daily.

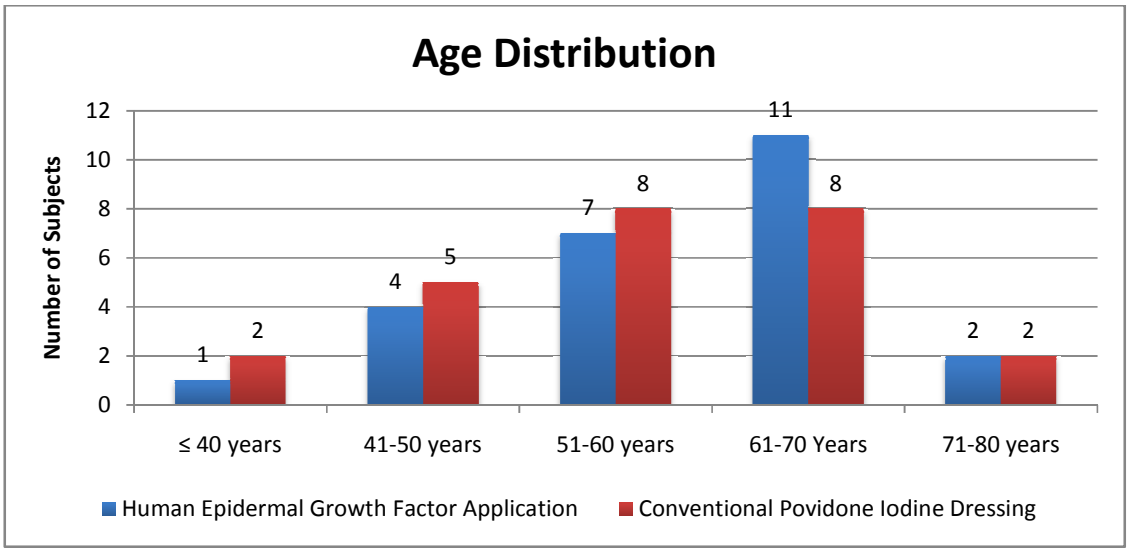
For each patient, wound dressings were done for 12 weeks.

The findings were analyzed and tabulated. The following observations were made:

Data Analysis

Age



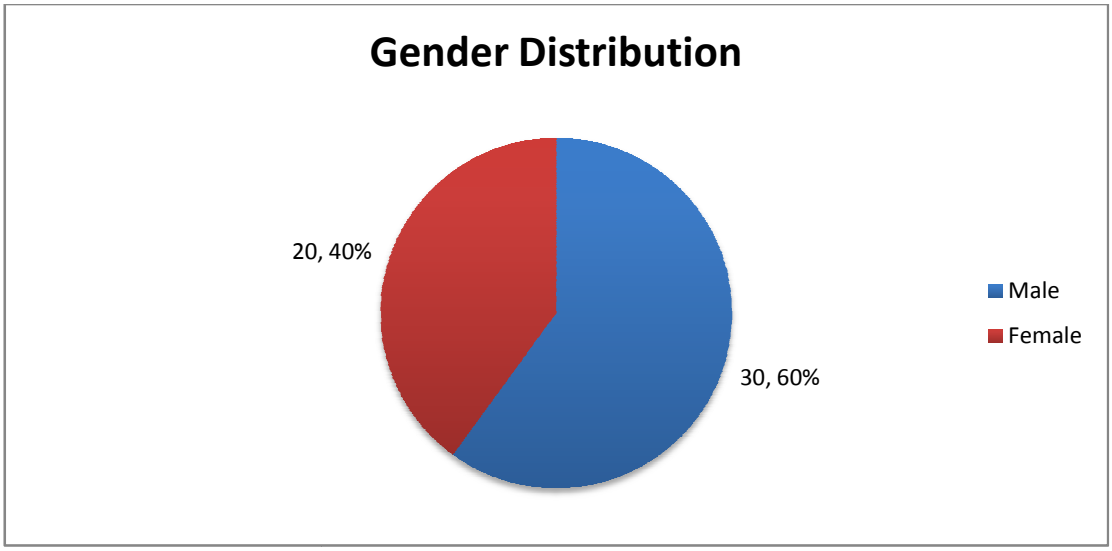


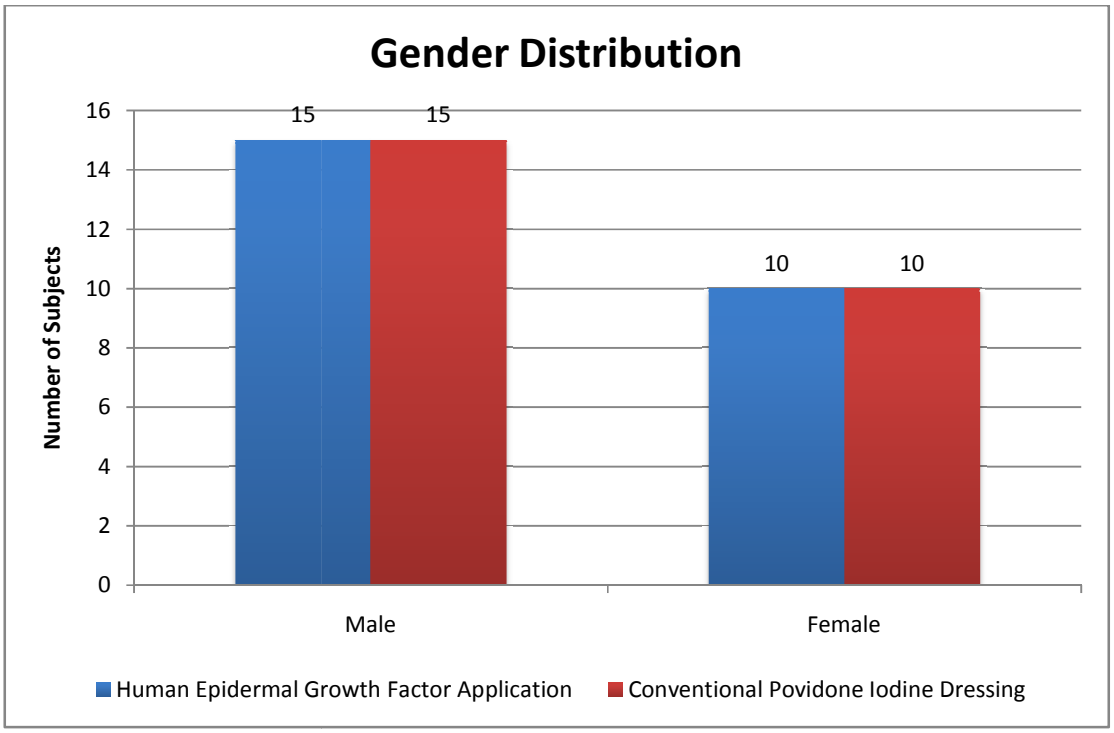
Age Distribution	All	%	Human Epidermal Growth Factor Application	%	Conventional Povidone Iodine Dressing	%
≤ 40 years	3	6.00	1	4.00	2	8.00
41-50 years	9	18.00	4	16.00	5	20.00
51-60 years	15	30.00	7	28.00	8	32.00
61-70 Years	19	38.00	11	44.00	8	32.00
71-80 years	4	8.00	2	8.00	2	8.00
Total	50	100	25	100	25	100

Age Distribution	All	Human Epidermal Growth Factor Application	Conventional Povidone Iodine Dressing
N	50	25	25
Mean	58.92	60.60	57.24
SD	10.15	9.62	10.57
P value Unpaired t Test			0.2457

Majority of the Human Epidermal Growth Factor Application Group patients belonged to the 61-70 years age class interval (n=19, 38%) with a mean age of 60.60 years. In the Conventional Povidone Iodine Dressing group patients, majority belonged to the same age class interval (n=8, 32%) with a mean age of 57.24 years. The association between the intervention groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

Gender

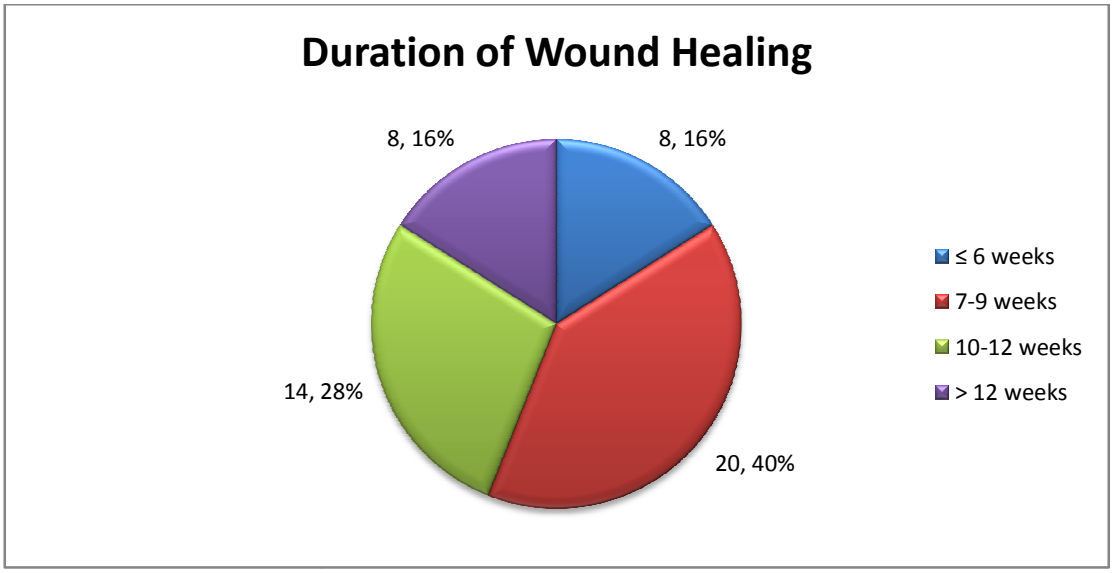

Gender Distribution
20, 40%
30, 60%
Male
Female

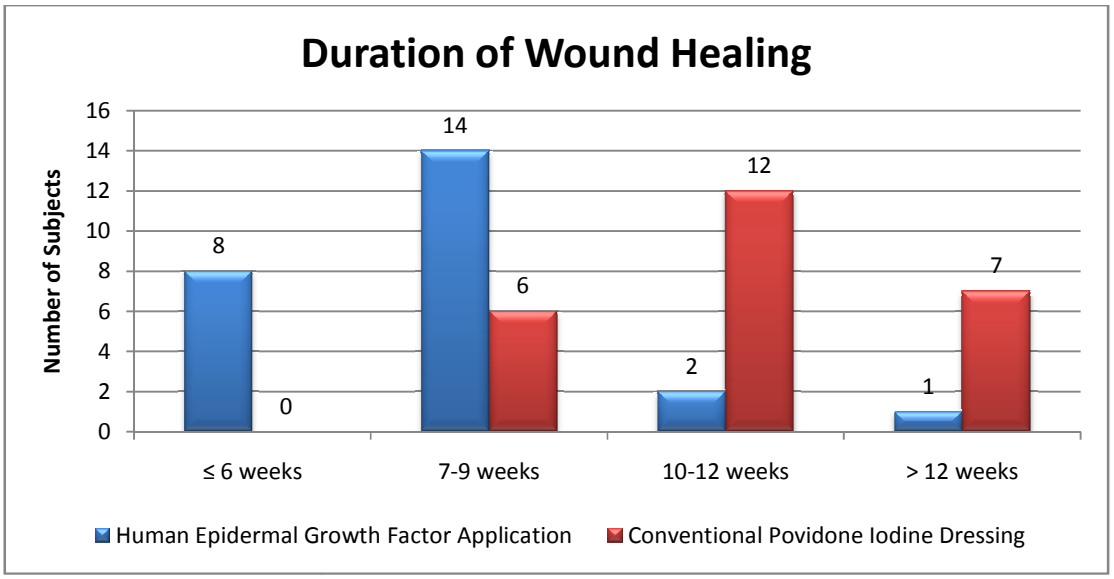

Gender Distribution
Number of Subjects
16
14
12
10
8
6
4
2
0
15
15
10
10
Male
Female
Human Epidermal Growth Factor Application
Conventional Povidone Iodine Dressing

Gender Distribution	All	%	Human Epidermal Growth Factor Application	%	Conventional Povidone Iodine Dressing	%
Male	30	60.00	15	60.00	15	60.00
Female	20	40.00	10	40.00	10	40.00
Total	50	100	25	100	25	100
P value Fishers Exact Test			0.9999			

The Human Epidermal Growth Factor Application group patients equally belonged to the male gender class interval (n=15, 50%). In the Conventional Povidone Iodine Dressing group patients, majority belonged to the male gender class interval (n=15, 50%). The association between the intervention groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

Duration of Wound Healing

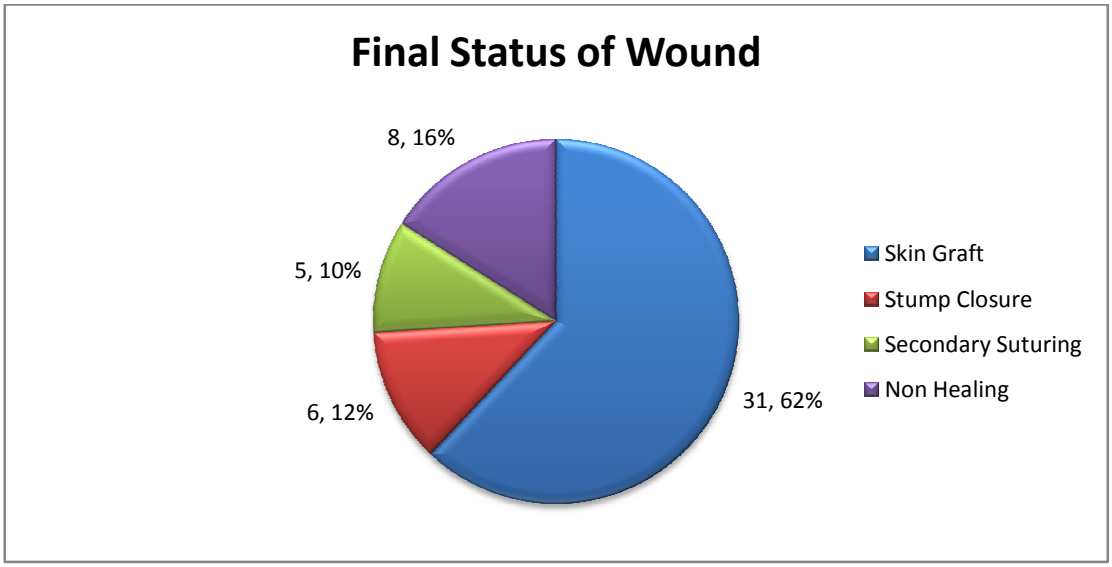


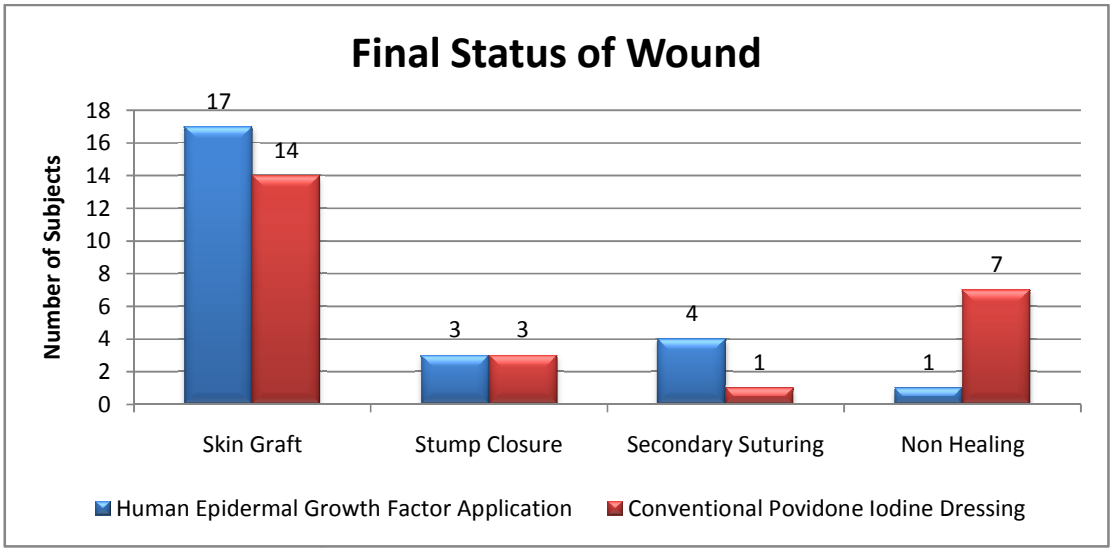


Duration of Wound Healing	All	%	Human Epidermal Growth Factor Application	%	Conventional Povidone Iodine Dressing	%
≤ 6 weeks	8	16.00	8	32.00	0	0.00
7-9 weeks	20	40.00	14	56.00	6	24.00
10-12 weeks	14	28.00	2	8.00	12	48.00
> 12 weeks	8	16.00	1	4.00	7	28.00
Total	50	100	25	100	25	100

Duration of Wound Healing	All	Human Epidermal Growth Factor Application	Conventional Povidone Iodine Dressing
N	50	25	25
Mean	9.30	7.72	10.88
SD	2.37	1.88	1.64
P value Unpaired t Test			0.0001

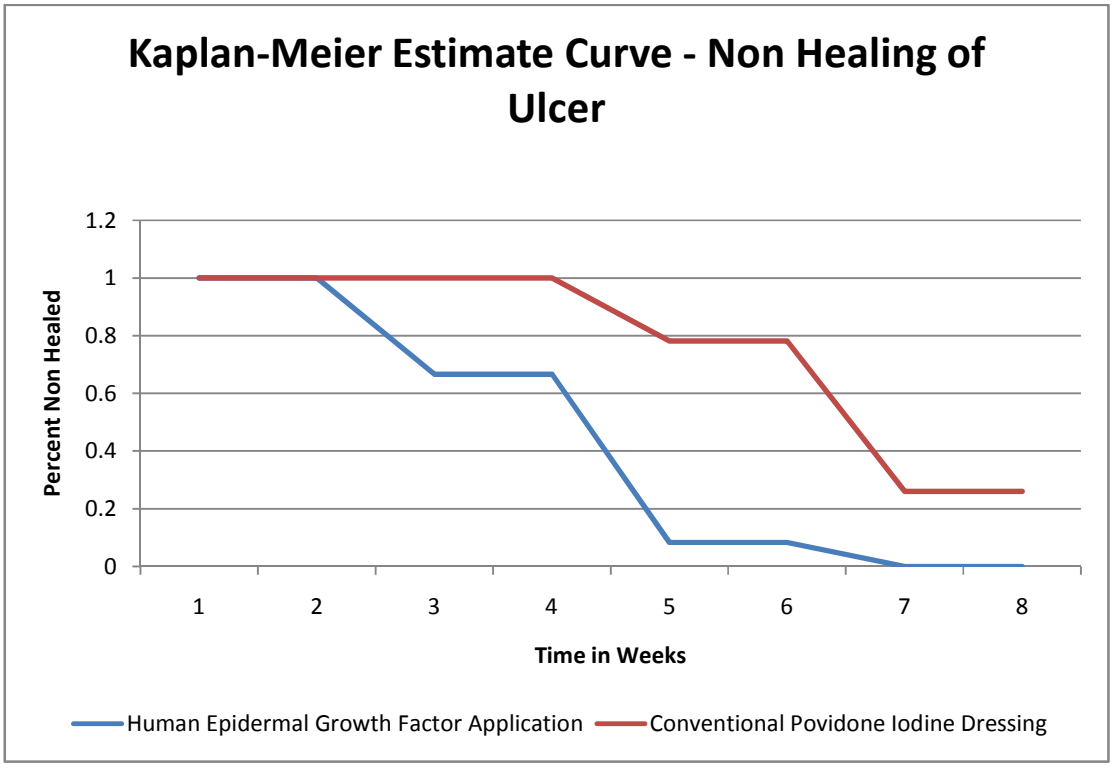
Final Status of Wound





Final Status of Wound	All	%	Human Epidermal Growth Factor Application	%	Conventional Povidone Iodine Dressing	%
Skin Graft	31	62.00	17	68.00	14	56.00
Stump Closure	6	12.00	3	12.00	3	12.00
Secondary Suturing	5	10.00	4	16.00	1	4.00
Non Healing	8	16.00	1	4.00	7	28.00
Total	50	100	25	100	25	100
P value Fishers Exact Test			0.0191			

KM Analysis



log-rank test; z = 0.98, p = 0.033

If you are in Epidermal Growth Factor Application Group, your probability of wound healing in 7 weeks is 100%.

If you are in Conventional Povidone Iodine Dressing Group , your probability of wound healing at the same time is slightly more than 76%.

It is statistically significant with a p-value of 0.033 as per log-rank test

DISCUSSION

Wound and wound healing is an important discussion topic for centuries. Wound healing is hindered by many factor. One of the most important hindrance to wound healing or that impedes the steps of wound healing is associated Type 2 Diabetes Mellitus. Major factor in diabetes that delays or hinder with wound healing are obesity, uncontrolled hyperglycemia, renal compromise, and insulin resistance . Uncontrolled diabetes results in reduced inflammation, angiogenesis, and collagen synthesis.

Additionally, the large- and small-vessel disease that is the hallmark of advanced diabetes contributes to local hypoxemia.

Defects in granulocyte function, capillary ingrowth, and fibroblast proliferation all have been described in diabetes.

Obesity, insulin resistance, hyperglycemia, and diabetic renal failure contribute significantly and independently to the impaired wound healing observed in diabetics.

The diabetic wound appears to be lacking in sufficient growth factor levels, which signal normal healing. It remains unclear whether decreased collagen synthesis or an increased breakdown due to an abnormally high proteolytic wound environment is responsible.

Careful correction of blood sugar levels improves the outcome of wounds in diabetic patients. Increasing the inspired oxygen tension, judicious use of antibiotics, and correction of other coexisting metabolic abnormalities all can result in improved wound healing.

Diabetes is still one of the major cause for limb amputations mainly in lower limb.

Increased level of glucose in tissues or uncontrolled level of glucose in tissues precipitates infection, and lead to vascular compromise which in turn results in a non-healing wound or even may lead to amputation if it is in extremities, mainly in lower extremities.

Human epidermal growth factor stimulates cell growth, differentiation, and proliferation by binding to it EGFR receptor.

In case of T2 DM previous studies has shown that topical application of epidermal growth factor is enhancing the wound healing than other conventional methods.

In our study total number of patients included was 50, each arm 25,that means, 25 patients were treated with topical application of human epidermal growth factor and other group of 25 was treated with application of conventional povidine iodine dressing. Also intermittent wound debridement was done to remove slough according to the need of the wound.

This study was conducted from July 2014 to June 2015.

This study has undertaken to know whether the topical application of human epidermal growth factor gel over diabetic wounds will enhance faster wound healing than conventional povidine iodine dressing or to say in any ways human epidermal growth factor is superior to conventional dressings.

Based on our study, following observations were made:

AGE

We conducted study with total 50 patients, each arm 25.

In case of epidermal growth factor more patients were in age group of 60–70 years, that is around 44%, that is, mean age of 60.6 years

In case of povidine iodine dressing more patients were in two groups 50-60 and 60-70 years, that is around 32% with a mean age of 57.24 years

The association between the intervention groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

SEX

In the study, of total patients 60% were male and 40% were females. The association between the intervention groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per fishers exact test.

DURATION OF WOUND HEALING

In our study, we found that in patients we used human epidermal growth factor, 16% healed within 6 weeks of time, another 56% healed by 9 weeks of time, 8% healed by 12 weeks and only 4% went for non healing wound.

In case of patients we used povidine-iodine dressing we found that no patients healed by 6 weeks of time, 24% patients healed by 9 weeks of time, another 48% healed by 12 weeks time and 28% patients did not heal, and went for non-healing wound.

The decreased mean duration of wound healing in Human Epidermal Growth Factor Application Group compared to the Conventional Povidone Iodine Dressing Group is statistically significant as the p value is 0.0001 as per unpaired t- test indicating a true difference among study groups.

The mean duration of wound healing was meaningfully less in Human Epidermal Growth Factor Application Group compared to the Conventional Povidone Iodine Dressing Group by 3.16 weeks. This significant difference of 29% decrease in mean duration of wound healing in Human Epidermal Growth Factor Application Group compared to the Conventional Povidone Iodine Dressing Group is true and has not occurred by chance

FINAL STATUS OF WOUND

In our study we found that, in case of patients we did dressings with human epidermal growth factor 68% patients wound resulted in skin graft, 12 % patients went for stump closure, 16% patients went for secondary suturing. In 4% patients wounds were non-healing.

In case of patients we did dressing with povidine iodine, 56% patients wound resulted in skin graft, another 12% patients wound resulted in stump closure, 4% patients wound went for secondary suturing finally. In this study group around 28% patients with diabetic wounds resulted as non-healing ulcer.

So our study strongly proves that with use of epidermal growth factor in diabetic wounds significantly reduces the incidence of non-healing ulcer as compared to povidine-iodine dressing.

SUMMARY

The study was done with 50 patients in all surgical units of department of general surgery, Govt. Stanley medical college & hospital, Chennai from july 2014 to june 2015. The purpose of the study was to compare human epidermal growth factor dressing with povidine iodine dressing in diabetic wounds and to prove whether topical application of human epidermal growth factor enhances wound healing better than conventional povidine iodine dressing.

All patients male and female from age 35 up to 75 years undergoing treatment for diabetic wounds were considered in the study

The observations of study summarized below:

- Patients we used topical application of human epidermal growth factor, healing of wounds on an average took about 7.72 weeks and in case of povidine-iodine dressing it took about 10.88 weeks to heal the wound.
- The mean duration of wound healing was meaningfully less in Human Epidermal Growth Factor Application Group compared to the Conventional Povidone Iodine Dressing Group by 3.16 weeks. This significant difference of 29% decrease in mean duration of wound healing in Human Epidermal Growth Factor Application Group compared to the Conventional Povidone Iodine Dressing Group is true and has not occurred by chance

- In case of final status of the wound we found that, in case of patients we treated with human epidermal growth factor 68% patients wound resulted in skin graft, 12 % patients went for stump closure, 16% patients went for secondary suturing and 4% patients wounds were non-healing.
- In case of patients we treated with povidine iodine, 56% patients wound resulted in skin graft, another 12% patients wound resulted in stump closure, 4% patients wound went for secondary suturing finally. In this study group around 28% patients with diabetic wounds resulted as non-healing ulcer.

CONCLUSION

- The results of the study concludes that the topical application of human epidermal growth factor enhances wound healing significantly and is better than conventional povidine iodine dressing.
- Results of the study also concludes that the topical application of human epidermal growth factor causes significant reduction in number of non-healing ulcers.

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ANNEXURES

PROFORMA

NAME: AGE/SEX:

OCCUPATION: IP NO:

SL.NO: ADDRESS
WITH CONTACT NO:

DATE OF ADMISSION:

DATE OF DISCHARGE:

CHIEF COMPLAINT:

HISTORY OF PRESENTING ILLNESS:

PAST HISTORY:

PERSONAL HISTORY:

OCCUPATIONAL HISTORY:

FAMILY HISTORY:

TREATMENT HISTORY:

GENERAL EXAMINATION:

LOCAL EXAMINATION:

CLINICAL DIAGNOSIS:

INVESTIGATIONS

A. Routine investigations:

- Complete blood count
- Renal function test
- Random blood sugar
- Liver function test
- Serum electrolytes
- X-ray chest pa view

B. Special investigations:

- Pus culture and sensitivity
- Fasting blood sugar
- Post prandial blood sugar
- Doppler scan (if needed)
- X-ray local area (if needed)

TYPE OF DRESSING
(human epidermal growth factor/povidine iodine) :

DURATION OF WOUND HEALING:

FINAL STATUS OF WOUND:

GOVT.STANLEY MEDICAL COLLEGE, CHENNAI- 600 001
INFORMED CONSENT

DISSERTATION TOPIC: "A COMPARATIVE STUDY ON WOUND HEALING WITH TOPICAL APPLICATION OF HUMAN EPIDERMAL GROWTH FACTOR VERSES APPLICATION OF POVIDONE-IODINE IN DIABETIC WOUNDS".

PLACE OF STUDY: GOVT. STANLEY MEDICAL COLLEGE, CHENNAI

NAME AND ADDRESS OF PATIENT:

I, _____ have been informed about the details of the study in my own language.
I have completely understood the details of the study.
I am aware of the possible risks and benefits, while taking part in the study.
I understand that I can withdraw from the study at any point of time and even then, I will continue to receive the medical treatment as usual.
I understand that I will not get any payment for taking part in this study.
I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.
I know what I am supposed to do by taking part in this study and I assure that I would extend my full co-operation for this study.

Name and Address of the Volunteer:

Signature/Thumb impression of the Volunteer

Date:
Witnesses:
(Signature, Name & Address)

Date:
Name and signature of investigator:

Date:

நீரிழிவுநோயாளிகளின் காயத்தை ஆற்றுவதில் மேன்மையானது மேற்பூச்சு மேற்றோலுக்குரிய வளர்ச்சிக்காரணியா அல்லது

அயோடின்தாது கட்டா என ஒப்பிட்டுப்பார்க்கும் aaggnnmvvbbஆய்வு

ஆய்வாளர்:மரு. ம்ருதுல் மாதியு,

முதுநிலைபட்டமேற்படிப்புமாணவர்,

அறுவைசிகிச்சைபட்டபடிப்பு.

வழிகாட்டி:பேராசிரியர் மரு.விஷ்வநாதன்,

அறுவைசிகிச்சைபேராசிரியர்,

அரசுஸ்டான்லிமருத்துவமனை.

சுயஒப்புதல்படிவம்

பெயர்: வயது:

உள்ளிருப்புஎண்:

இந்த மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களைக் கேட்கவும், அதற்கான தகுந்த விளக்கங்களைப் பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் இவ்வாய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்தகாரணத்தினாலும், எந்த கட்டத்திலும், எந்தசட்டசிக்கலும் இன்றி இந்த ஆய்விலிருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

நான் ஆய்விலிருந்து விலகிக்கொண்டாலும் ஆய்வாளர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கோ அல்லது உபயோகிக்கவோ என் அனுமதி தேவையில்லை எனவும் அறிந்துகொண்டேன். என்னைப் பற்றிய தகவல்கள் இரகசியமாகப் பாதுகாக்கப்படும் என்பதையும் அறிவேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும் பரிசோதனை முடிவுகளையும் ஆய்வாளர் அவர் விருப்பத்திற்கேற்ப எவ்விதமாகப் பயன்படுத்திக்கொள்ளவும், அதனை பிரசுரிக்கவும் முழுமனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்துகொள்வதுடன் ஆய்வாளருக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல்நலம் பாதிக்கப்பட்டாலோ அல்லதுவழக்கத்திற்கு மாறான நோய்க்குறிதென்பட்டாலோ உடனே அதை தெரிவிப்பேன் என உறுதிகூறுகிறேன்.

இந்த ஆய்வில் எனக்கு எவ்விதமான பரிசோதனைகளையும், சிகிச்சைகளையும் மேற்கொள்ள நான் முழுமனதுடன் சம்மதிக்கிறேன்.

இப்படிக்கு

நோயளியின்கையொப்பம்
ஆய்வாளர்கையொப்பம்

பெயர்

(மரு.ம்ருதுல் மாதியு.)

நீரிழிவுநோயாளிகளின் காயத்தை ஆற்றுவதில் மேன்மையானது மேற்பூச்சு மேற்றோலுக்குரிய வளர்ச்சிக்காரணியா அல்லது

அயோடின்தாது கட்டா என ஒப்பிட்டுப்பார்க்கும் aaggnnmvvbbஆய்வு

ஆய்வாளர்:மரு.ம்ருதுல் மாதியு,

முதுநிலைபட்டமேற்படிப்புமாணவர்,

அறுவைசிகிச்சைபட்டபடிப்பு.

வழிகாட்டி:பேராசிரியர்மரு.விஷ்வநாதன்,

அறுவைசிகிச்சைபேராசிரியர்,

அரசுஸ்டான்லிமருத்துவமனை.

பங்கேற்பாளரின்தகவல்படிவம்

நீங்கள் இந்த ஆய்வில் பங்கேற்க அழைக்கப்படுகிறீர்கள். இந்த ஆய்வில் பங்கேற்கும் முன், இதன் நோக்கத்தையும், முறைகளையும்,

இதனால் ஏற்படும் பின் விளைவுகளையும் நீங்கள் அறிந்துகொள்ள ஆய்வாளர் அளிக்கும் தகவல்:

நீரிழிவு நோயாளிகள் இந்த ஆய்வில் சேர்த்துக்கொள்ளப்படுவார்கள். உங்கள் நோயின் வரலாறும், உங்களின் முழு உடல் பரிசோதனையும் தெளிவாகவும் விரிவாகவும் பதிவு செய்யப்படும். உங்களின் காயம் மேர்க்குரிய இரு முரைகளில் ஏதேனும் ஒரு முறையில் ஆற்றப்படும்.

இந்த ஆய்வின் முடிவுகள் மருத்துவ காரணங்களுக்காகவும், மருத்துவ கல்விக்காகவும் பயன்படுத்தப்படும். இந்த ஆய்வு பற்றிய சந்தேகங்களுக்கு உரிய முறையில் விளக்கமளிக்கப்படும். தங்களைப் பற்றிய தகவல்கள் இரகசியமாக பாதுகாக்கப்படும்.

இந்த ஆய்வில் இருந்து எப்போது வேண்டுமானாலும் தாங்கள் எவ்வித முன்னறிவிப்பின்றியும், எவ்வித சட்டசிக்கலும் இன்றி விலகிக்கொள்ளலாம்.

இந்த ஆய்வில் பங்கேற்குமாறு கேட்டுக்கொள்கிறேன்.

நன்றி,

ஆய்வாளர்கையொப்பம்
நோயாளியின்கையொப்பம் (மரு. ம்ருதுல் மாதியு)
(பெயர்:)

MASTER CHART

Sl. no	age	sex	IP no.	Diagnosis	time limit for study	DURATION OF WOUND HEALING WITH EPIDERMAL GROWTH FACTOR	FINAL STATUS OF WOUND
1	56	F	1541650	DIABETIC WOUND	12 WEEKS	6 WEEKS	SKIN GRAFT
2	58	F	1540539	DIABETIC WOUND	12 WEEKS	8 WEEKS	SKIN GRAFT
3	69	F	1541250	DIABETIC WOUND	12 WEEKS	7 WEEKS	SKIN GRAFT
4	68	M	1541351	DIABETIC WOUND	12 WEEKS	11 WEEKS	STUMP CLOSURE
5	66	M	1541127	DIABETIC WOUND	12 WEEKS	8 WEEKS	SKIN GRAFT
6	48	M	1540589	DIABETIC WOUND	12 WEEKS	6 WEEKS	SECONDARY SUTURING
7	69	M	1554531	DIABETIC WOUND	12 WEEKS	9 WEEKS	SKIN GRAFT
8	73	F	1552948	DIABETIC WOUND	12 WEEKS	10 WEEKS	SKIN GRAFT
9	70	M	1544596	DIABETIC WOUND	12 WEEKS	> 12 WEEKS	NON HEALING
10	67	M	1544549	DIABETIC WOUND	12 WEEKS	8 WEEKS	STUMP CLOSURE
11	66	M	1554075	DIABETIC WOUND	12 WEEKS	7 WEEKS	SKIN GRAFT
12	57	F	1554164	DIABETIC WOUND	12 WEEKS	6 WEEKS	SKIN GRAFT
13	49	F	1535450	DIABETIC WOUND	12 WEEKS	6 WEEKS	SKIN GRAFT
14	39	M	1564653	DIABETIC WOUND	12 WEEKS	5 WEEKS	SECONDARY SUTURING
15	73	F	1534009	DIABETIC WOUND	12 WEEKS	9WEEKS	SKIN GRAFT
16	56	F	1554611	DIABETIC WOUND	12 WEEKS	6WEEKS	SKIN GRAFT
17	47	F	1515550	DIABETIC WOUND	12 WEEKS	6WEEKS	SKIN GRAFT
18	54	M	1544750	DIABETIC WOUND	12 WEEKS	7 WEEKS	SKIN GRAFT
19	70	M	1551603	DIABETIC WOUND	12 WEEKS	9 WEEKS	SKIN GRAFT
20	67	M	1554128	DIABETIC WOUND	12 WEEKS	9 WEEKS	STUMP CLOSURE
21	69	M	1545466	DIABETIC WOUND	12 WEEKS	8 WEEKS	SKIN GRAFT
22	61	M	1554715	DIABETIC WOUND	12 WEEKS	8 WEEKS	SKIN GRAFT
23	59	M	1545322	DIABETIC WOUND	12 WEEKS	8 WEEKS	SECONDARY SUTURING
24	60	F	1553172	DIABETIC WOUND	12 WEEKS	8 WEEKS	SKIN GRAFT
25	44	M	1558614	DIABETIC WOUND	12 WEEKS	5 WEEKS	SECONDARY SUTURING

Sl. no	age	Sex	IP no.	diagnosis	time limit for study	DURATION OF WOUND HEALING WITH POVIDINE IODINE DRESSSING	FINAL STATUS OF WOUND
1	46	M	1512949	DIABETIC WOUND	12 WEEKS	10 WEEKS	SKIN GRAFT
2	55	F	1554114	DIABETIC WOUND	12 WEEKS	9 WEEKS	STUMP CLOSURE
3	74	F	1544844	DIABETIC WOUND	12 WEEKS	> 12 WEEKS	NON HEALING
4	70	F	1543561	DIABETIC WOUND	12 WEEKS	11 WEEKS	STUMP CLOSURE
5	68	M	1541688	DIABETIC WOUND	12 WEEKS	>12 WEEKS	NON HEALING
6	47	M	1542701	DIABETIC WOUND	12 WEEKS	10 WEEKS	SKIN GRAFT
7	54	M	1544321	DIABETIC WOUND	12 WEEKS	9 WEEKS	SKIN GRAFT
8	60	M	1544211	DIABETIC WOUND	12 WEEKS	12 WEEKS	SKIN GRAFT
9	59	M	1543765	DIABETIC WOUND	12 WEEKS	>12 WEEKS	NON HEALING
10	38	M	1542899	DIABETIC WOUND	12 WEEKS	10 WEEKS	SKIN GRAFT
11	66	F	1547544	DIABETIC WOUND	12 WEEKS	10 WEEKS	SKIN GRAFT
12	68	F	1537345	DIABETIC WOUND	12 WEEKS	> 12 WEEKS	NON HEALING
13	53	M	1549476	DIABETIC WOUND	12 WEEKS	11 WEEKS	SKIN GRAFT
14	63	M	1533675	DIABETIC WOUND	12 WEEKS	11 WEEKS	SKIN GRAFT
15	44	M	1537109	DIABETIC WOUND	12 WEEKS	9 WEEKS	SKIN GRAFT
16	71	F	1530637	DIABETIC WOUND	12 WEEKS	>12 WEEKS	NON HEALING
17	59	F	1540013	DIABETIC WOUND	12 WEEKS	10 WEEKS	SKIN GRAFT
18	65	M	1538909	DIABETIC WOUND	12 WEEKS	12 WEEKS	SECONDARY SUTURING
19	52	M	1547701	DIABETIC WOUND	12 WEEKS	9 WEEKS	SKIN GRAFT
20	47	F	1549001	DIABETIC WOUND	12 WEEKS	9 WEEKS	SKIN GRAFT
21	40	M	1537890	DIABETIC WOUND	12 WEEKS	8 WEEKS	STUMPCLOSURE
22	44	M	1546780	DIABETIC WOUND	12 WEEKS	10 WEEKS	SKIN GRAFT
23	54	F	1531400	DIABETIC WOUND	12 WEEKS	11 WEEKS	SKIN GRAFT
24	70	M	1541234	DIABETIC WOUND	12 WEEKS	> 12 WEEKS	NON HEALING
25	64	F	1534390	DIABETIC WOUND	12 WEEKS	>12 WEEKS	NON HEALING