"Treatment of Chronic Venous Ulcers with Topical Sucralfate" - A Prospective Study

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In partial fulfilment of the

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Department of General Surgery

Coimbatore Medical College Hospital

Coimbatore - 641018

CERTIFICATE

This is to certify that this dissertation titled ***"Treatment of Chronic Venous Ulcers with Topical Sucralfate – A Prospective Study"*** submitted to the Tamil Nadu Dr. M. G. R. Medical University, Chennai, in partial fulfilment of the requirement for the award of M. S Degree Branch – I (General Surgery) is a bonafide work done by **Dr. Shreyamsa M**, post graduate student in General Surgery under my direct supervision and guidance during the period of November 2012 to November 2013.

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I hereby declare that the dissertation entitled ***"Treatment of Chronic Venous Ulcers with Topical Sucralfate – A Prospective Study "*** was done by me at Coimbatore Medical College & Hospital, Coimbatore – 641018, during the period of my post graduate study for M.S. Degree Branch-1 (General Surgery) from 2011 to 2014.

This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of the University regulations for the award of M.S. Degree in General Surgery.

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"TREATMENT OF CHRONIC VENOUS ULCERS WITH TOPICAL SUCRALFATE" – A PROSPECTIVE STUDY

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ABSTRACT

Chronic venous ulcer is an important surgical condition due to high incidence and lack of standard therapeutic protocols. The care of these is often palliative and mostly unsuccessful. A variety of medical therapies to influence wound repair and regeneration are currently being investigated. Topical drugs have shown promise in this regard. Wound healing is a complex process with angiogenesis, cell proliferation, inflammation and re-epithelialization. Thus the ideal drug to treat such ulcers should possess properties to enhance all these parameters.

Sucralfate is a cytoprotective agent, which is used in treatment of GIT related diseases like peptic ulcers. Recent studies have shown the stimulating effect of sucralfate over EGF expression and other growth factors involved in tissue repair. Furthermore, the stimulating effects of sucralfate on vascular factors have been demonstrated. Several studies show that sucralfate increases wound contraction, re-epithelialization and diminishes inflammatory reactions. It is safe as demonstrated by complete lack of side effects. Multiple studies using sucralfate for treating epithelial wounds showed encouraging results and served as basis for conducting this study.

30 patients were randomized into study and control groups and treated with topical sucralfate and saline dressings respectively. Parametric analysis of decrease in ulcer size, granulation and decrease in pain over ulcer. Majority of the study group showed improvement in all parameters while that in control group was drastically low. The current study involved a small group of patients but showed promising results with decrease in objective and subjective

symptoms. Sucralfate being an inexpensive drug lessens the need for heavy expenditure. We conclude that sucralfate can be one such alternative solution to this age old problem and deserves thorough research, exploration and evaluation in this regard.

Key Words: Chronic venous ulcer, sucralfate topical application, wound healing, epithelial wounds.

INTRODUCTION

"**Not all wounds heal, not all scars show**"

- An age old English philosophical statement. But when we look at the history of wounds and wound care, it's not surprising if one finds this saying apt and relevant in this context. Famous French war surgeon Ambroise Parĕ while treating a wounded soldier exclaimed "**I bandaged him, god treated him**". The art and science of wound treatment has come a long way from its philosophical and rather religious beginnings and in the present day, it is observing a revolution of sorts with the rapidly developing methods of treatments and newer inventions.

The history of wounds and wound management is as old as mankind itself. From the time of cavemen who developed ingenious primitive techniques to treat wounds to the sophisticated present day, the field of wound management still remains an ever-evolving and extensively researched issue. Management of wounds, especially those acute, still pose a great challenge to the surgeons worldwide, in spite of numerous treatment options available. Advances in the management of wounds have advanced the whole art of surgery. Although the causes of injury are most of the times obvious and the wound easily observed, it is only in the previous two or three decades that the different processes occurring in wound and wound healing as well as the factors influencing them have been understood.

Despite that most of the historical concepts of wound healing are based on mysticism, empirical logic with reasoning and unfounded conclusions, there was a commendable sense of imagination and brilliance among a few who thought objectively and clearly, and were brave enough to defend the new ideas spawned in the process. Unfortunately, this new knowledge has not led us to significant breakthroughs in the treatment of wounds, as observed usually in other areas of surgery. Although much has been accomplished in this regard, the pieces have yet to be fit together in a way that it is truly beneficial and meaningful to the suffering patient.

Though wounds tend to heal naturally irrespective of whether recovery to full structural integrity and appropriate functioning is possible, the early man noticed that several external factors and herbal remedies assist or hasten the process of wound healing. This was followed by the realization of importance and absolute requirement of hygiene in a wound environment. The vital finding of halting bleeding from a wound gave a new dimension to management of wounds. The early healers observed that covered wounds bled less and any applied pressure stilled a rather serious haemorrhage. A number of substances, by trial and error, were used to soothe pain and perhaps hasten up the healing process.

The earliest documented evidence of wounds, healing and treatment dates back to the early civilizations of Sumeria and Egypt (circa 2000 BC). Healers

and priests started employing physical methods to treat a wound along with religious incantations. The Egyptians were the first ones to differentiate infected and diseased wounds from non-infected and clean wounds. Concoctions and pastes containing antibacterial, absorbent properties like honey, resins and herbs were used for treatment of wounds. Cleaning of wounds with fresh water and milk was encouraged, emphasising on the fact that the Egyptians possessed a sound knowledge of wound irrigation, albeit less scientific. They also made use of minerals, like the green copper pigment obtained from malachite and certain mercury compounds for application over wounds. These minerals possessed powerful astringent and antiseptic properties.

Greek medicine borrowed a lot from the exploits of much older Egyptians. The early Greek physicians classified wounds into acute and chronic types. Hippocrates, the father of western medicine, proposed that contused wounds should be treated with salves in order to reduce inflammation. He also stressed on the importance of removing necrotic material from the wound in order to prevent further infection and promote better healing. Hippocrates also engrained the humoral theory of diseases among his contemporaries, thus considering wounds as diseases, which require local care as well as bodily humoral balance for proper healing. The Greeks also extensively used moist dressings, emphasizing on the importance of maintaining a moist environment for better healing. It is now proved beyond doubt that moist wounds re-epithelialize at a

rate double that of wounds which are kept in a dry environment. These concepts of wound debridement and moist dressings are still in vogue.

The Romans took over where the Greeks left, with Cornelius Celsus describing the four cardinal signs of inflammation and introducing elementary suturing techniques for chronic wounds after thorough debridement. He established, along with other Roman physicians, that different types of wounds need different treatment. Galen of Pergamum advocated polypharmacy along with local wound care.

There was a significant decrease in advances during the middle ages and renaissance period. More recently in the 19th century, antiseptics were a significant find in the history of wound healing. Sterile practices and use of dressings impregnated with antiseptics and/or antibiotics considerably reduced wound infection and promoted better healing. In the mid-20th century the focus shifted from trials to evidence based practices and research in the field of wound care. The advent of fibrous synthetics like polyethylene, polyvinyl compounds and nylon provided new resources from which practitioners in the field of wound care could explore better avenues of protecting and treating wounds and perhaps even accelerating the natural wound healing process. The importance of moist dressings was ‘rediscovered’. This dawn of modern wound management initiated a process of improvement in the surgeon’s ability to bolster wound-site healing and re-epithelialization.

In the late 20th century, new discoveries and improvements in hybrid and composite polymers expanded the spectrum of substances available for dressing of wounds. Graft techniques and biotechnology have paved way for production of useful protective covering made of actual human skin created through cloning procedures. Other recent developments have been the reiterated focus on the patient concern of pain. Today, the practice of wound healing not only involves local wound care but also manipulation and modulation of wound environments by use of inflammatory mediators, cytokines, growth factors and bioengineered tissues. A combined and discrete use of all the above will enable optimal wound healing.

OBJECTIVES OF THE STUDY

To study the efficacy of topical Sucralfate application over chronic venous ulcers with respect to the following parameters:

- Size of the lesion
- Granulation
- Decrease in pain over the ulcer**.**

REVIEW OF LITERATURE

Wound healing is a dynamic and complex sequence of biological events aimed at replacing devitalized and destroyed cellular structures and tissue layers. It can be described as an interplay of various cellular and biochemical processes that ultimately leads to restitution of structural integrity and normal functions of any tissue. Individual tissues vary in their healing properties but the underlying mechanisms will essentially remain the same.

The amalgam of events that make up the well-coordinated process of wound healing are intricate and closely orchestrated. The classic model of wound healing comprises of sequential, yet overlapping phases with a fairly predictable course and defined by characteristic cellular populations and biochemical events. The key stages in the procession of wound healing include:

- Haemostasis
- Inflammation
- Proliferation
- Maturation and remodelling.

An analogous system depicts the phases as inflammation, the fibroblastic phase, scar maturation and wound contracture.

❖ PHASES OF WOUND HEALING:

HEMOSTASIS:

Wounds disrupt tissue integrity leading to damage of vascular structures resulting in an outflow of blood and lymphatic fluid. This results in the formation of an initial reparative coagulum. Both the extrinsic and intrinsic pathways of coagulation cascade are activated by virtue of tissue damage and exposure of thrombocytes sub-endothelial collagen and extra cellular matrix respectively.

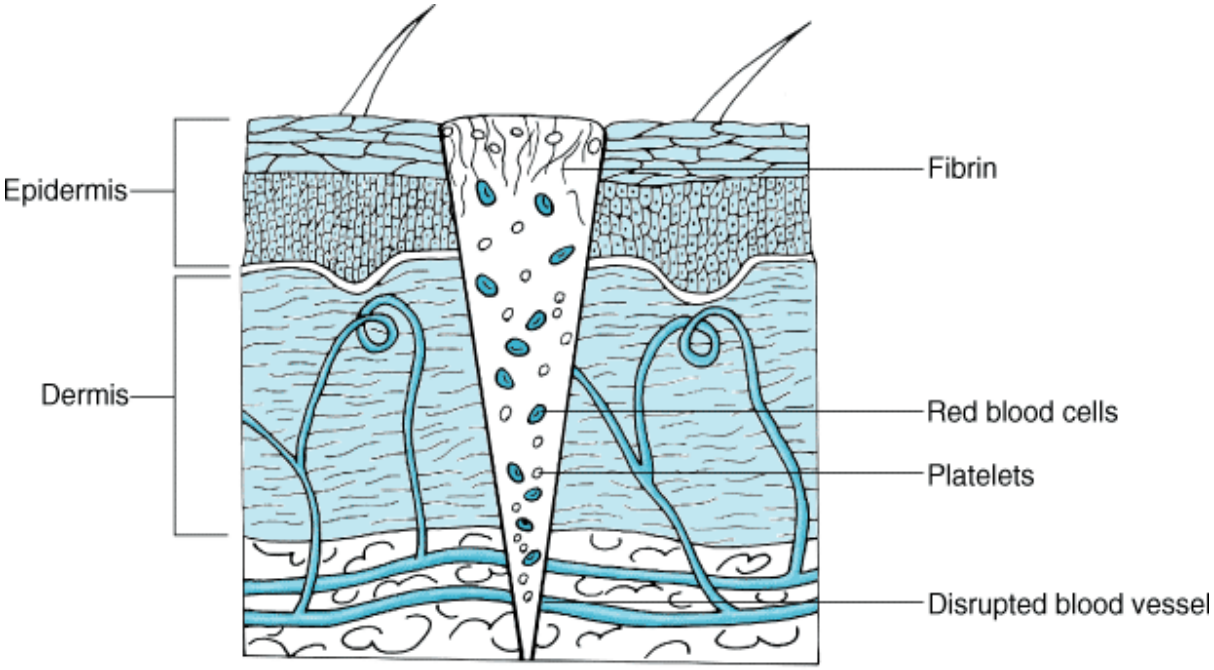


FIGURE 1- STAGE OF HEMOSTASIS

A short lived phase of vasoconstriction is observed at this time. The thrombocytes also promote aggregation, which temporarily dam the wound. Constricted vessels dilate and make way for influx of more thrombocytes and other blood cells. This heralds the initiation of the inflammatory phase as well as other processes like collagenogenesis, collagenolysis, angiogenesis and re-epithelialization, indicating the overlapping nature of the healing compendium as mentioned earlier. These processes are mediated by a host of growth factors and cytokines.

Towards the end of this phase, fibrinogen is cleaved into fibrin and the coagulation cascade is thus completed. The fibrin clots formed not only aid in achieving hemostasis but also serve as structural support in the form of scaffolding for migration and deposition of cellular components of inflammation into the wound. The hemostatic phase starts immediately after the offense has occurred and may continue for several days

INFLAMMATION:

The phase of inflammation is construed to consist of an early and late components, the early part of which is predominated by the influx of polymorphonuclear neutrophils and the latter characterized by invasion of the wound by macrophages. The polymorphonuclear neutrophils infiltrate wounds

in the first 24- 48 hours of injury. Their primary function is phagocytosis of bacteria and tissue debris. They are also a major source of cytokines early during inflammation, especially TNF α, as well as proteases such as collagenase which partake in ground substance and matrix degradation in the initial phases of wound healing. By 72 hours, the neutrophils are either interred in the wound scab or sequestered by the macrophages.

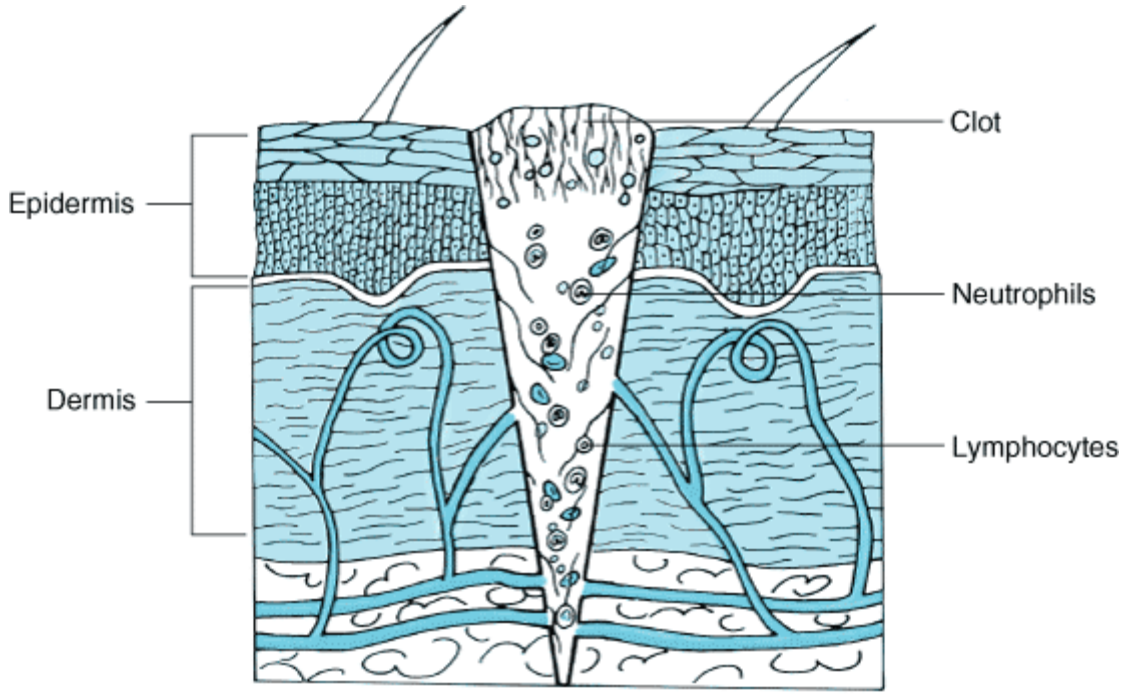


FIGURE 2- STAGE OF INFLAMMATION

The second population of inflammatory cells to invade wounds are macrophages, which are derived from circulating monocytes. They appear after 48- 96 hours after injury, and remain present till the healing process is

complete. Macrophages, like neutrophils, participate in phagocytosis and contribute to microbial stasis via oxygen radical and nitric oxide synthesis. The most crucial function of macrophages is activation and recruitment of other cells via mediators such as cytokines and growth factors as well as directly by cell-cell interactions. Macrophages also play a significant role in regulating angiogenesis as well as orchestrate multiplication of smooth muscle cells, matrix deposition and remodelling.

T-lymphocytes are the third type of inflammatory cells to invade a wound. They are seen about a week post injury, although very less in number compared to the macrophages. They bridge the transition from inflammatory to the proliferative phase of wound healing and play an active role in modulation of wound environment. Depletion of lymphocytes decreases wound strength and collagen content. It is worthwhile noting that selective depletion of CD8+ suppressor T-cells enhance wound healing.

As inflammation dies down towards the end of this phase, fewer inflammatory mediators are manufactured and released, while the existing ones are subjected to disintegration. The number of cells of inflammation also reduces at the wound site indicating that the proliferative phase is underway. It is important to know that inflammation, if lasts longer than necessary will delay wound healing and result in a chronic wound.

PROLIFERATION:

This is the third phase of wound healing that roughly spans day 4 through 12 post injury. It is also known as the phase of granulation, as a robust granulation tissue is formed during this period. This phase is characterized by numerous undefined and overlapping sub phases. These do not occur in a distinct time frame but represent an ongoing process, which stretch beyond the realms of the phase of proliferation. The major events in this phase are fibroplasia, matrix deposition, angiogenesis and re-epithelialization.

It is in this phase that the last cell populations of fibroblasts and endothelial cells invade the wound environment. After entering the wound, recruited fibroblasts proliferate and get activated in order to carry out their basic function of matrix synthesis and remodelling, which is mediated by cytokines and growth factors released by macrophages. Wound fibroblasts also aid in matrix contraction. In addition to cytokines, lactate, which is accumulated in wounds, also serves as a potent regulator of collagen synthesis via ADP ribosylation mechanism. Collagen plays a pivotal role in completion of the process of wound healing. Types I and III are absolute essentials for this, and its deposition, maturation and finally remodelling are necessary to restore the functional integrity of a healing wound. Early in normal wound healing, type III collagen predominates but as healing process progresses it is replaced by type I collagen.

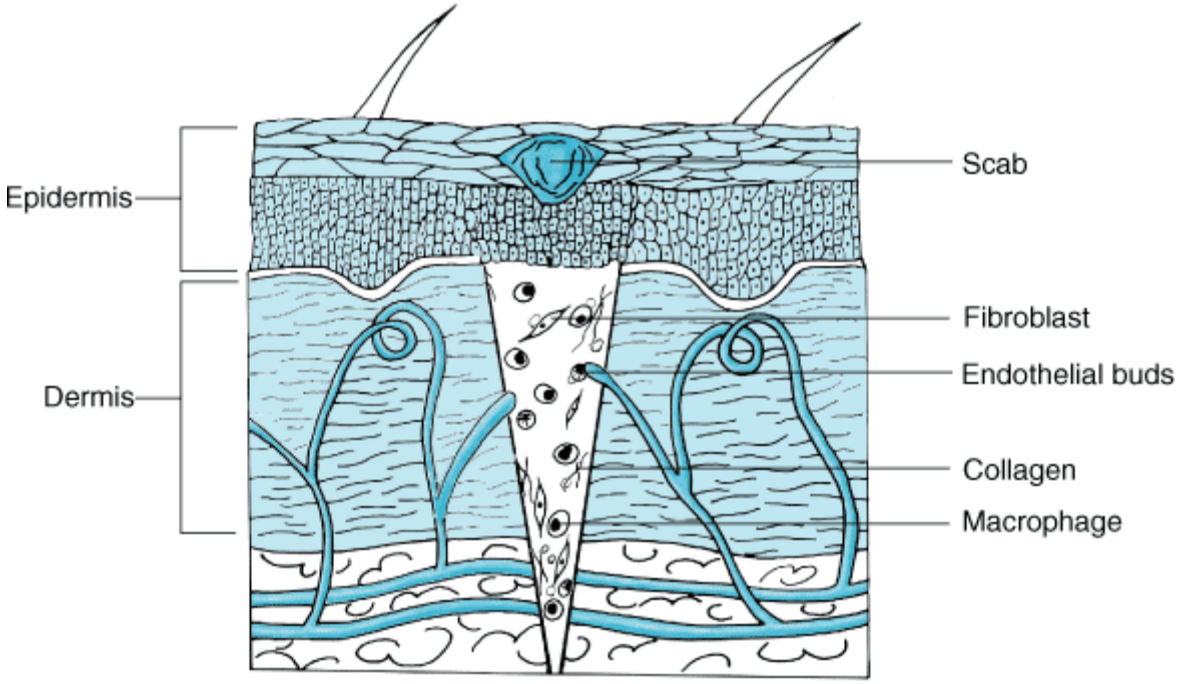


FIGURE 3- STAGE OF PROLIFERATION

The wound at this stage is suffused with glycosaminoglycans and fibronectin synthesized by the fibroblasts. Glycosaminoglycans constitute most of the "ground substance" that makes up extra cellular matrix. They are found in the form of 'proteoglycans' in association with proteins. They peak during the first three weeks of wound healing. Assembly of collagen subunits as fibrils and fibres is based on the lattice structure provided by sulphated proteoglycans. Heparan sulphate, dermatan sulphate and chondroitin sulphate constitute the important glycosaminoglycans.

Angiogenesis or neovascularization is a process that occurs concurrently with fibroblastic proliferation. It is initiated by the migration of endothelial cells to the wound area. They are attracted to the wound area by the fibronectin present in the fibrin scaffold and chemotactically by the angiogenic mediators secreted by inflammatory cells and fibroblasts. Tissue anoxia or hypoxia and accumulation of lactic acid in the wound also result in direct stimulation of endothelial cell growth and proliferation. When the macrophages and other growth factor synthesizing cells no longer encounter hypoxic and lactic acidotic surroundings, the manufacture of angiogenic factors is stopped. Excess vessels which are no longer required are destroyed by apoptosis.

The resultant of above processes put together is the formation of a rudimentary tissue called the granulation tissue. It appears in the wound already during the phase of inflammation; three to five days post injury, and continues to form until the wound bed is completely covered. Granulation is a conglomeration of freshly formed blood vessels, inflammatory cells, fibroblasts, myofibroblasts, endothelial cells and a provisional extra cellular matrix. This provisional extra cellular matrix mainly consists of fibronectin and hyaluronic, which create a well hydrate bed which facilitates cell proliferation. Later this provisional matrix is replaced by a mature one which consists mainly of glycosaminoglycans, collagen, elastin and glycoproteins aplenty.

MATURATION AND REMODELLING:

This phase begins during the fibroplastic phase, the characteristic feature of which is reorganization of already laid collagen. Collagen is disintegrated by matrix metalloproteinases and the total collagen content in a wound is the result of end product of difference between collagen synthesis and breakdown. Few weeks or months after injury, the amount of collagen reaches a plateau but there is a constant increase in the tensile strength for many more days. Fibril formation and cross linking result in reduced collagen solubility, increase in strength and enhanced resistance to degradation of the matrix by proteolytic enzymes. Remodelling continues from 6 months to 1 year post wounding, forming a mature, acellular and avascular scar.

❖ RE-EPITHELIALIZATION:

In this phase, there is an attempt to restore the external barrier, characterized by proliferation and migration of cells from areas adjacent to the wound. It begins within a day of injury and continues throughout. Re-epithelialization is completely achieved in less than 48 hours in incised wounds but may take substantially longer in those which contain larger defects of dermis or epidermis. Exposure of epithelial cells in wound margins to the constituents of

extracellular matrix (namely fibronectin) and cytokines are believed to be the initiators of this process.

Basal keratinocytes from the edges of wounds and appendages of the skin such as sweat glands, sebaceous glands and hair follicles are the cells which epithelialize a healing wound. They migrate across the wound bed in a sheet, proliferate at edges and cease when they meet the cells from another side by contact inhibition. Integrins, matrix metalloproteases along with various growth factors aid in the process of keratinocyte migration and proliferation and formation of a healthy barrier. Wound healing is completed with some degree of contraction, observed more so in cases of healing by secondary intention.

The process of wound healing, thus, constitutes an array of inter-related and concomitant events. Understanding of these events and the factors affecting these events continues to expand rapidly.

PHASE	*CELLULAR AND HUMORAL EVENTS*
HEMOSTASIS	Vasoconstriction Platelet aggregation, degranulation Formation of Fibrin
INFLAMMATION	Neutrophil invasion Monocyte differentiation to Macrophages and infiltration Lymphocyte influx
PROLIFERATION	Re-epithelialization Angioneogenesis Collagenogenesis Formation of Extra Cellular Matrix
REMODELLING	Collagen remodelling Vascular maturation and regression

TABLE 1: PROCESS OF NORMAL WOUND HEALING

❖ FACTORS AFFECTING WOUND HEALING:

A number of intrinsic and extrinsic factors affect the process of wound healing, by interfering with one or multiple stages of healing thus causing inappropriate or impaired wound repair. A better understanding of these factors is of prime importance as the effects of these factors over healing process may lead to devising better therapeutics that resolve impaired wounds and improve wound healing. The influences of these factors over the healing process effectors are not mutually exclusive. Numerous adverse factors may act together complicating the scenario.

The factors adversely influencing wound healing can be broadly divided into:

- Local factors
- Systemic factors

Local factors influence the characteristics and cellular/ biochemical behaviour of the wound itself while the systemic factors affect a person's overall health and ability to heal. Many of these factors can be interrelated as well.

LOCAL FACTORS	*SYSTEMIC FACTORS*
Hypoxia Infection Ischemia Venous insufficiency Foreign body Mechanical factors Edema	Age Gender Sex hormones Stress Comorbid conditions Diabetes mellitus, Uremia, Connective tissue disorders Obesity Medications Corticosteroids, NSAIDS, Cancer chemotherapies Alcoholism and smoking Immunocompromised status AIDS, Radiation exposure Poor nutrition

TABLE 2: FACTORS AFFECTING WOUND HEALING

❖ TYPES OF WOUND HEALING:

Wound healing is classified into three major types, namely:

- Healing by Primary Intention/ Primary wound healing
- Healing by Secondary intention/ Secondary healing
- Delayed primary healing

Even though wound healing is classified into different classes, the interactions of cellular/ extracellular components and biochemical parameters remain the same.

PRIMARY HEALING:

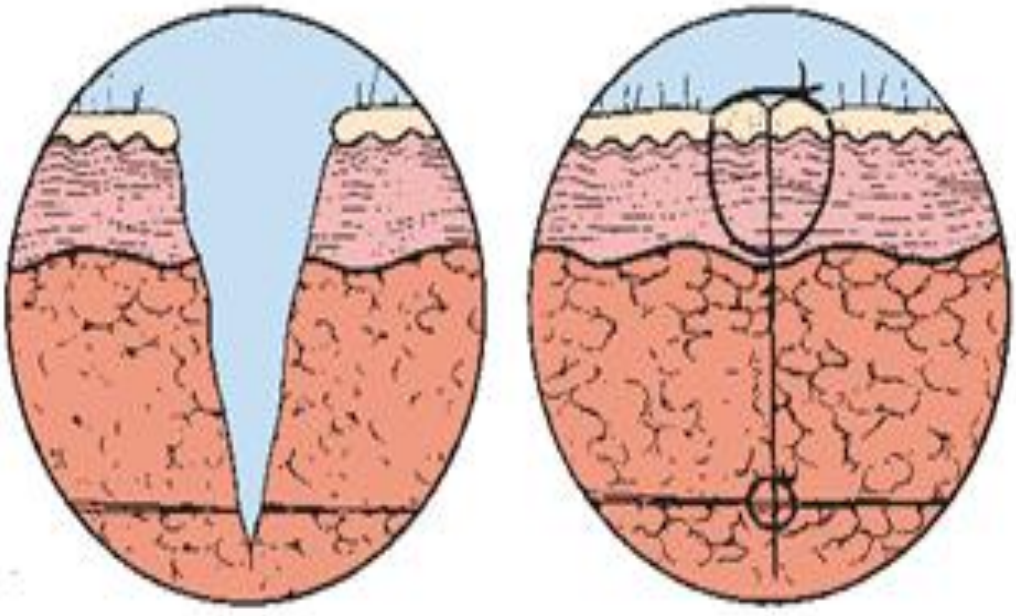


FIGURE 4: PRIMARY HEALING

This type of healing is seen in a clean cut wound involving epidermis and dermis and not totally penetrating the dermis. The wound edges are close together in the wounds that eventually heal by primary intention. Most surgical wounds heal by this method and the healing is enhanced by use of sutures, staples etc. examples of wounds that heal by primary intention are- well repaired laceration, properly reduced fracture, healing after flap surgeries. These wounds scar minimally and show very less or no contracture.

SECONDARY HEALING:

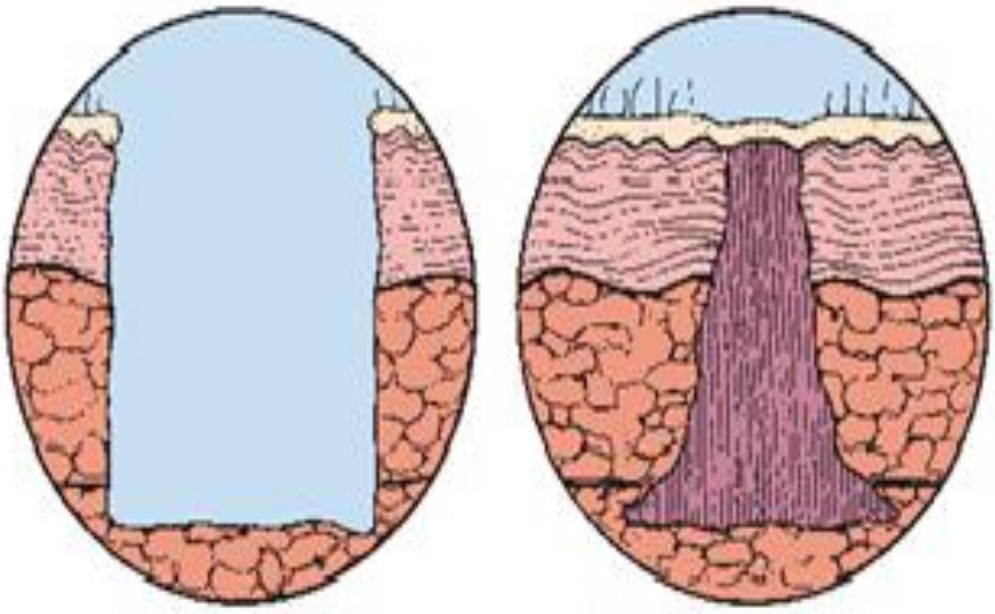


FIGURE 5: SECONDARY HEALING

Wounds healing with secondary intention exhibit a higher inflammatory response compared to primary healing. In this type, a full thickness, large wound is let alone to heal by granulation. Healing by secondary intention causes pronounced contraction of wounds. Fibroblastic differentiation into myofibroblasts, which are similar to contractile smooth muscles are postulated to contribute to contracture of healing wounds. Healing can be hampered by the presence of drainage from infection. Examples of healing by second intention are- venous ulcers, diabetic ulcers, gingivectomy, sockets after extraction of teeth and badly reduced fractures.

DELAYED PRIMARY HEALING:

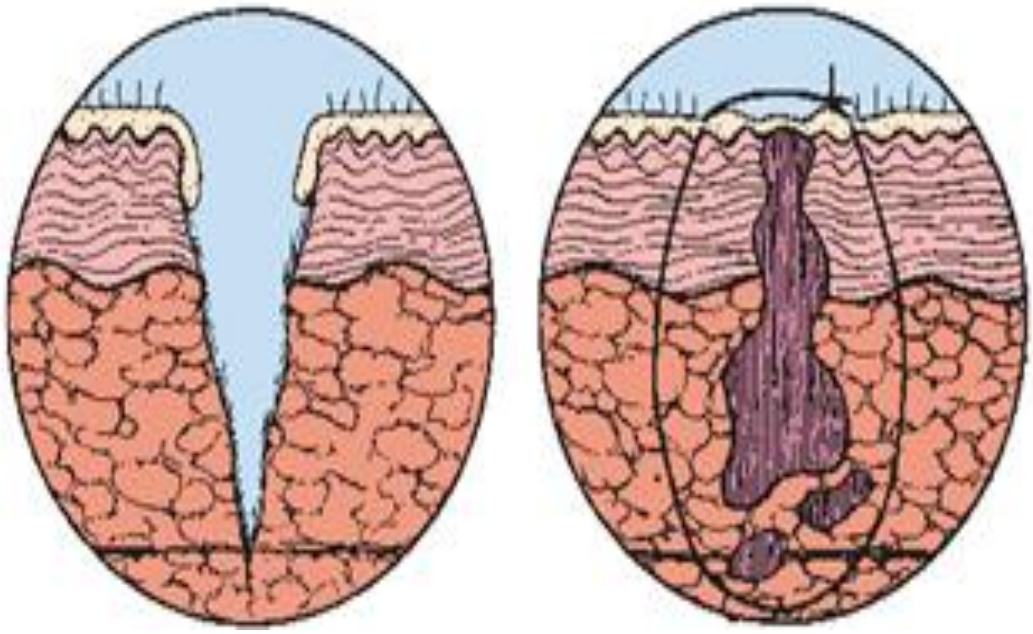


FIGURE 6: TERTIARY HEALING

This type of healing is desired in wounds that are contaminated. If the wound edges are not re-approximated immediately after a surgery/ traumatic event, delayed primary healing transpires. The wound is debrided, cleaned and deprived of necrotic material and foreign bodies and is deliberately left open for few days. The wound is then closed. Example of this type is healing by use of tissue grafts after thorough debridement and cleaning.

❖ CHRONIC WOUNDS:

Chronic wounds are defined as open wounds, which have failed to undergo the orderly set of stages of healing and re-epithelialization that produces a satisfactory structural and functional result. Wounds that have not healed in a period of about 3 months are termed as chronic. Chronic wounds seem to be arrested in one or more stages of wound healing. Most of the chronic wounds are found to remain in the inflammatory period for too long, as compared to a normally healing wound. Unresponsiveness to normal regulatory signals is implicated as a major predictive feature of chronic wounds.

These wounds may take years to heal and sometimes, never heal. Along with the physical discomfort, chronic wounds also produce severe emotional and mental stress on the patients. They also impose heavy financial burden as the patients will undergo many therapies in order to gain relief, most of which are unsuccessful.

Causes of chronic wounds are enumerated as:

- Hypoxia/ hypoperfusion
- Anemia
- Metabolic disorders
- Nutritional disorders
- Neuropathic disorders

- Steroids, chemotherapeutic drugs
- Infections
- Repeated trauma
- Excessive inflammation

Typically, chronic wounds are clinically stagnant and fail to form a healthy and robust granulation tissue.

Chronic wounds are grossly classified as:

- Vascular origin
    - Venous
    - Arterial
- Diabetic ulcers
- Pressure ulcers
- Radiation induced
- Miscellaneous
    - Ischemic, traumatic, iatrogenic etc.

Venous ulcers are a major cause of chronic leg wounds. They are the most common form of leg ulcers and constitute about 70- 90% of all leg ulcers.

❖ ANATOMY OF LOWER LIMB VENOUS SYSTEM:

The venous system of the lower limbs functions as a reservoir to hold extra blood as well as conduit to return blood from the peripheries. Unlike arteries, whose walls possess three distinct structural layers, most veins are made up of a solitary tissue layer. The effective functioning of a vein is dependent on a complex series of valves and pumps, which function as a unit.

The primary collecting veins of the lower limbs are passive, thin walled channels which are massively dilatable. They are suprafascial in situation, enclosed in loose areolar and fatty tissues which are easily displaced. These veins belong to the superficial venous system. Outflow from the superficial veins is into the secondary (conduit) veins that are less distensible and possess thicker walls. These veins are subfascial and constitute the deep venous system.

- SUPERFICIAL VEINS:

The superficial venous system is a highly variable and complicated web-like network of interconnected veins, many of which are not named. A few large veins are fairly consistent in their anatomical location. Principal named superficial veins are the great saphenous vein (GSV) and the short saphenous vein (SSV).

GREAT SAPHENOUS VEIN:

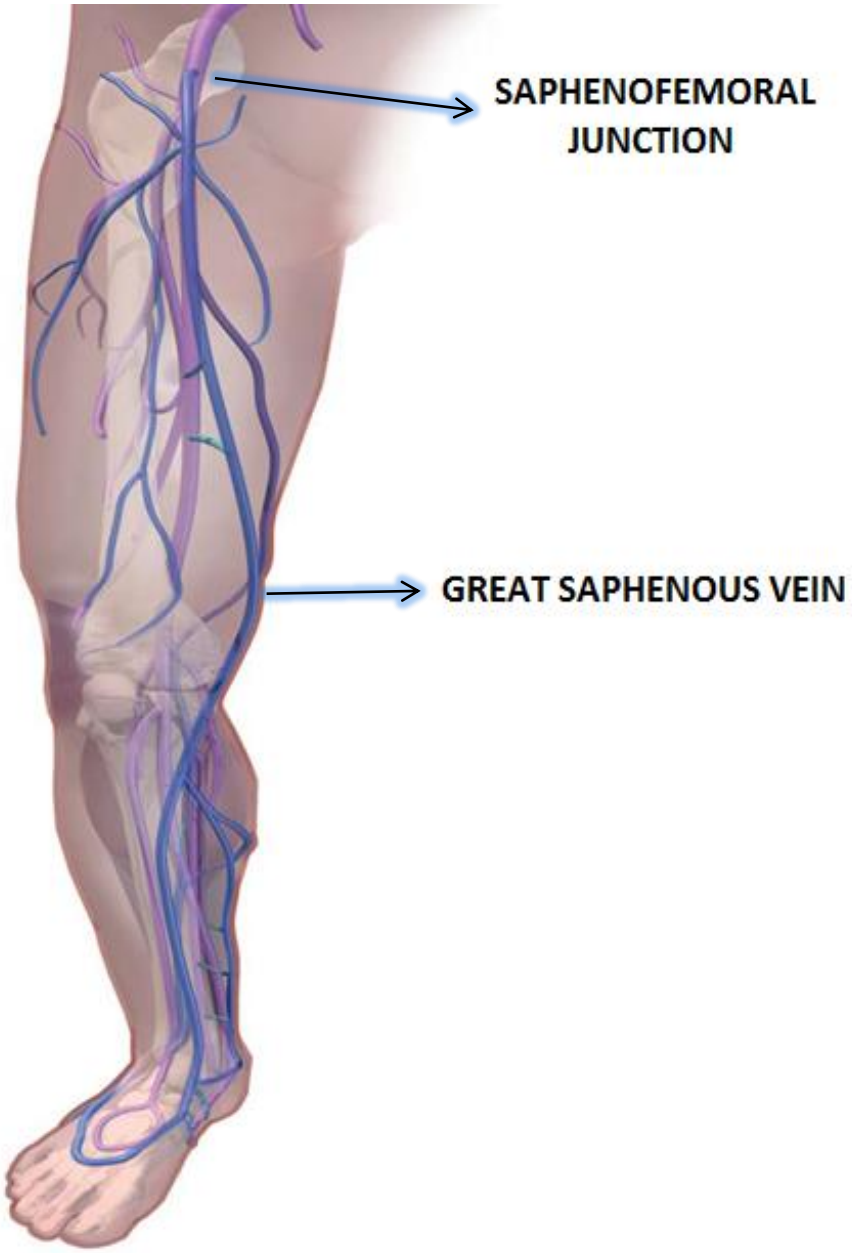


FIGURE 7: GREAT SAPHENOUS VEIN

The great saphenous vein has its origin in the medial part of foot from the dorsal venous arch and passes anterior to the medial malleolus. It runs in a posterior direction to ascend across the tibia medially towards knee. Above the knee it traverses an anteromedial course superficial to the deep fascia to reach

the foramen ovale. Here it pierces the cribriform fascia to join the common femoral vein at the saphenofemoral junction. Numerous named and unnamed tributaries drain into the great saphenous vein along its course.

SHORT SAPHENOUS VEIN:

The short saphenous vein begins in the lateral part of the foot from the dorsal venous arch.

It passes across the lateral malleolus posteriorly and ascends lateral to the Achilles tendon to the calf. It lies in the midline in the calf, directly above the superficial fascia and traverses through to the upper part of calf, where it enters the popliteal space in between the two origins of gastrocnemius muscle. The termination site of short saphenous vein is highly variable. In two third of the population, it terminates in the popliteal vein above the knee joint.

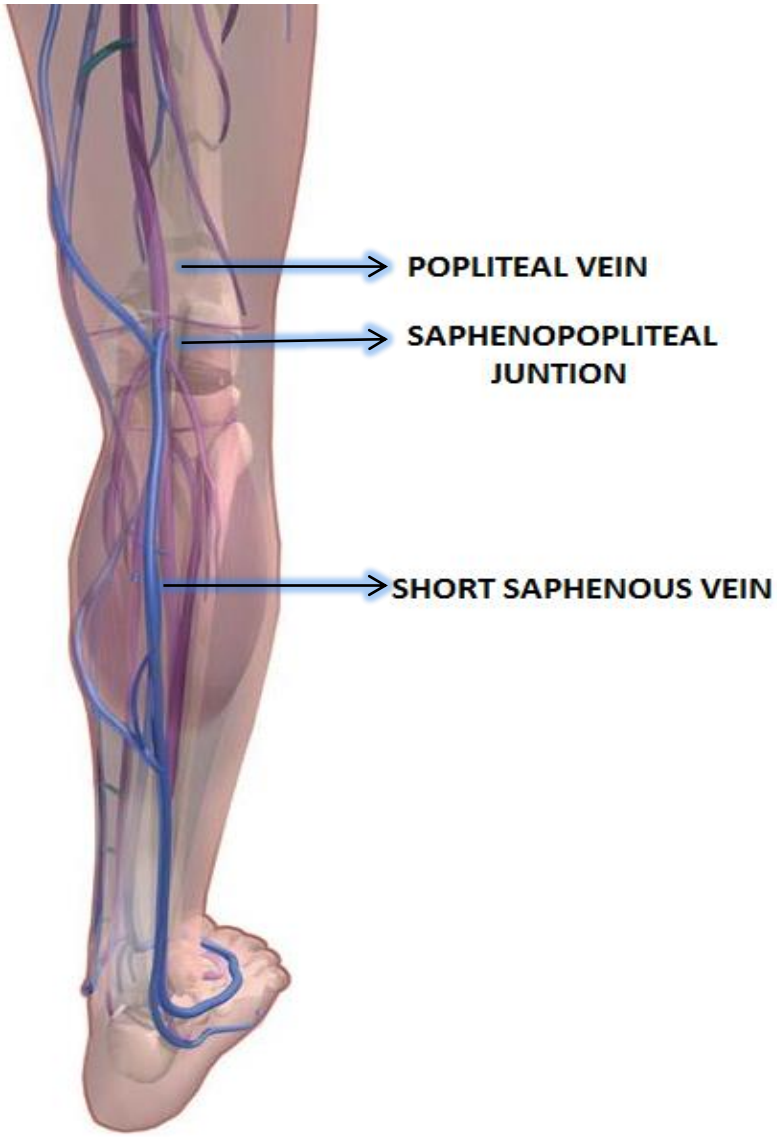


FIGURE 8: SHORT SAPHENOUS VEIN

PERFORATING VEINS:

Most of the blood from the superficial veins is delivered to the deep veins via the saphenofemoral or the saphenopopliteal junctions. However, the SPJ and the SFJ are not the only means to carry out this task. Superficial veins are connected to numerous perforator veins that pierce the deep fascia and join deep

veins in calf as well as thigh. These perforator veins usually are valved, preventing reflux of blood from deep to superficial veins

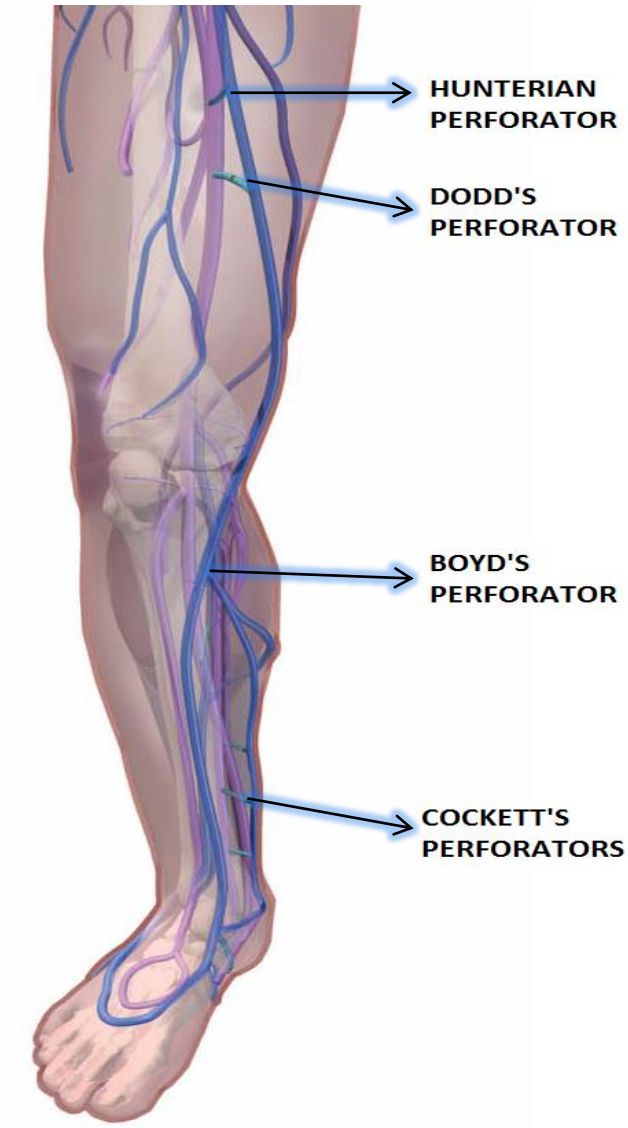


FIGURE 9: THE PERFORATOR VEINS

A few constant perforators are named, which represent a vague group of

perforating veins in that region, namely;

- Hunterian perforator of mid-thigh
- Dodd's perforator present in the distal thigh
- Boyd's perforator situated in the knee
- Cockett's perforators at the ankle

- **DEEP VEINS:**

The deep veins eventually receive all the venous blood from the superficial system and pass it to the major vessels of the pelvis. The important deep vein of the leg is the popliteal vein. The major deep vein of the thigh is formed by the continuation of the popliteal vein, called the femoral vein.

❖ CHRONIC VENOUS INSUFFICIENCY:

It is a condition where blood escapes its regular antegrade stream of flow in a vein and refluxes back into the preceding veins, rendering those veins dilated and insufficient. Venous insufficiency is most commonly due to the incompetence of the valvular system of superficial veins. Rarely, incompetence of deep veins and congenital conditions like absence of valves also contribute to the genesis of this condition. Chronic venous insufficiency leads to severe infections of the leg, pain especially after walking, and lipodermatosclerosis of the legs eventually resulting in skin ulceration. The burden of the disease along with poor cosmesis of this condition is distressing to the patient.

PATHOPHYSIOLOGY:

Congenitally weak walls of a vein dilate even under normal pressures causing secondary valvular failure. Valves which are congenitally abnormal are incompetent at normal pressures. Superficial phlebitis or direct injury to the vessels/ valve may cause primary valve failure. Increased venous pressure is directly responsible for many aspects of chronic venous disease. The pathogenesis due to increased venous pressures can be described in a predictable sequence as shown below:

Increased venous pressure from venules to capillaries, impedance of flow

Low pressure flow states in capillaries, results in "leucocyte trapping"

Release of oxygen free radicles and proteolytic enzymes by the trapped leucocytes, damage to basement membrane of the capillaries

Fibrinogen and other plasma proteins leak into the pericapillary areas, forming a "fibrin cuff" around the vessels

Fibrin in interstitium and subsequent edema prevent transport of oxygen to tissues leading to local hypoxia

Inflammation and loss of tissues

Another hypothesis states that the neutrophils which are stagnant in capillaries adhere to the endothelium and plug them, diminishing the dermal blood flow leading to ulceration and other complications.

Superficial veins develop a high pressure due to failure of critical valves at any point of communication between them and the deep veins. The major sources for high pressure leakage from the deep to the superficial veins are:

i. JUNCTIONAL VALVE FAILURE: most frequently due to failure of valve between the great saphenous vein and the femoral vein at the saphenofemoral junction. Less commonly, it is due to the failure of the valve at the saphenopopliteal junction, present between the short saphenous vein and popliteal vein
ii. PERFORATOR VALVE FAILURE: ensues as a result failure of any valves of perforator veins.

Venous hypertension and damage to capillaries lead to extravasation of haemoglobin and its degradation products which are harmful to the skin, acting as irritants. They cause skin damage as well as dark pigmentation, which along with loss of subcutaneous fat constitute lipodermatosclerosis, a characteristic feature of chronic venous disease.

It is necessary to note that not all the sequelae of venous insufficiency are due to venous hypertension and not every individual with it develops venous ulcers.

Few patients with prominent ulcers do not have evidence of venous hypertension. Ineffective clearance of products of cellular respiration, lactate and carbon dioxide also contribute to the genesis of chronic venous insufficiency and/or ulceration. The majority of venous ulcers are caused by venous reflux that is mostly limited to the superficial system of veins. Without addressing the underlying pathology, venous insufficiency is inexorably progressive. Subjective symptoms slowly worsen over time.

❖ **VENOUS ULCERS**:

"Ulcus Cruris Venosum" or venous ulcers are stasis ulcers, a dreaded complication of chronic venous insufficiency. Characteristically, a venous ulcer fails to re-epithelialize in spite of possessing adequate granulation tissue. Several ulcers may form and coalesce as they increase in size. They are usually found at sites of incompetent perforators. Most common site of venous ulcer is just above the medial malleolus (Cockett's perforator). They are shallow, margins are irregular and surrounded by pigmented skin.

C.E.A.P CLASSIFICATION OF CHRONIC VENOUS DISORDERS

This is a comprehensive classification system involving the clinical, etiological, anatomical and pathophysiological parameters for chronic venous diseases. This severity score helps in the assessment of magnitude of ulcers and the venous disorder as whole.

CLINICAL	**ETIOLOGY**
C_0 - NO CLINICAL SIGNS **C_1** - TELANGIECTASIAS/ RETICULAR VEINS **C_2** - VARICOSE VEINS **C_3** - OEDEMA **C_4** - SKIN CHANGES, WITHOUT ULCERS **C_5** - HEALED ULCERS **C_6** - ACTIVE ULCERS	**E_C** – CONGENITAL **E_P** – PRIMARY **E_S** - SECONDARY
ANATOMY	**PATHOPHYSIOLOGY**
A_S – SUPERFICIAL VEINS **A_D** – DEEP VEINS **A_P** – PERFORATORS	**P_R** – REFLUX **P_O** - OBSTRUCTION

TABLE 3: C.E.A.P CLASSIFICATION

❖ TREATMENT OPTIONS FOR VENOUS INSUFFICIENCY/ ULCERS:

Treatment of chronic venous ulcers is multimodal. No single therapy is found to be effective. The treatment is aimed at correcting the underlying causes if possible and more importantly, ameliorating symptoms. The primary intention of therapy is to address the issue of venous hypertension. Following are the common methods used for treatment:

- COMPRESSION BANDAGING:

  The standard approach has been to use gradient compression stockings around the leg and thigh. These provide 30-50 mm Hg of compression at the ankle, with a gradual decrease in compression pressure as it is applied more proximally. This amount of graded compression is enough to restore normal flow patterns in superficial veins in many or most patients with venous reflux. It is also known to improve venous flow, even in patients with severe incompetence of deep veins.

  Along with compression therapy, other physical measures may also be helpful. Elevation of leg causes venous flow to be augmented by gravity, decreasing venous pressures and reversing edema. While seated, the patient's legs should be above his/ her thighs and while recumbent, they should be above the level of the cardia. The Unna boot, first described in 1854, is a common method of treatment of venous ulcers. Unna boots are

rolled bandages that contain combinations of different chemicals like glycerine, calamine lotion and gelatin.

- VENOABLATION:

Venoablation is reserved for those with ulcers refractory to medical management or discomfort. The primary goal of endovenous and surgical interventions is to correct venous insufficiency by eliminating the major reflux pathways. Various techniques for venoablation include the following:

  - Ligation of GSV with stripping
  - Simple ligation and division of varicose veins
  - Stab evulsion (with or without ligation)
  - Sclerotherapy
  - Endovenous laser therapy (ELVIS)
  - Radiofrequency ablation

All methods of venoablation are effective. Once the overall venous reflux volume is brought down below a critical threshold, venous ulcers usually recover, and symptoms are alleviated.

- Other methods like local wound care, dressings, antibiotics, physical activity, prevention of standing for long periods, control of smoking etc. are also followed in every case.

- Case specific treatment like split skin grafting for huge ulcers.

- NOVEL METHODS:
    - Alginates
    - Extracellular matrix
    - Iloprost
    - Sucralfate
    - Ultrasound patch
    - Nexagon etc.

SUCRALFATE:

Sucralfate is a cytoprotective molecule, which is employed in prevention and/ or treatment of diseases of gastrointestinal system such as peptic ulcer, stress ulcers, gastritis and gastro- esophageal reflux. Chemically, it is the aluminium hydroxide salt of sucrose octasulfate, the sulphated derivative of the disaccharide sucrose. Though it is related to sucrose, it is not utilized by the body as sugar. Sucralfate is also related to heparin but lacks any anticoagulant activity. It is known to have multiple beneficial effects influencing wound healing. The physical barrier character of sucralfate helps reduce inflammation and improve mucosal healing. Along with its cytoprotective action, stimulating effects on vascular factors which play a critical role in wound healing have been demonstrated.

MOLECULAR MECHANISM OF SUCRALFATE:

Besides the ability of sucralfate to enhance the secretion and hydrophobicity of mucus gel in the gastric and duodenal mucosa and to bind bile acids, several other molecular mechanisms have been observed. These mechanisms are primarily responsible for the influence of sucralfate over wound healing.

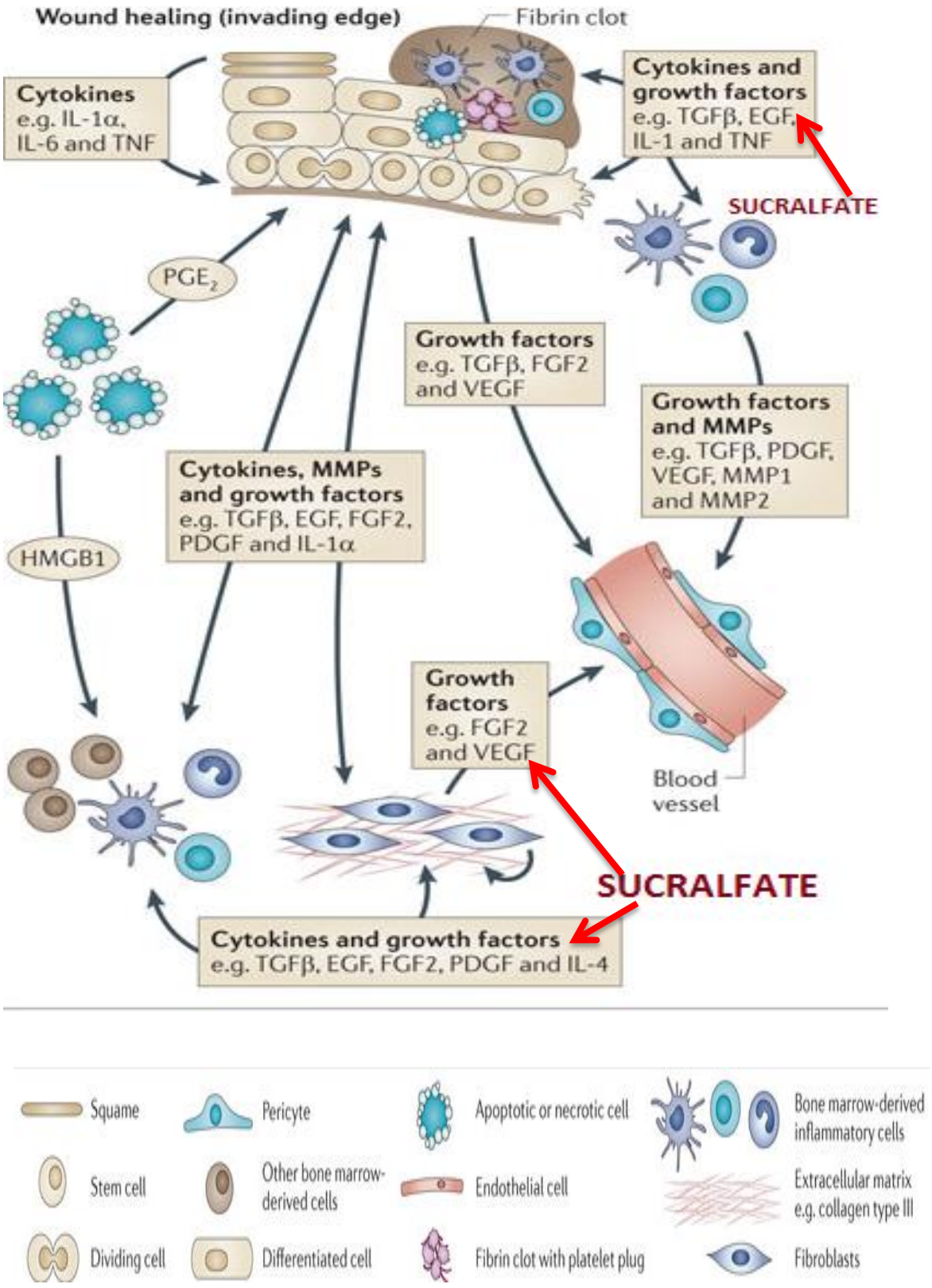


FIGURE 10: MOLECILAR MECHANISM OF SUCRALFATE IN EPITHELIAL WOUND HEALING

i. Increased growth factor bio availability:

It is now a well-known fact that chronic wounds lack growth factors and topical application of such factors would benefit the healing process.

The long time required for growth factors to act on wounds may make them prone to degradation by proteases. Sucralfate binds to the likes of fibroblast growth factor, tumor growth factor β, vascular endothelial growth factor etc., preventing their protease mediated degradation. Sucralfate also promotes healing by increasing expression of receptors like human epidermal growth factor receptor.

ii. Protection of cells apoptosis:

Inflammatory mediators and signals developed in damaged tissues are involved in cell apoptosis which is the main molecular cause of decrease in cellularity during stages of healing. Sucralfate is postulated to inhibit caspase- 3 activation, a major signal for apoptosis initiation.

iii. Reduction of oxygen free radicals:

Oxygen free radicals inhibit wound healing by suppressing migration of cells and their proliferation by inducing cell apoptosis. It is now shown by studies that high concentrations of sucralfate inhibit these free radicals by an ischemia- reperfusion mechanism or direct contact with the free radical moieties.

iv. Antibacterial activity:

Sucralfate decreases the magnitude of translocation of bacteriae in several tissues, especially skin after injuries and preserves mucosal integrity. In the stomach, sucralfate also decreases the minimum inhibitory concentration of many antibiotics.

v. Induction of prostaglandin production:

In vitro studies have effectively shown that sucralfate enhances the synthesis of prostaglandin E2 in basal keratinocytes and dermal fibroblasts and induce their proliferation. This helps in diminishing inflammation and enhanced wound healing.

USES OF SUCRALFATE:

- Gastric and duodenal ulcers- prevention and treatment. It is also used in the medical management of gastro-esophageal reflux.
- Treatment of burns.
- Venous stasis ulcers where sucralfate promotes neoangiogenesis and wound healing.
- Treatment of peristomal skin excoriation/ ulceration.
- Treatment of intertrigo. It is more effective when used with another adjuvant anti-inflammatory agent.
- Treatment of non-neoplastic vaginal ulcers

- Treatment of aphthous ulcers, mucocutaneous lesions in disorders like Behcet's disease.
- Treatment of stomatitis and recurrent aphthous stomatitis.
- Application over healing haemorrhoidectomy wounds.
- Treatment of radiation induced acute skin reactions and dermatitis.
- As enemas in control of radiation induced proctocolitis.

METHODOLOGY AND MATERIALS

METHODOLOGY

STUDY DESIGN: prospective, comparative and interventional study

This study was conducted in the wards of Department of General Surgery, Coimbatore Medical College and Hospital, Coimbatore. 30 patients admitted with complaints of chronic venous or stasis ulcers are included the study in the period of 19-11-2012 to 18-11-2013.

INCLUSION CRITERIA:

- Chronic venous stasis ulcers in lower limbs
- Non infected, clean ulcers

EXCLUSION CRITERIA:

- Neoplastic diseases
- Hypersensitivity
- Mixed wounds (Acute and chronic)
- Acute or chronic renal failure
- Pregnancy
- Ulcers with underlying osteomyelitis
- Thromboangitis obliterans

- Co-morbidities like anaemia, hypertension and diabetes will be treated appropriately in all patients.
- Appropriate antibiotics will be given to prevent secondary infection and/or to treat co-existing infections systemically or in any similar lesions.
- Each patient is assigned to study group or control group by virtue of order of admission, i.e.: all even numbers will be allotted to case group and odd numbers to control group.
- Both groups will be treated with standard wound cleaning methods following which the cases under study group will receive topical sucralfate dressing, while the control group will receive topical saline dressing, once a day.
- All patients in both the groups will be treated with compression bandage therapy after application of sucralfate/ saline dressings.
- Dressings will be changed every day. In case of excessive soakage, dressing will be changed according to the need.
- Examination of the ulcer will be done with particular emphasis on size of the lesion, nature of granulation and relief of pain. The patients will be clearly instructed to make their own observations on decrease in size of the lesion and pain.

- Dressing will be continued for 2 weeks, and the above mentioned parameters will be noted down using a visual scale by the investigator and a colleague (To minimize observation bias) on days 5, 10 and 14.
- Both the groups under study will be given appropriate treatment after the study period till their ulcers are healed. Both groups will also be treated with definitive procedures for underlying cause after the study period.
- All standard routine and specific investigations will be done in both the groups.
- For final analysis, the parametric values recorded on day 14 will be considered as it is most reliable and will give a definite picture of process of wound healing. However, the findings of day 5 and day 10 will be analysed as well, to monitor the progress of wound healing and efficiency of the treatment modality used.

- Results will be interpreted using the following observations made.

1. <u>SIZE OF THE ULCER</u>:

   It is noted in terms of whether the ulcer has decreased in size or remains the same. The dimensions are observed on three days by both the investigator and an observer colleague and any decrease in the size is noted with a "↓" mark.

SIZE OF THE ULCER		
DAY	INVESTIGATOR	OBSERVER
5		
10		
14		

The size of the ulcer is not assigned any scoring system as the size of the ulcers will be different in each individual and the rate of contraction of the wound cannot be easily standardized.

2. GRANULATION:

This will be studied over the ulcer on all three days and computed as:

GRANULATION		
DAY	INVESTIGATOR	OBSERVER
5		
10		
14		

A score of 2 is assigned for healthy granulation while 1 is assigned for absent or unhealthy granulation. The mean of final day observations of both the observers are taken for final analysis to avoid any subjective or observational bias.

3. DECREASE IN PAIN:

This parameter will be recorded on all three days as per the history given by the patient. All patients are clearly instructed to notice any changes in the magnitude of pain after the starting of therapy.

DECREASE IN PAIN		
DAY	**INVESTIGATOR**	**OBSERVER**
5		
10		
14		

A score of 3 is assigned if there is good pain relief, 2 for moderate pain relief and 1 for minimal/ absent pain relief. The mean of final day observations are considered for analysis as explained earlier.

- The effect of sucralfate will be analysed and compared on all 3 days.
- Statistical analysis will be done using the final observation on day 14, using '**Paired T Test**', given by the formula:

$$t = \frac{\Sigma d}{\sqrt{\frac{n\left(\Sigma d^2\right) - \left(\Sigma d\right)^2}{n-1}}}$$

- The numerator of the formula is the sum of differences of all the values.
- The denominator is the square root of n times the sum of the differences squared minus the sum of the squared differences, all over n-1.
    - $\sum d^2$ = each difference in turn, square it, and add up all those squared numbers.
    - $(\sum d)^2$ = add up all the differences and square the result.

- Paired t test was selected for statistical analysis, as this study contains paired parametric data at different points of intervention.

MATERIALS

Sucralfate is soluble in strong acids and alkali but insoluble in polar solvents. It is insoluble in water. It reacts with acids like hydrochloric acid, forming an amorphous paste. It is known that sucralfate topical application is more effective in the form of a paste than slurry, which is formed if it is dissolved in water. The paste is prepared by incomplete reaction of sucralfate with an acid. This incomplete reaction negates the necessity of any further pharmaceutical steps. More importantly, the incomplete reaction results in the generation of a fully biologically active compound with no side effects or added effects of the solvent [12].

The incomplete reaction can be achieved through provision of quantity of acid sufficient enough to cause sucralfate polymerization. At the same time, care should be taken to restrict the total acid availability so as to prevent complete dissolution of sucralfate molecules. Stoichiometric experimentations and tests have resulted in the generalized consensus that it is ideal to subject approximately 5 gram of sucralfate to react with 2- 8 millimole of hydrochloric acid, at a concentration of 0.1N. The surface area of sucralfate available for contact with acid should be increased by finely powdering the sucralfate tablets. This will prevent the initial polymerization reaction at the surface which will hamper the polymerization of deep seated molecules. The resultant of this

reaction is a smooth and fine paste which can be stored in containers and used as topical application as desired.

For the purpose of use in this study, the sucralfate cream is prepared in the following way; 5 gram of sucralfate is well triturated to form a fine powder. To this powder, 1millilitre of 1.0N hydrochloric acid is added. The mixture is stirred constantly until it forms a fine paste. Few additional drops can be added in order smoothen the paste if required. Water can be added purely to aid in the process of mixing. After formation of the paste, any excess fluid is washed off. The paste mass hence formed is smooth and less viscous. This paste should be kept covered in order to prevent drying. Alternatively, it can be stored in acid free water [12].

TREATMENT PROTOCOL:

All the patients of both study and control group after admissions are subjected to the same initial assessment and evaluation.

- Thorough clinical history is elicited and recorded.
- Significant past history is noted.
- Any cases coming under the realm of exclusion criteria are omitted and the next patient is considered in that place.
- Detailed clinical examination is performed.

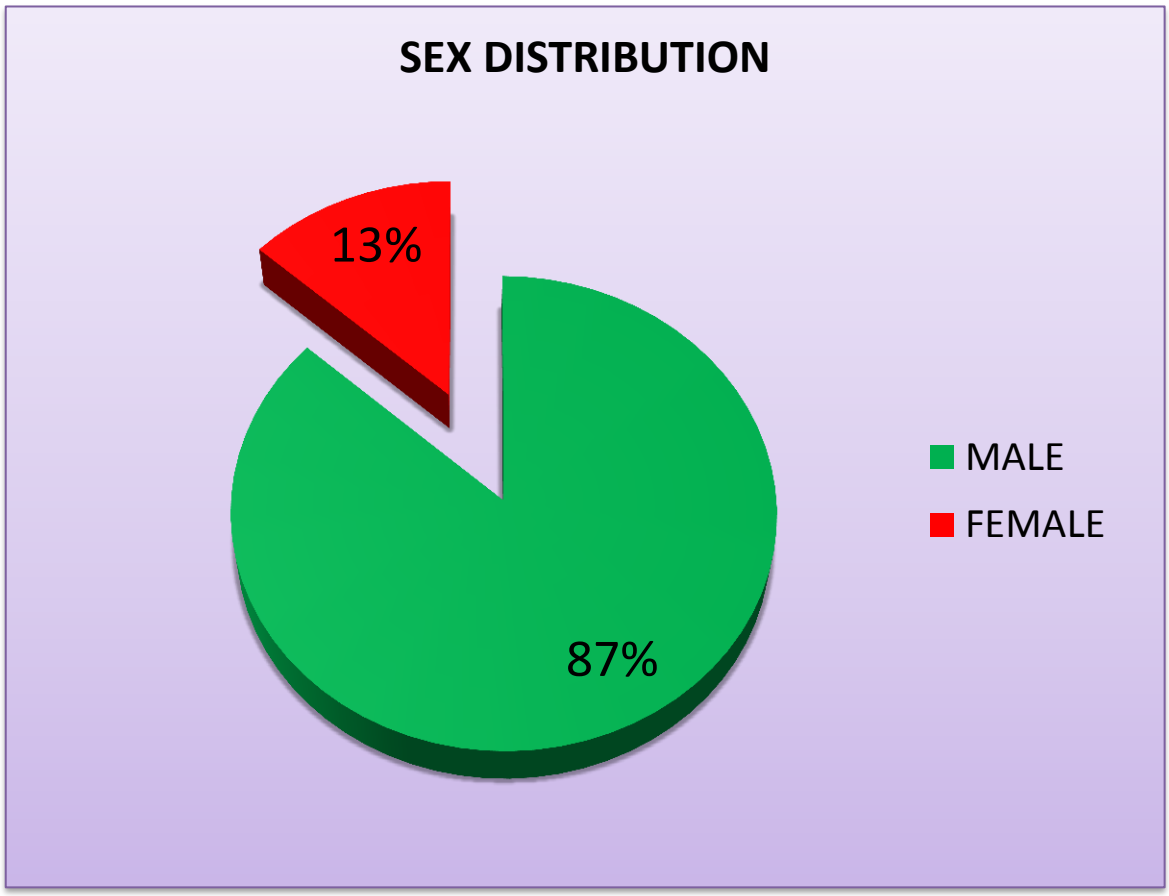
- Local examination of the ulcer is performed with emphasis on size and granulation. Co-existing infections noted if any.
- Thorough wound debridement is done in both the groups till all the devitalized tissues are removed.
- Antibiotics are administered only if necessary.
- Once the wound is ready for the further management, the study cases are treated with daily application of sucralfate gel, while the control cases are treated with saline dressing.

RESULTS AND DISCUSSION

Study was conducted on 30 patients admitted after analysing the nature of the wound according to the inclusion and exclusion criteria described. Patients were randomized as mentioned before and treated accordingly. All patients were followed up for the complete study period with no defaulters or drop-outs in either the study or the control groups.

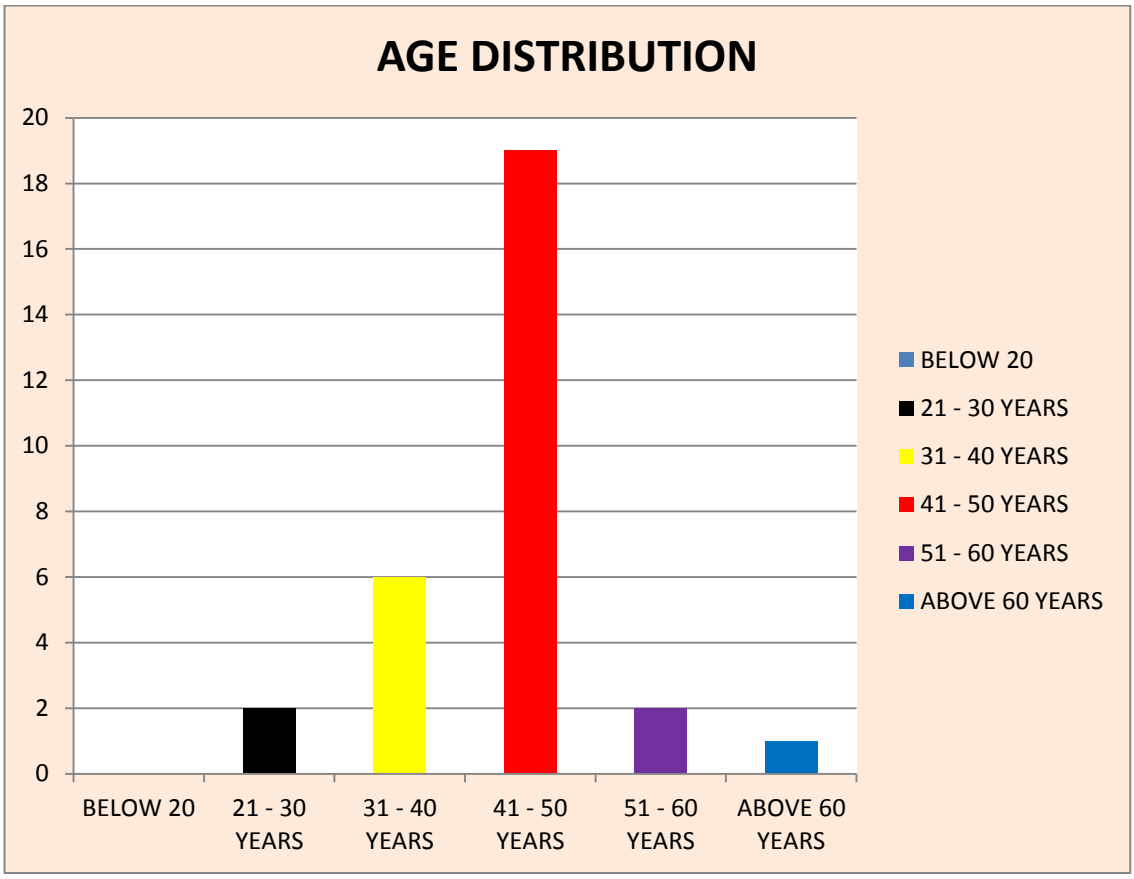
Both cases and controls were observed for parametric analysis on days 5, 10 and 14. Results tabulated by both the observers were compared and a mean score obtained to avoid bias. Patients were also followed up for a period of 2 months afterwards to ensure there were no recurrences of complications.

I. SEX DISTRIBUTION

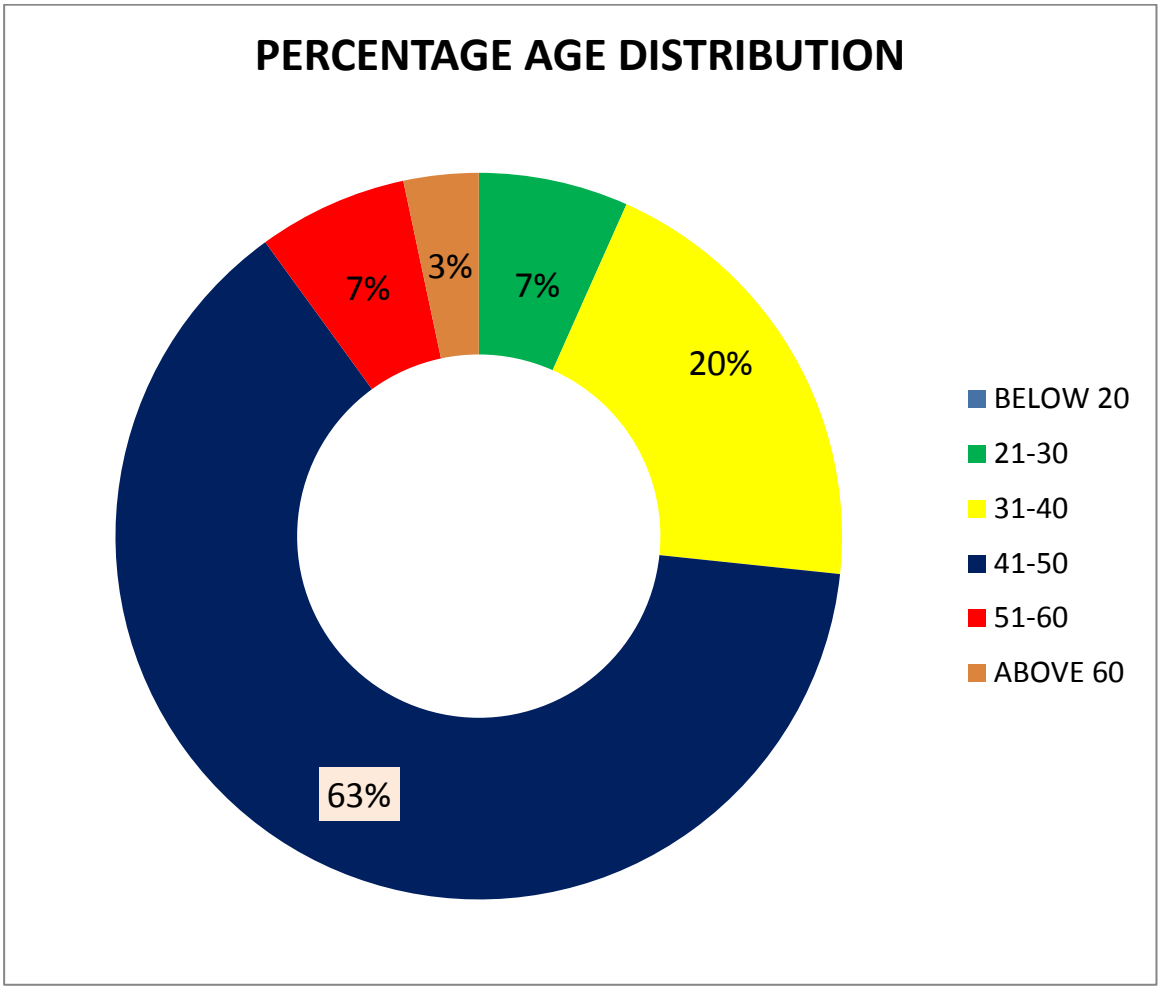


TOTAL CASES	**30**
MALES	**26**
FEMALES	**4**

II. AGE DISTRIBUTION

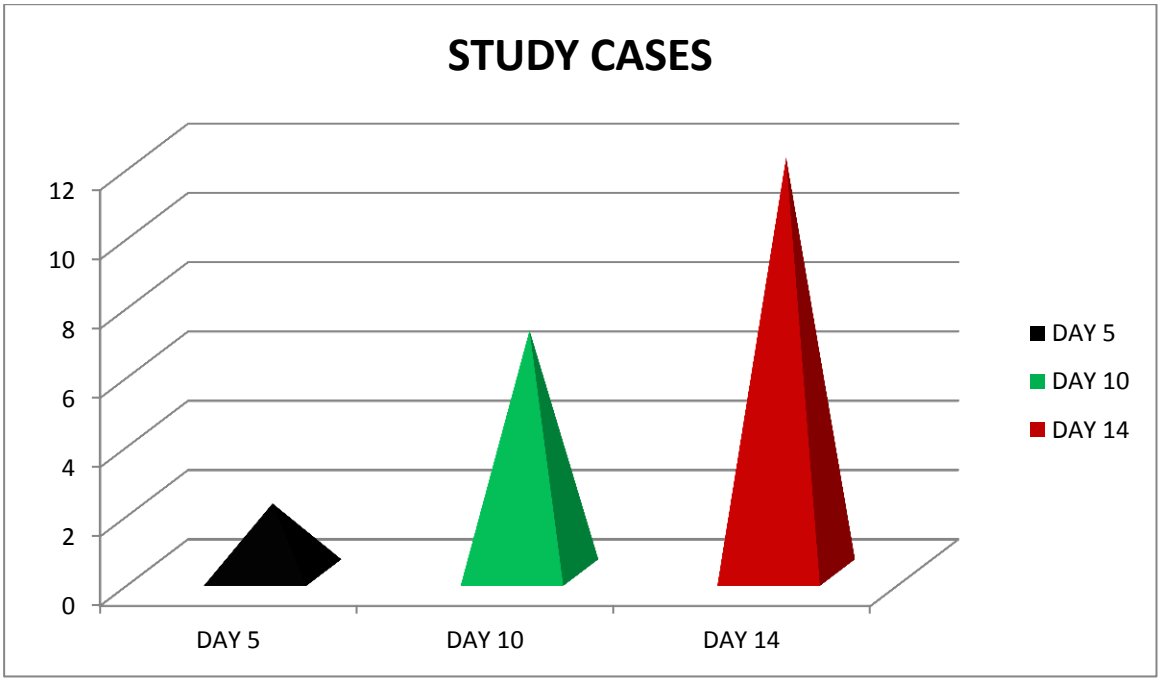


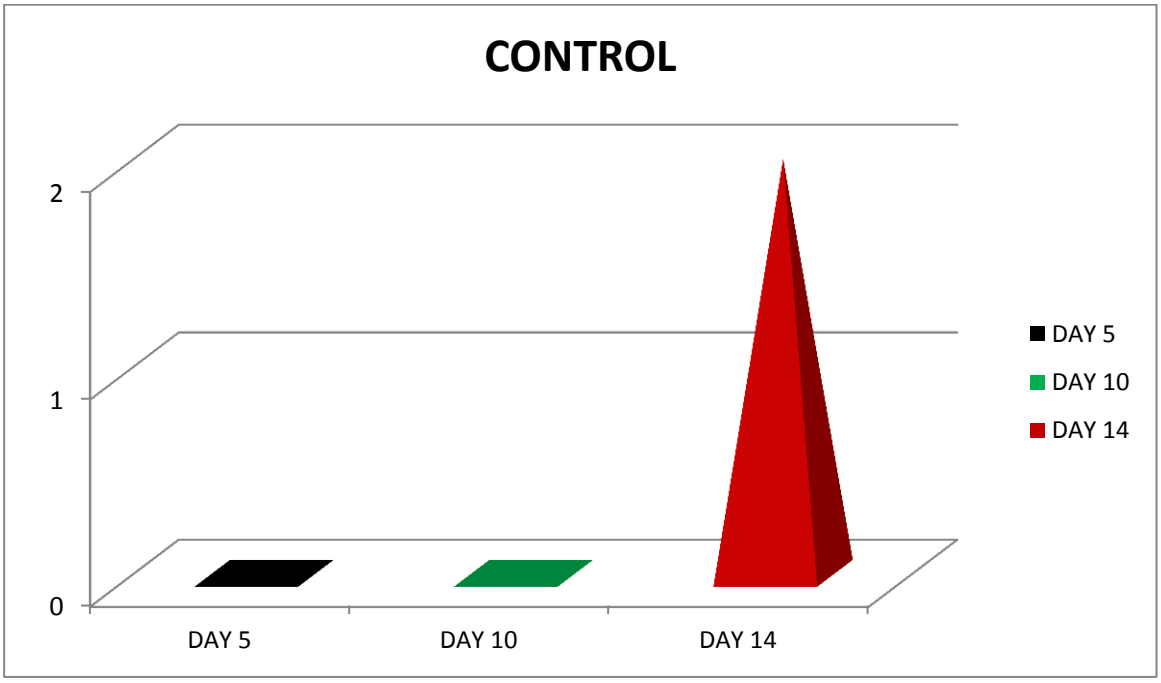
NUMBER OF PATIENTS < 20 YEARS	**0**
NUMBER OF PATIENTS AGED 21- 30	**2**
NUMBER OF PATIENTS AGED 31- 40	**6**
NUMBER OF PATIENTS AGED 41- 50	**19**
NUMBER OF PATIENTS AGED 51- 60	**2**
NUMBER OF PATIENTS AGED > 60	**1**



This chart shows that venous ulcers are seen maximum in the 5th decade of life, followed by the 4th decade.

III. DECREASE IN SIZE OF ULCER





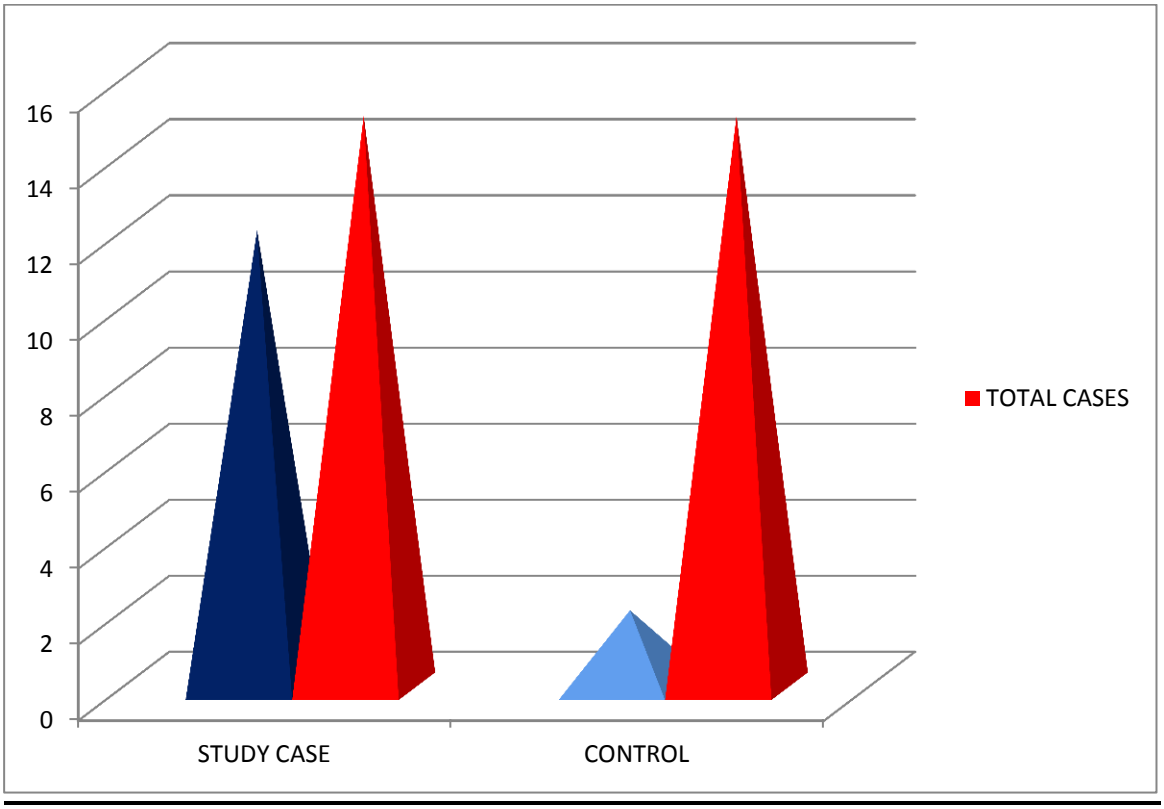
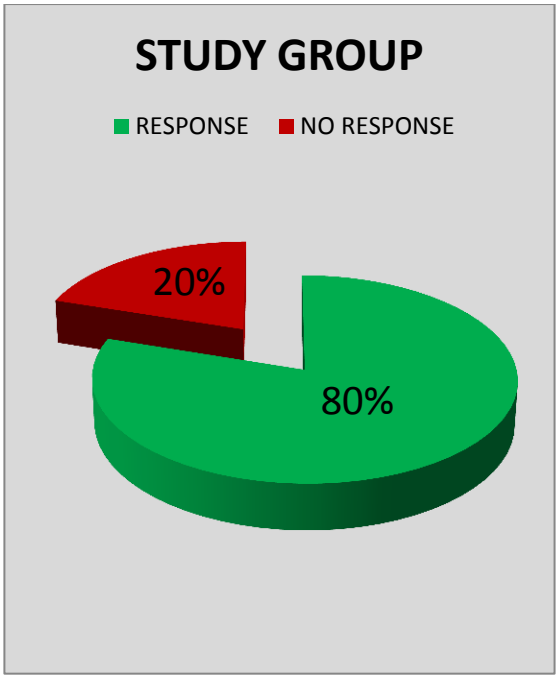
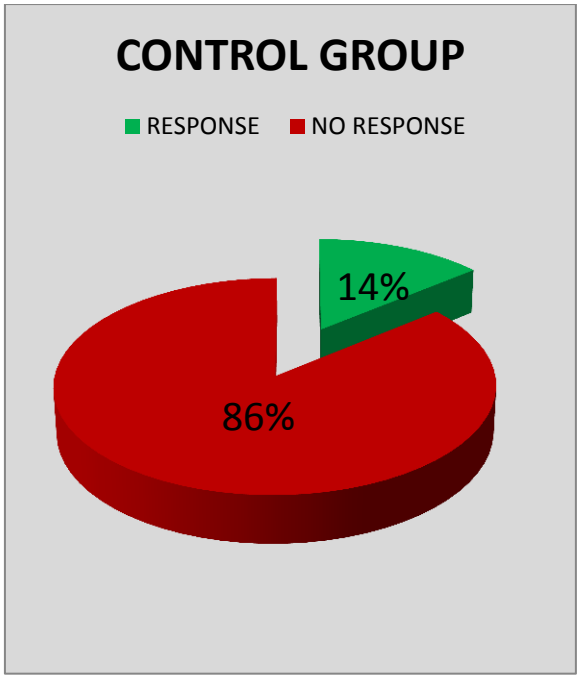


CHART COMPARING 14TH DAY OUTCOME OF CASE V/S CONTROL IN DECREASE IN ULCER SIZE

These charts show the superiority of sucralfate in decreasing the ulcer size effectively. The 14th day graphs clearly exhibit the difference in the performance of both sucralfate and saline dressing.

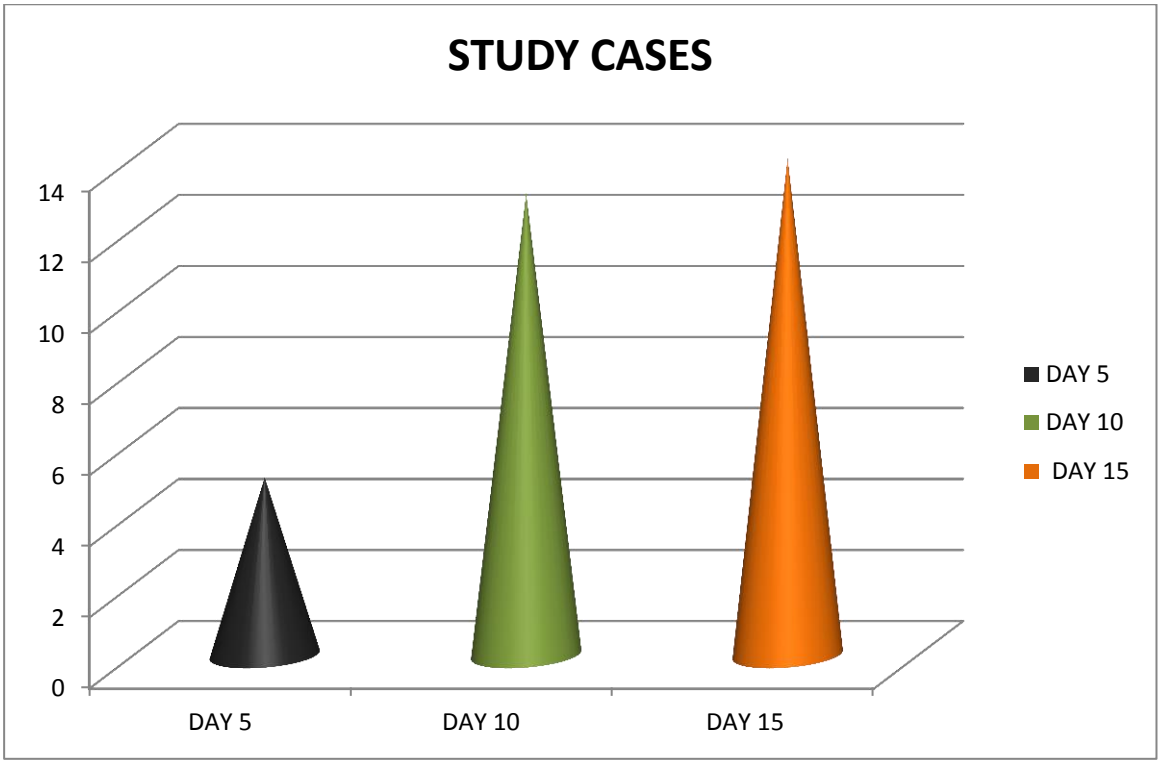


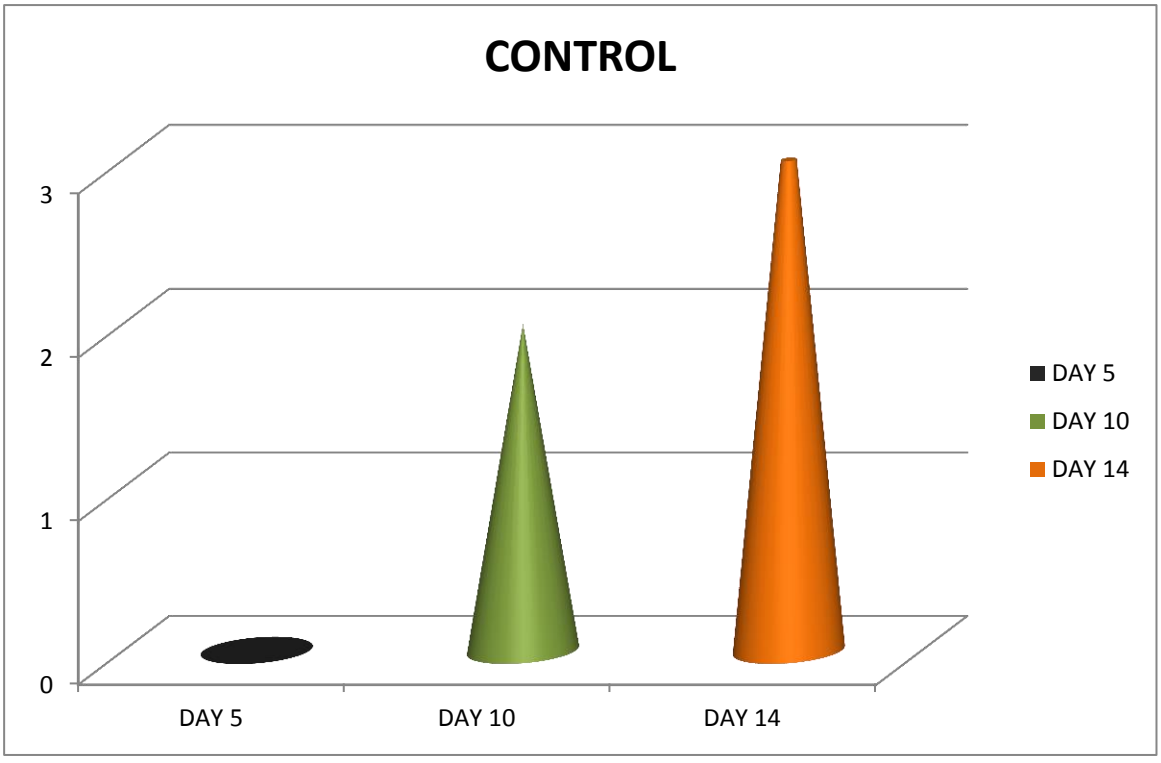


PERCENTAGE CHARTS OF PATIENTS WITH DECREASE IN ULCER SIZE IN STUDY CASES V/S CONTROL

	STUDY CASES	CONTROL
TOTAL CASES	15	15
NUMBER SHOWING DECREASE ON DAY 14	12	2
RESPONSE [IN %]	80%	14%

IV. GRANULATION





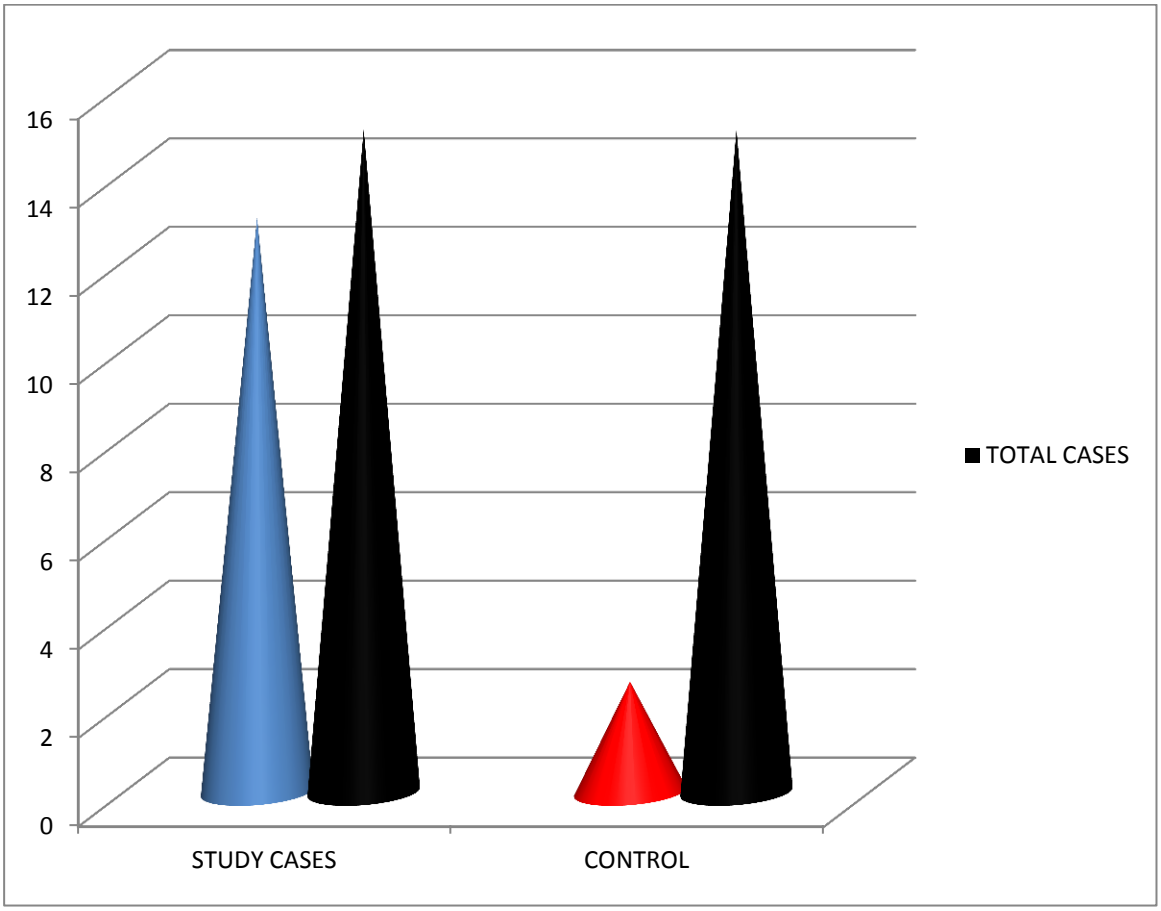
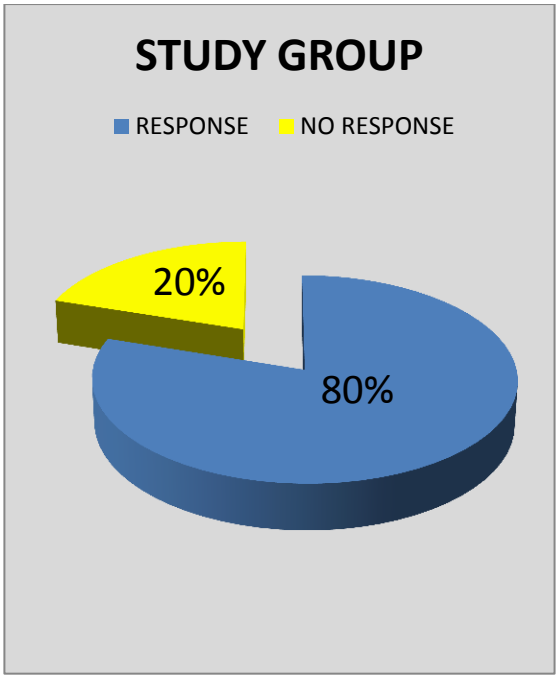
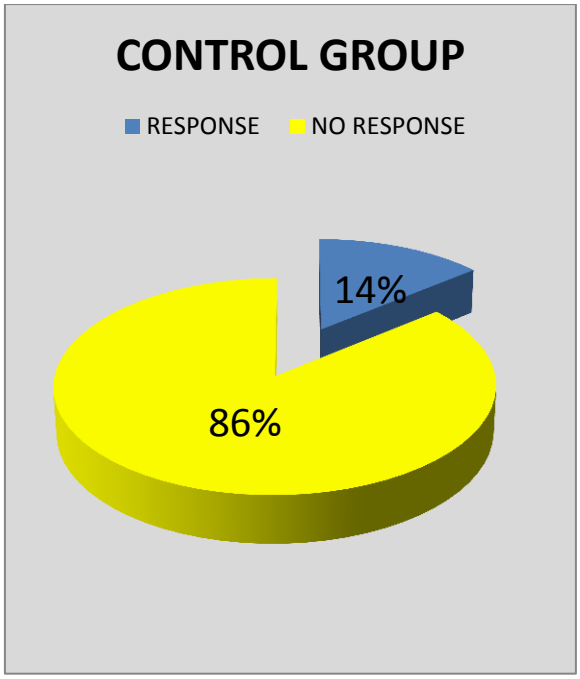


CHART SHOWING 14TH DAY OBSERVATION ON GRANULATION IN CASES V/S CONTROLS

The above 3 charts show that sucralfate helps wounds granulate at a faster rate compared to standard saline dressing.

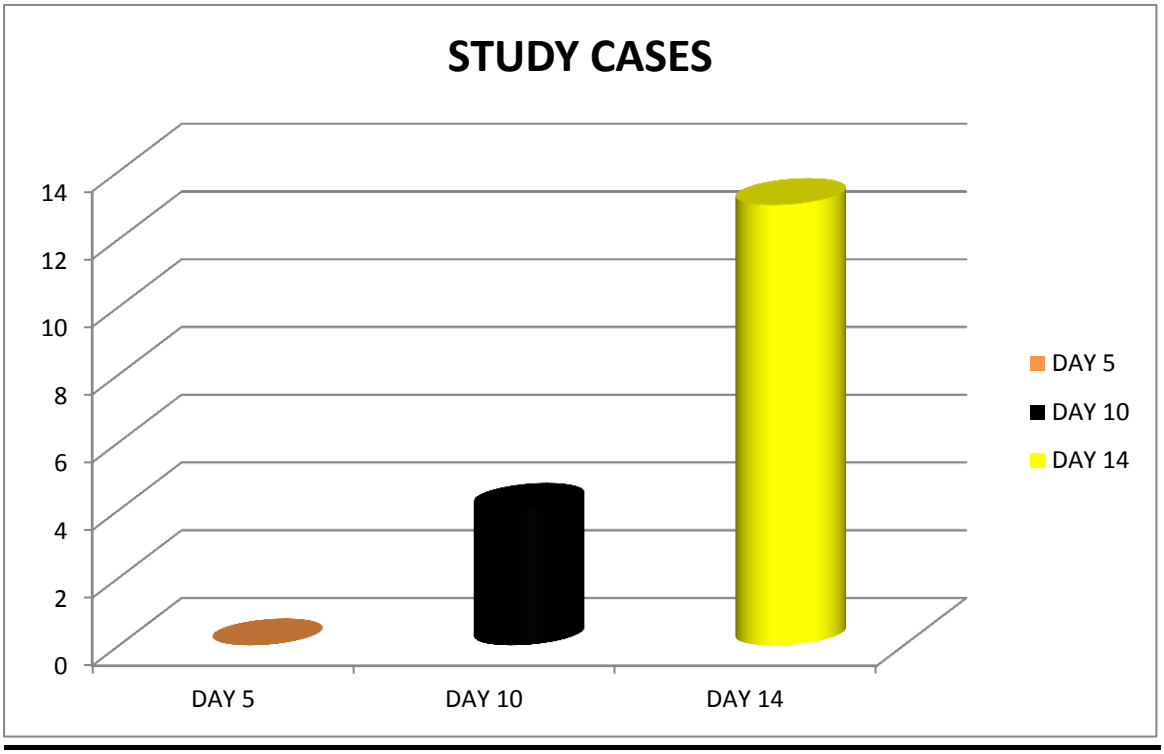


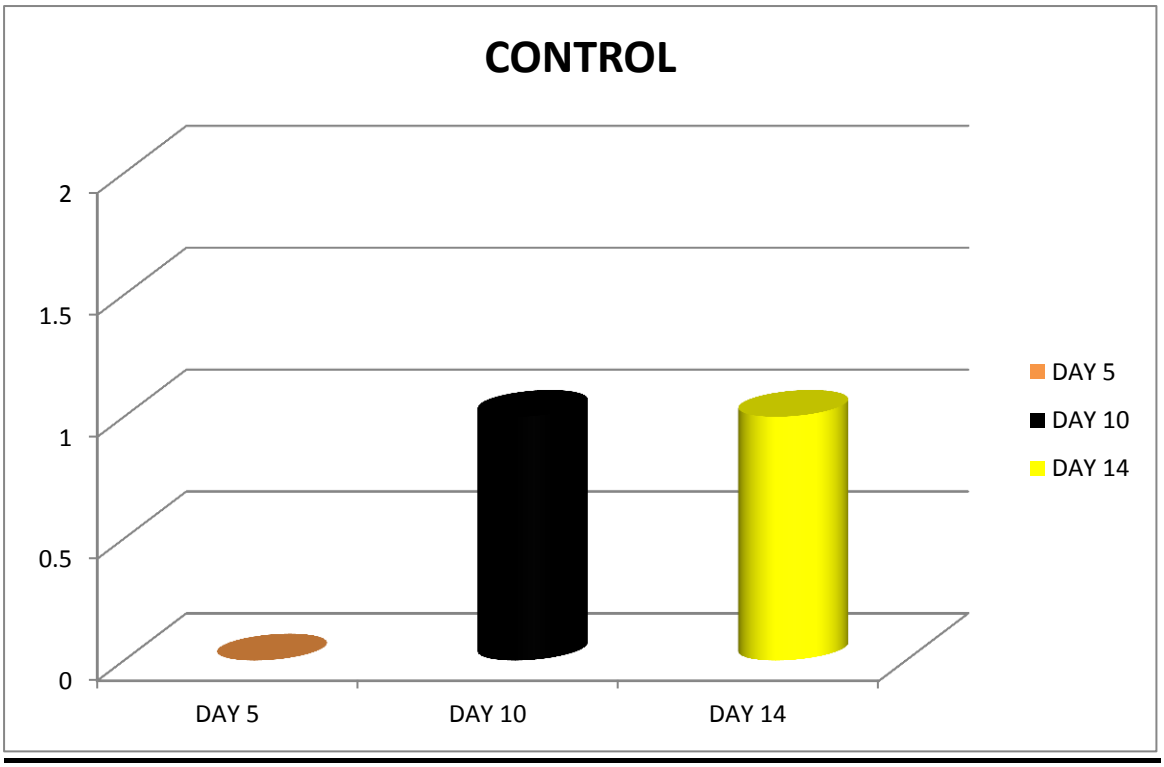


PERCENTAGE CHARTS OF PATIENTS SHOWING HEALTHY GRANULATION IN STUDY CASES V/S CONTROL

	STUDY CASES	CONTROL
TOTAL CASES	15	15
NUMBER SHOWING DECREASE ON DAY 14	12	2
RESPONSE [IN %]	80%	14%

V. DECREASE IN PAIN





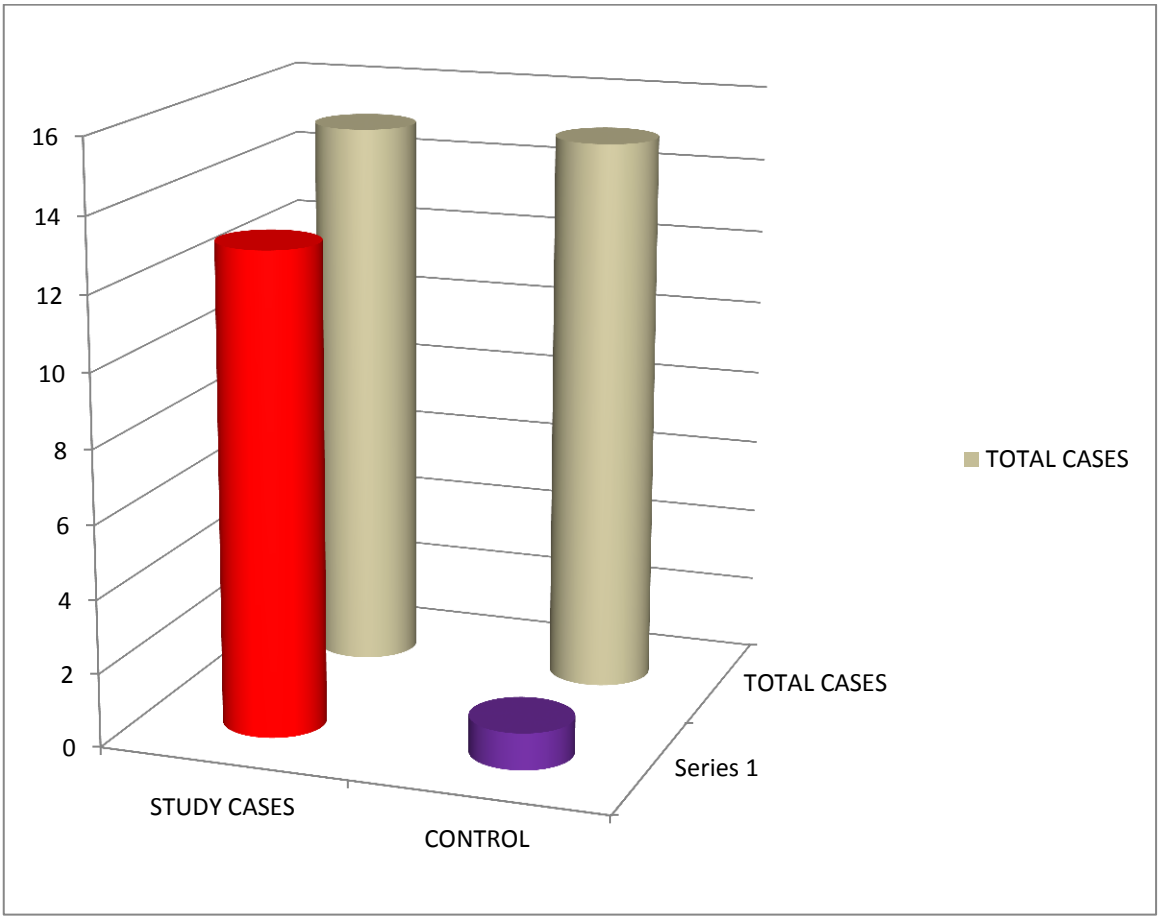
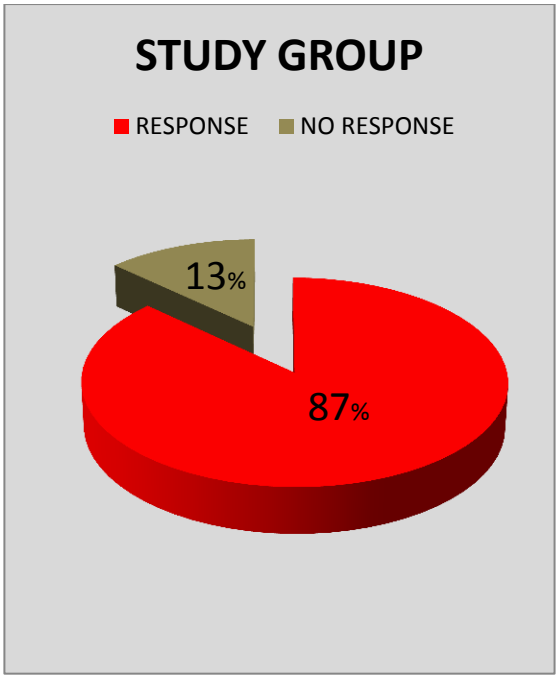
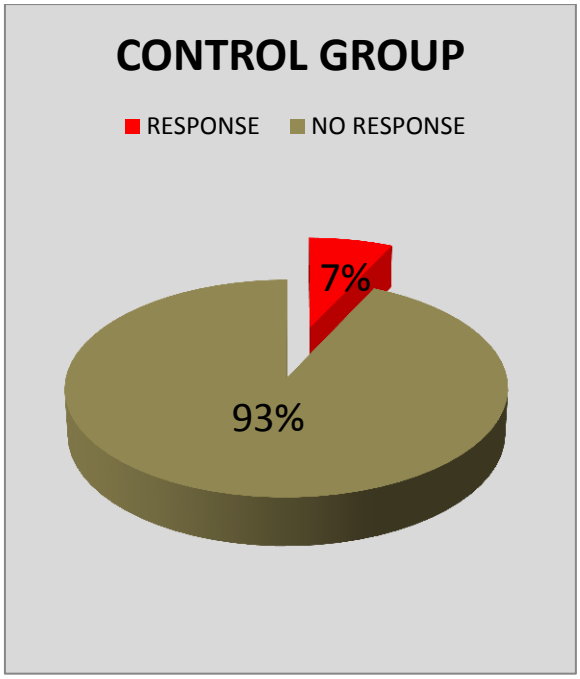


CHART SHOWING 14TH DAY OBSERVATION OF DECREASE IN PAIN-CASE V/S CONTROL

The above charts clearly indicate that sucralfate cause reduction in pain over the ulcer at a rate higher than saline dressed wounds.





PERCENTAGE CHARTS OF PATIENTS WITH DECREASE IN PAIN IN STUDY CASES V/S CONTROL

	STUDY CASES	CONTROL
TOTAL CASES	15	15
NUMBER SHOWING DECREASE ON DAY 14	13	1
RESPONSE [IN %]	87%	7%

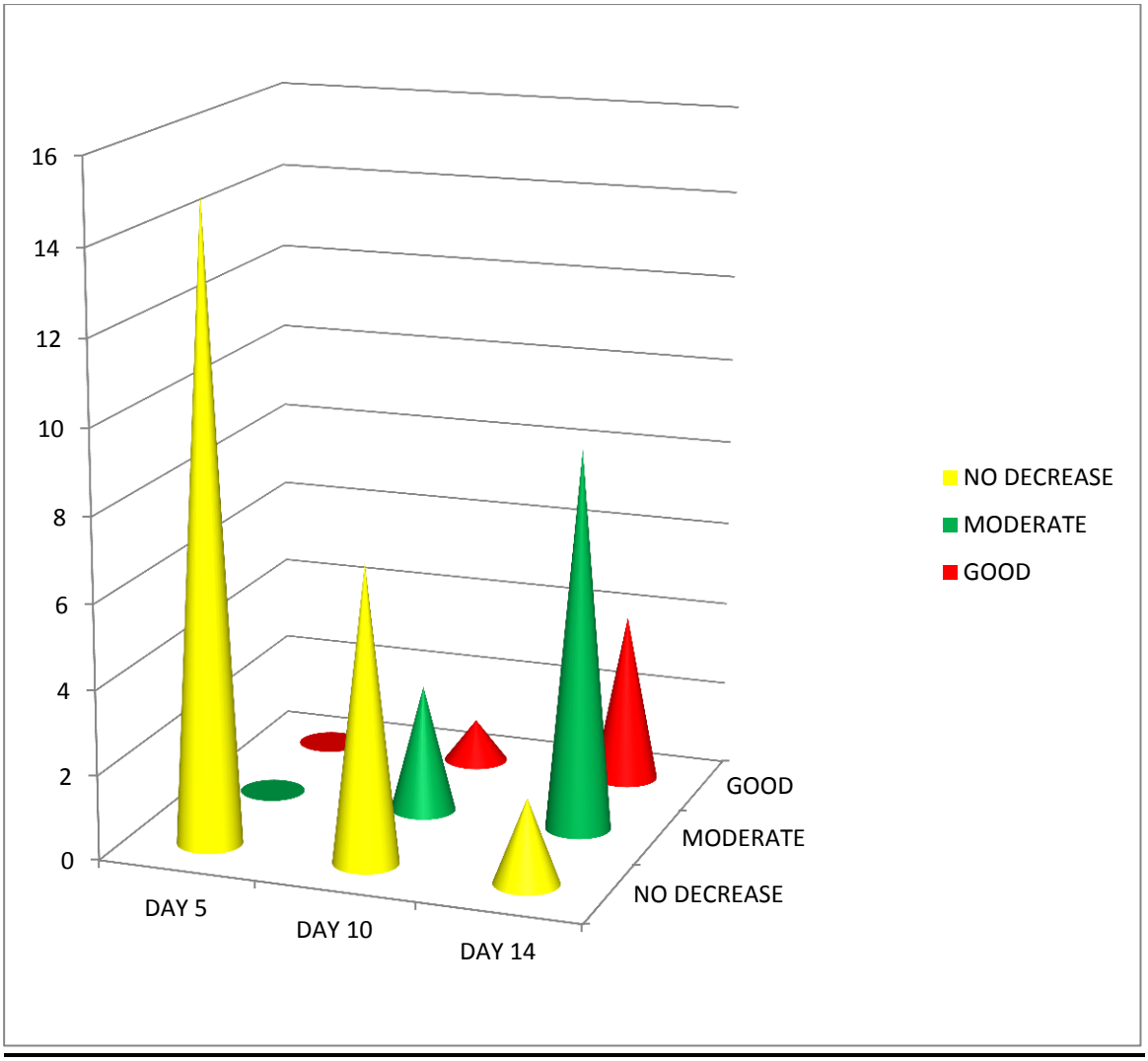


CHART DEPICTING OBSERVATIONS OF RESPONSE TO SUCRALFATE WITH RESPECT TO DECREASE IN PAIN ON ALL DAYS

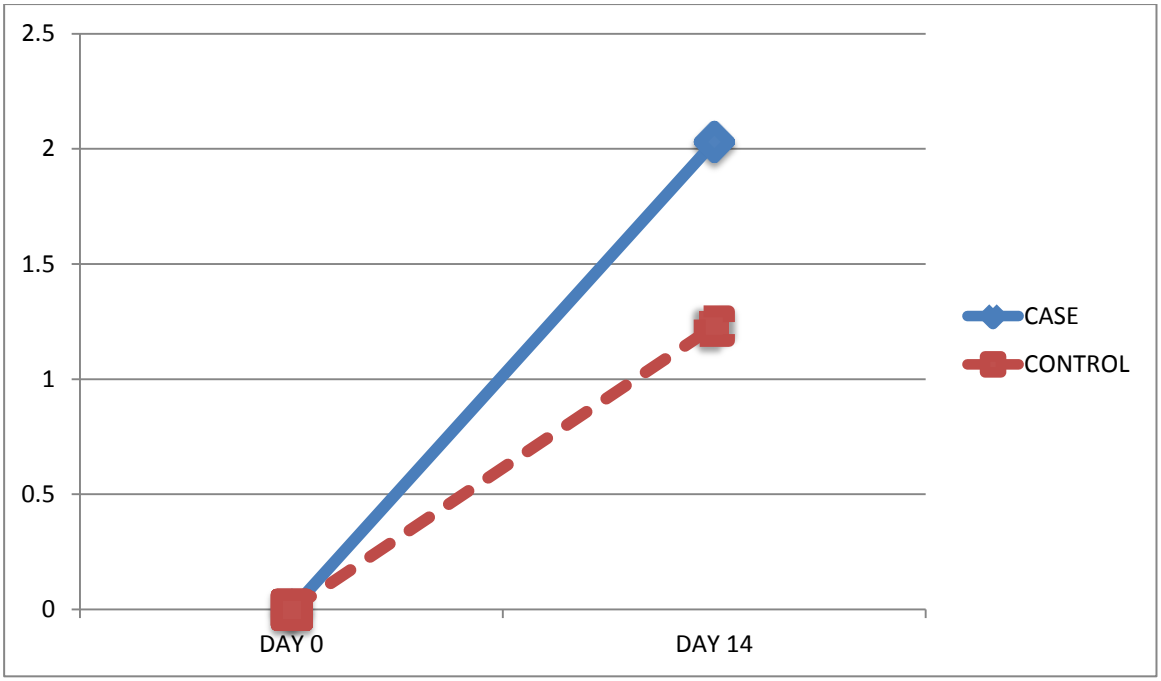
It can be noted that as the time goes on, the response improves, that is many patients experience reduction in pain.

STATISTICAL ANALYSIS

The variables were analysed statistically based on the 14th day observation values and it was tested by 'paired t test'.

- As mentioned earlier, the decrease in size of ulcer was not assigned any scoring due to difficulties in standardization. It was assessed on the basis of visual observation and quality of the wound.
- Granulation scores were tabulated and the scores of final observation were considered. Mean of the scores obtained from both the observers were subjected to the paired t test and the following results were obtained.

		GRANULATION		
		MEAN	S.D	NUMBER
GROUP	CONTROL	1.23	0.42	15
	STUDY	2.03	0.30	15



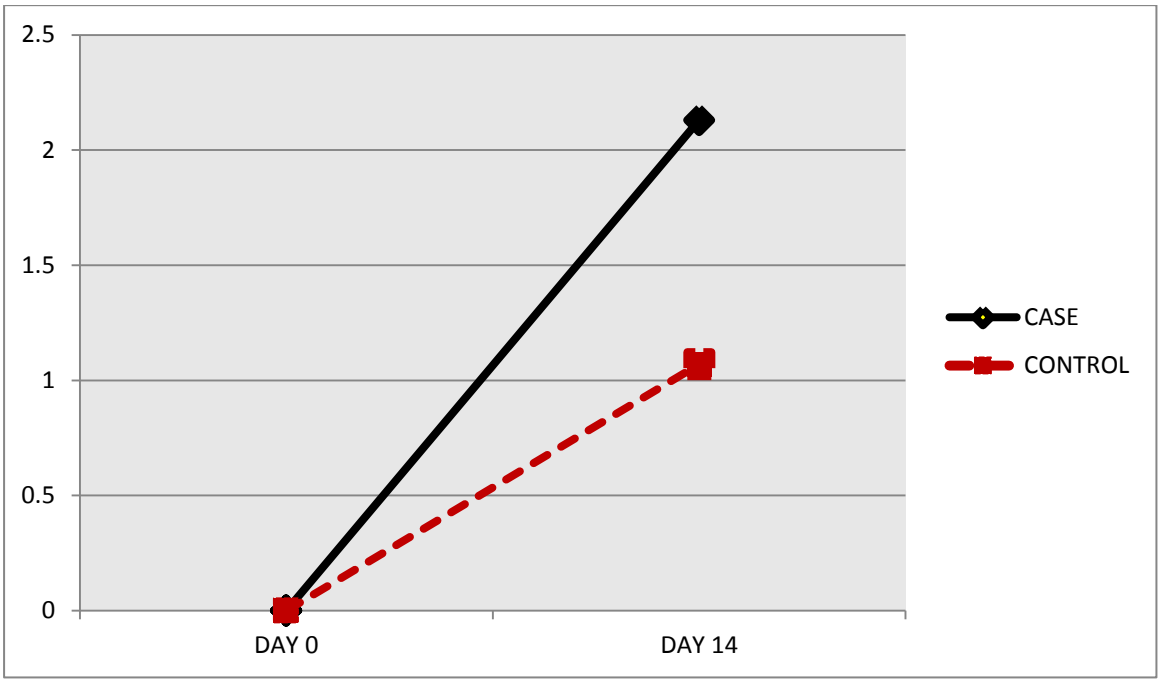
GRAPH 1: MEAN SCORES FOR GRANULATION- STUDY CASES V/S CONTROL

- TEST FOR EQUALITY OF MEANS

t	DF	PROBABILITY	SIGNIFICANCE
6.054	**28**	**0.001**	**P < 0.01**

- Decrease in pain over the ulcer was dealt with in similar way and the following results were obtained.

		DECREASE IN PAIN		
		MEAN	S.D	NUMBER
GROUP	CONTROL	1.07	0.26	15
	STUDY	2.13	0.64	15



GRAPH 2: MEAN SCORES FOR DECREASE IN PAIN

- TEST FOR EQUALITY OF MEANS

t	DF	PROBABILITY	SIGNIFICANCE
5.987	**28**	**0.001**	**P < 0.01**

P VALUE OF BOTH THE TESTS = LESS THAN 0.01

(P < 0.01)

Hence the study is statistically significant at 1% interval

DISCUSSION

Chronic venous ulcer is an important surgical condition due to the high incidence and lack of a standard therapeutic protocol. The care of chronic venous ulcers often relies on palliative and mostly unsuccessful therapies. Apart from surgical approach, a variety of medical therapies to influence wound repair and regeneration are currently being investigated. Topical drugs in this regard have proven to be promising and very useful in treatment of chronic venous ulcers. It is now clear that wound healing is a complex procedure dependent on angiogenesis, cell proliferation, extracellular matrix remodelling, tissue inflammation and good re-epithelialization. Thus the ideal drug to treat such ulcers should possess properties to enhance all these parameters.

Sucralfate is a cytoprotective agent, which is extensively used in treatment or prevention of several gastrointestinal tract related diseases such as gastroesophageal reflux disease, gastritis, dyspepsia, gastric and duodenal ulcers, stress ulcer and in the treatment of recurrent aphthous stomatitis. Recent studies have shown the stimulating effect of sucralfate over EGF expression and expression of other growth factors involved in tissue repair processes. Furthermore, the stimulating effects of sucralfate on vascular factors, including angiogenesis have been well demonstrated. Several studies have also shown that sucralfate increases wound contraction, re-epithelialization and diminishes

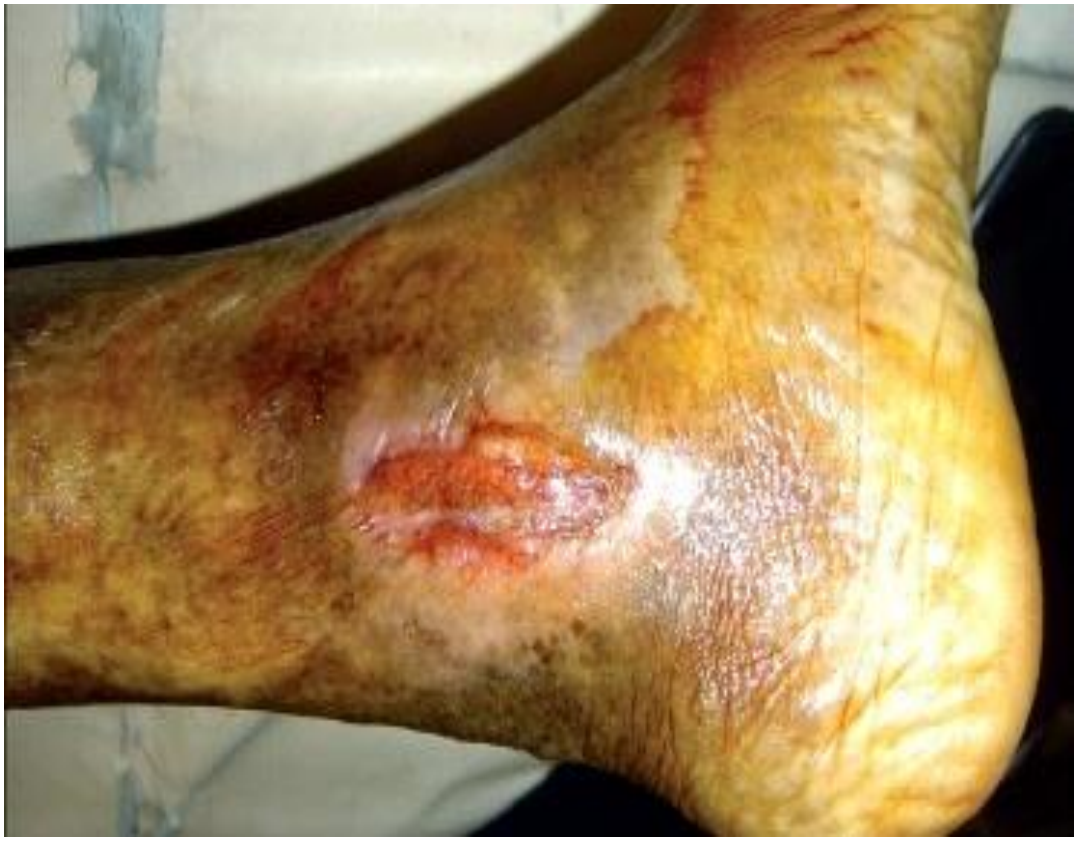
inflammatory reactions. It is safe and well tolerated, as demonstrated by complete lack of side effects.

The recent case reports and sporadic study- analyses are coherent and consistently indicate the favourable and effective influence of topical sucralfate in wound healing. A pilot study [1] with topical sucralfate on full thickness, non-healing venous stasis ulcers (even after 8 weeks of therapy with other modalities) showed very encouraging results. This study was conducted on a group of 9 patients while Tumino et al [2] expanded this number in another study to 100 patients. All the cumulative data provided enough supportive evidence to conduct this study.

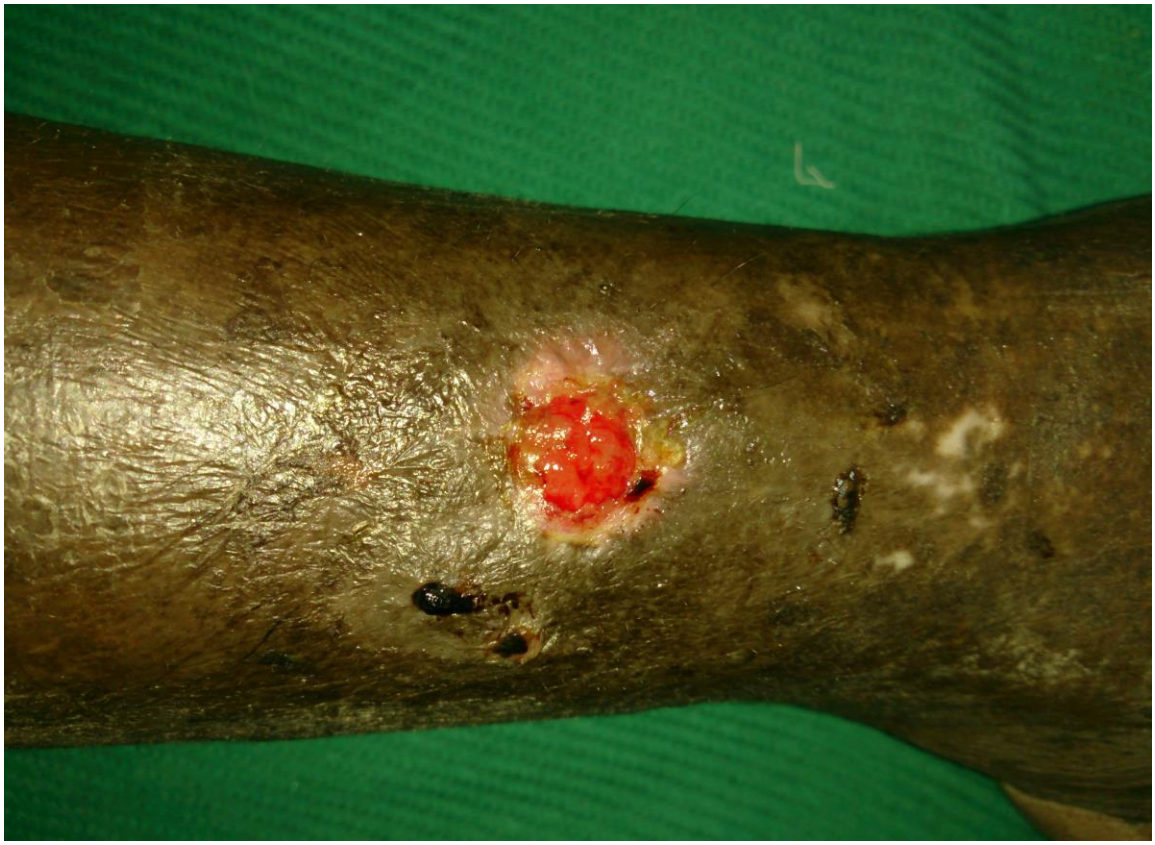
Our study consisted of 30 patients randomly selected. 26 of the patients were male which comprises 87% of the study population and 4 of them females, which is 13% of the total study population. Most of these patients are in the 5^{th} decade of life, closely followed by the late forties age group. The worldwide statistics show that venous ulcer is a common disease of the adults and elderly, and our study is in tune with that. More than half of the study population is above the age of forty (63%).

12 out of the 15 study cases, that is 80% of the study population exhibited decrease in size of the ulcer at the end of 14 days while only 2 in the control group reported a decrease in the size. This is consistent with the study by Tumino et al [2] where 43 out of 45 study population (95.6%) exhibit dramatic

complete cure of the ulcer with topical sucralfate application for a period of 40 days, as against 5 out of the 46 (11%) control population who were treated with a placebo. This finding is also potentiated by other studies concerning various types of epithelial lesions, where the patients using topical sucralfate have demonstrated complete cure or a healthy remission. These studies include ulcers due to radiation, vaginal ulceration, second and third degree burns etc. [3, 4, 5, 6, 7, 8, 9, and 10]



PHOTOGRAPH 1: CHRONIC VENOUS ULCER BEFORE TREATMENT WITH TOPICAL SUCRALFATE



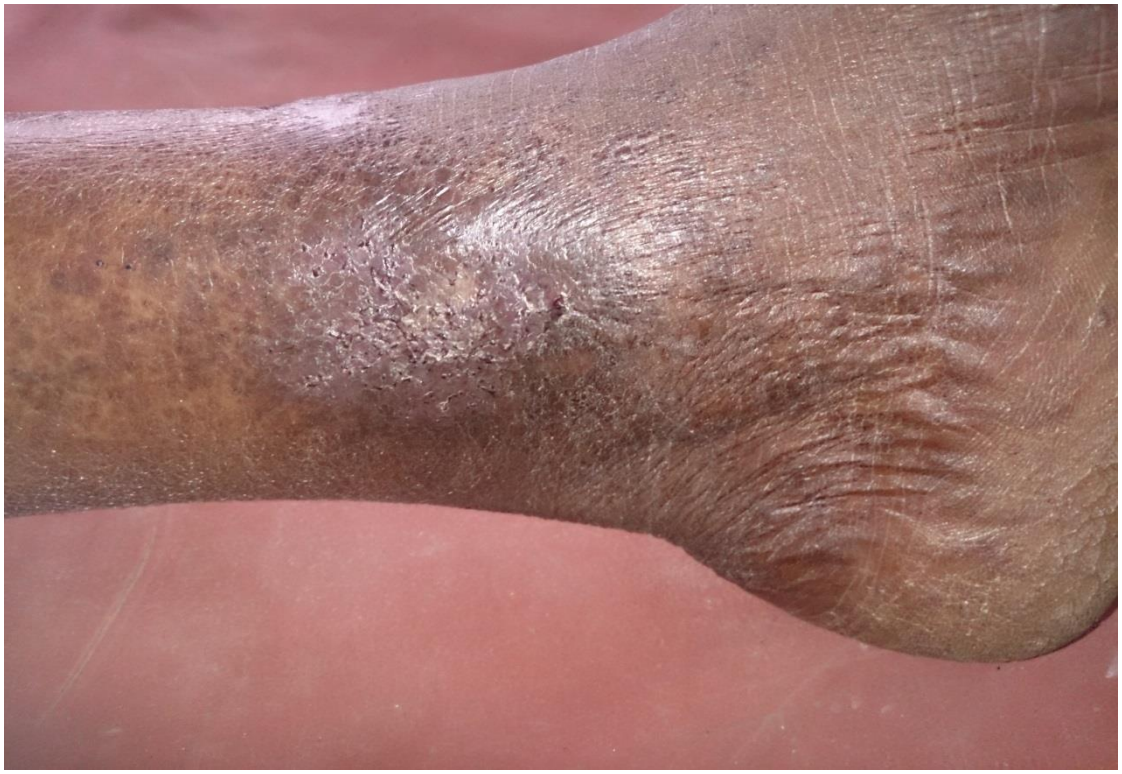
PHOTOGRAPH 2: HEALTHY GRANULATION AFTER TREATMENT WITH TOPICAL SUCRALFATE IN A PATIENT

Analysis of the granulation tissue over the ulcer bed revealed that 12 out of the 15 study cases, that is 86% of the study population developed very healthy granulation over the wound and eventually achieved good re-epithelialization. On the contrary, only 2 out of 15 patients from the control group, that is 14% of total control population, developed good granulation tissue. The remainder continued to exhibit the non-healing nature of the ulcer. This finding is again

consistent with the study by Tumino et al [2], which showed healthy granulation and/or total cure in 43 out of 45 study cases (95.6%), while the control group consisted only 4 out the 46 patients showing cure with placebo, that is 8.6% of the total control population.

Statistical analysis of the same was also comparable to the results of study by Tumino et al [2], the mean score for granulation in that being 2.5 and in our study the same was 2.03. 'p' value for the analysis of granulation in the study by Tumino et al [2] was 0.0001 which is statistically significant. The 'p' value for granulation in our study is < 0.01 which is statistically significant. The results of our study is also comparable to other studies, namely by Tsakayannis et al [1]. Lentz [8] and Banati et al [10], which showed the significant influence of topical sucralfate over other types of epithelial wounds.

Analysis of decrease in pain over the ulcer in our study shows that 13 out of the 15 study cases, that is 93% showed noteworthy improvement in the nature and magnitude of pain. Only 1 out of the 15 control subjects, that 7% of the total control population showed significant decrease in pain. This is again coherent with the study by Tumino et al [2], which showed decrease of pain in 42 out of the 45 study cases (93.3%) and 4 out of 46 controls (8.7%). The mean score for pain reduction in our study is 2.13 for study subjects while that of the control group is 1.07. In the study by Tumino et al [2], the 'p' value for this parametric study is 0.0023, while in our study it is < 0.01 showing the statistical significance.



PHOTOGRAPH 3: AFTER ONE MONTH TREATMENT WITH TOPICAL SUCRALFATE IN A PATIENT

Overall, the cumulative results of this study indicate that sucralfate has a positive and curative influence over chronic venous ulcers. It is effective in promoting wound healing process and re-epithelialization and is also safe for topical application. Patients suffering from chronic venous ulcers can benefit from the use of topical sucralfate.

CONCLUSIONS

In this study:

- The majority of the patients belonged to the fifth decade of life.
- Male predominance was observed in both the groups.
- All the patients had received treatment for the condition by one or the other approved method and did not obtain any cure prior to this study.
- Sucralfate in the topical application form showed favourable results in healing a chronic venous ulcer by promoting healthy granulation and good re-epithelialization.
- Subjective symptoms of the patient, most important of which being pain, was effectively reduced by topical sucralfate.
- The efficacy of sucralfate in treatment of chronic ulcers and epithelial wounds are statistically significant, which is consistent with a multitude of worldwide studies.
- Sucralfate topical gel is easy to prepare [11,12], easy to store and easy to use
- The preparation of topical gel does not involve high costs and can be easily afforded.

Chronic venous ulcer still remains a hard nut to crack for the surgeons, owing to its complex pathophysiology, debilitating course and limited treatment options. The research and trials into the various modalities of treatment are ongoing, but there is a need to find a solution which is effective and less financially burdening to the patients. The current study involved a small group of patients but showed promising and encouraging results with respect to wound granulation, epithelialization and decrease in subjective symptoms. Sucralfate being an inexpensive drug lessens the need for heavy expenditure, considering the financial burden a patient has to bear when getting a chronic ulcer treated.

We conclude that sucralfate can be one such alternative solution to this age old problem and deserves thorough research, exploration and evaluation in this regard.

APPENDICES

APPENDIX – I: REFERENCES

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APPENDIX II – PROFORMA

NAME:

AGE/ SEX: *DOA:*

OCCUPATION: *DOD*:

ADDRESS:

CHIEF COMPLAINTS:

1. *Ulcer over legs - onset and progress*
2. *H/O trauma*

PAST HISTORY

1. *H/O DM/ HTN/ Asthma/ TB/ Epilepsy*
2. *H/O malignancy/irradiation.*
3. *H/O chronic cardiac disease/chronic liver disease/ chronic renal disease/ vasculitis*

PERSONAL HISTORY:

H/O of present conception
Smoking/ Alcoholism
Bowel and bladder habits
Sleep pattern.

GENERAL PHYSICAL EXAMINATION:

1. *Hydration*
2. *Nutritional status*
3. *Pallor*
4. *Icterus*
5. *Cyanosis/ clubbing/ edema*
6. *Generalized/ regional lymphadenopathy*
7. *Pulse rate*
8. *Blood pressure.*

SYSTEMIC EXAMINATION:

- *CARDIOVASCULAR SYSTEM:*
  Inspection
  Auscultation

- *RESPIRATORY SYSTEM:*
  Inspection
  Percussion
  Auscultation

- *CENTRAL NERVOUS SYSTEM:*
  Consciousness
  Orientation
  Higher mental functions

- *PER ABDOMEN:*
  Inspection
  Auscultation

LOCAL EXAMINATION:

- *INSPECTION: Number, site, extent, shape, size.*
  Margin- undermined, punched out, sloping, raised/ rolled out or raised/ everted
  Floor of the ulcer
  Discharge
  Adjacent area
- *PALPATION: Temperature, tenderness, margin for induration, base for underlying structure and mobility.*
- *Examination for any regional lymph nodes, vascular diseases, nerve lesions and tuberculosis.*

DIAGNOSIS:

INVESTIGATIONS:

- Complete hemogram, random blood sugar, blood urea, serum creatinine, serum electrolytes.

- Liver function tests, serum proteins

- Pus culture and sensitivity

- Electrocardiogram.

- Chest radiograph.

-Test for HIV 1 &11; HBsAg

-And relevant investigations for associated medical conditions

SAFETY CONSIDERATIONS:

The safety of the patients will be foremost. The procedures of taking blood samples will be under aseptic conditions using necessary precautions. All procedures done, both operative and non-operative will be done after the due consent of the patient or his/her attendant

CONSENT FORM

It has been explained to me in my mother tongue and I completely understand my condition, its related complications and the treatment options available. I have been explained in detail regarding this study- "TREATMENT OF CHRONIC VENOUS ULCERS WITH TOPICAL SUCRALFATE". I hereby give my voluntary and willful consent to participate in the above mentioned study.

DATE: PLACE:

SIGNATURE OF THE PATIENT (WITH NAME)

SIGNATURE OF THE RELATIVE (WITH NAME)

SIGNATURE OF THE WITNESS (WITH NAME)

MASTER CHART

	NAME	AGE	SEX	STUDY GROUP	OBSERVATION DAYS	DECREASE IN SIZE		GRANULATION		DECREASE IN PAIN		TOTAL SCORE
						I	II	I	II	I	II	
1	KARUPPATHAL	46	F	CASE	5	-	-	1	1	1	1	G- 2 P- 1
					10	↓	↓	2	2	1	1	
					14	↓	↓	2	2	1	1	
2	PALANIVELU	47	M	CONTROL	5	-	-	1	1	1	1	G- 2 P- 1
					10	-	-	1	1	1	1	
					14	-	-	2	2	1	1	
3	DANIEL	42	M	CASE	5	-	-	2	2	1	1	G- 2 P- 2
					10	↓	↓	2	2	1	1	
					14	↓	↓	2	2	2	2	
4	RAMACHANDRAN	50	M	CONTROL	5	-	-	1	1	1	1	G- 1 P- 1
					10	-	-	1	1	1	1	
					14	-	-	1	1	1	1	
5	NAGARAJ	52	M	CASE	5	-	-	2	2	1	1	G- 2 P-2
					10	-	-	2	2	1	1	
					14	-	-	2	2	2	2	

6	JAWAHAR ALI	35	M	CONTROL	5	-	-	1	1	1	1	G- 1 P- 1
					10	-	-	1	1	1	1	
					14	↓	↓	1	1	1	1	
7	ANNAMALAI	46	M	CASE	5	-	-	1	1	1	1	G- 2 P- 1
					10	-	-	2	2	1	1	
					14	↓	↓	2	2	1	1	
8	MANI	42	M	CONTROL	5	-	-	1	1	1	1	G- 1 P-1
					10	-	-	1	1	1	1	
					14	-	-	1	1	1	1	
9	GOVINDARAJ	32	M	CASE	5	↓	↓	2	2	1	1	G- 2 P- 3
					10	↓	↓	2	2	1	1	
					14	↓	↓	2	2	3	3	
10	BALAMURUGAN	42	M	CONTROL	5	-	-	1	1	1	1	G- 1 P- 1
					10	-	-	1	1	1	1	
					14	-	-	1	1	1	1	
11	DHARMALINGAM	55	M	CASE	5	-	-	1	1	1	1	G- 1.5 P- 1
					10	-	-	1	1	1	1	
					14	↓	↓	2	1	2	2	
12	KARUN KANNAN	29	M	CONTROL	5	-	-	1	1	1	1	G- 2 P- 2
					10	-	-	2	2	2	2	
					14	↓	↓	2	2	2	2	

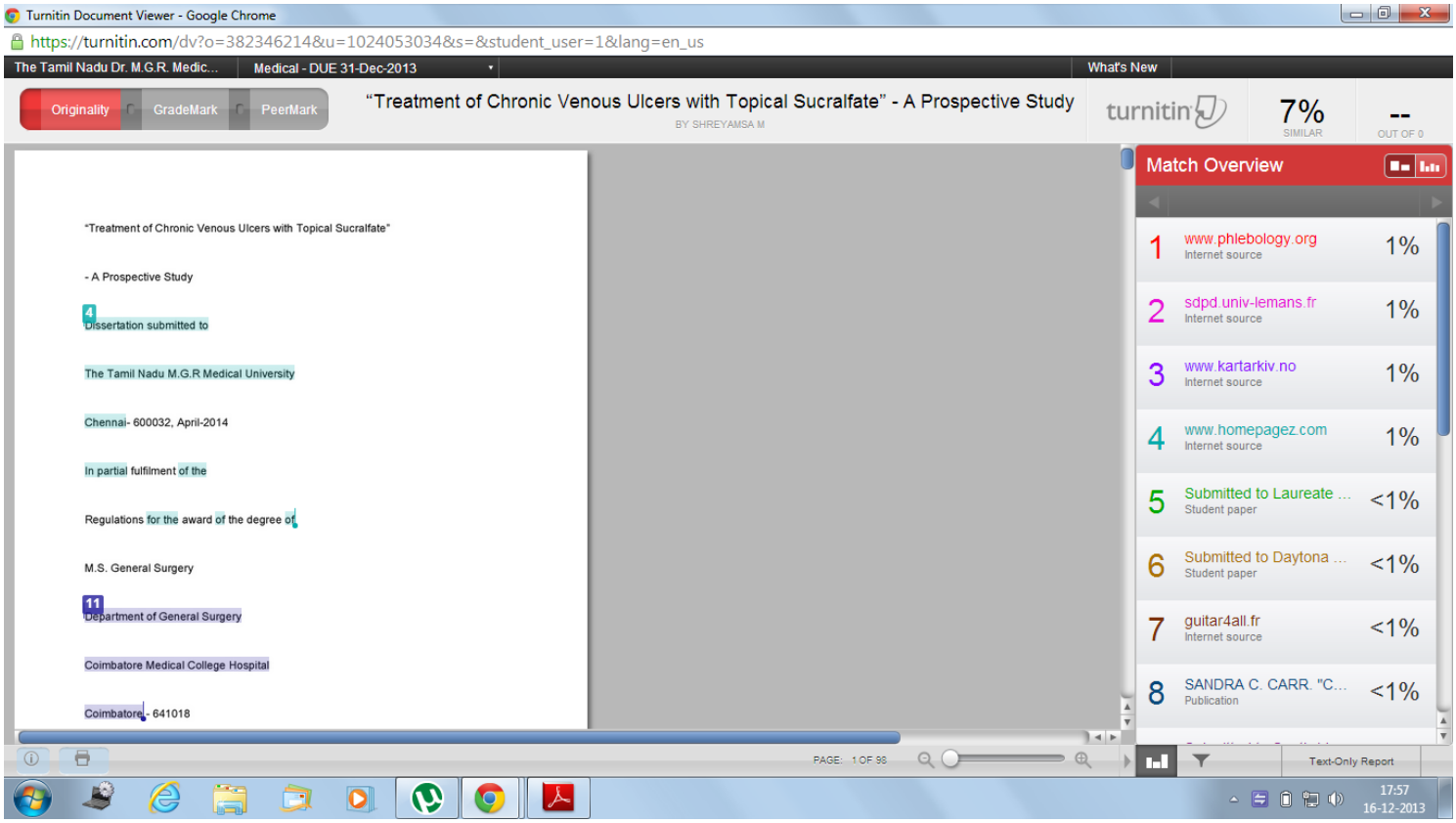
13	MARIYA BEGUM	36	F	CASE	5	-	-	1	1	1	1	G- 2 P= 3
					10	-	-	2	1	3	3	
					14	↓	↓	2	2	3	3	
14	SIVARAMAN	47	M	CONTROL	5	-	-	1	1	1	1	G- 1 P- 1
					10	-	-	1	1	1	1	
					14	-	-	1	1	1	1	
15	MURUGESAN	41	M	CASE	5	-	-	1	1	1	1	G- 2 P- 2
					10	-	-	2	2	1	1	
					14	-	-	2	2	2	2	
16	SRIJIL	42	M	CONTROL	5	-	-	1	1	1	1	G- 2 P- 1
					10	-	-	1	1	1	1	
					14	-	-	2	2	1	1	
17	ABU TAHIR	39	M	CASE	5	-	↓	1	1	1	1	G- 2 P- 3
					10	↓	↓	2	2	2	2	
					14	↓	↓	2	2	3	3	
18	SIVA LAKSHMI	41	F	CONTROL	5	-	-	1	1	1	1	G- 1 P-1
					10	-	-	1	1	1	1	
					14	-	-	1	1	1	1	
19	KARUPPUSAMY	72	M	CASE	5	-	-	1	2	1	1	G- 2 P- 2
					10	-	-	1	2	2	2	
					14	-	-	2	2	2	2	

20	MUTHU KUMAR	43	M	CONTROL	5	-	-	1	1	1	1	G- 1.5
					10	-	-	1	1	1	1	P- 1
					14	-	-	1	2	1	1	
21	TAMILAN	22	M	CASE	5	-	-	1	1	1	1	G- 2
					10	-	-	2	2	2	2	P- 2
					14	↓	↓	2	2	2	2	
22	FRANCIS	34	M	CONTROL	5	-	-	1	1	1	1	G- 1
					10	-	-	1	1	1	2	P- 1
					14	-	-	1	1	1	1	
23	PARTHIBAN	41	M	CASE	5	-	-	2	2	1	1	G- 2
					10	↓	↓	2	2	1	1	P- 2
					14	↓	↓	2	2	2	2	
24	SINGARAM	41	M	CONTROL	5	-	-	1	1	1	1	G- 1
					10	-	-	1	2	1	1	P- 1
					14	-	-	1	1	1	1	
25	RAJENDRAN	49	M	CASE	5	-	-	2	2	1	1	G- 2
					10	-	-	2	2	1	2	P- 3
					14	-	-	2	2	3	3	
26	MANNAM	42	M	CONTROL	5	-	-	1	1	1	1	G- 1
					10	-	-	1	1	1	1	P- 1
					14	-	-	1	1	1	1	

27	VIVEK	33	M	CASE	5	-	-	1	1	1	1	G- 2 P- 2
					10	↓	↓	2	2	1	1	
					14	↓	↓	2	2	2	2	
28	VIGHNESHWARI	48	F	CONTROL	5	-	-	1	1	1	1	G- 1 P- 1
					10	-	-	1	1	1	1	
					14	-	-	1	1	1	1	
29	SARAVANAN	41	M	CASE	5	↓	↓	1	1	1	1	G- 2 P- 2
					10	↓	↓	2	2	1	1	
					14	↓	↓	2	2	2	2	
30	RAJU	44	M	CONTROL	5	-	-	1	1	1	1	G- 1 P- 1
					10	-	-	1	1	1	1	
					14	-	-	1	1	1	1	

** G = GRANULATION

P = DECREASE IN PAIN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