THE ROLE OF GABAPENTIN IN POST BURN ITCHING

A dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University in the partial fulfillment of the requirement for the award of M.Ch. Branch III (Plastic Surgery) degree August 2007-2010.

CERTIFICATE

I hereby declare that this dissertation entitled **"The role of Gabapentin in Post burn itching"** is a bonafide research work carried out by **Dr.Aravind Lakshmanarao** In partial fulfillment of requirement for the degree of M.Ch. in Plastic Surgery.

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This is to certify that this dissertation entitled "The **role of Gabapentin in Post burn itching"** is a bonafide and genuine research work carried out by **Dr.Aravind Lakshmanarao** under the guidance of **Dr. Ashish Kumar gupta.M.S. M.Ch.** Professor and Unit head, Department of Plastic Surgery, Christian Medical College, Vellore.

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INTRODUCTION

Post burn itching is one of the common problem faced by burn victims. Burn injuries can lead to severe and persistent itching as the wounds heal. The itching may not necessarily stop when the wound is completely healed but may continue for many months. About 87% of discharged adults with burn injury complain of itching. Most children who have suffered a burn usually experience itching at some point during the healing process. Not only does it cause distress to both child and parent, but also the frequent excoriation may damage skin graft and necessitate further surgery.[1]

The extent of burns is not a valid indicator of the degree of post-burn itch. As regards to the depth, the longer the healing time or re-epithelialization time, the higher the risk of significant itching. Burns healing in less than 10 days rarely itch. Burns requiring over three weeks to heal usually have some degree of itching. Grafted burns are insensate for months and do not itch.

The degree of wound erythema and early scarring are good markers, but the itching usually precedes the peak scar formation. There is considerable variability in the degree of tissue reaction to any burn depth. Treatment for pruritus is initiated when itching begins, as there are no preventative measures, with the exception of skin moisturizers, to decrease dryness. Pressure garments are used to decrease the wound blood flow, but the value of pressure garments in controlling itching is variable.

Currently the standard measures of controlling itching using antihistamines, pain medication, skin moisturizers, and pressure are effective in less than 20 percent of burn patients who have severe itch. Although the exact mechanism of post-burn itching is unclear, it is clear that histamine plays a major role as is the case in other forms of dermatitis-induced itch. Increased histamine release in the healed burn wound is well documented as is the increased number of wound mast cell histamine release. In addition, a host of other inflammatory mediators are present in an inflammatory wound, such as kinins and substance P, which increase histamine release and also can potentiate the pruritogenic effects of histamine.[1]

Anticonvulsant drugs have been used for a considerable time in the management of neuropathic pain . The pathway for itch, like the pathway for pain , invoves the spinothalamic tracts and C fibres. Because of the similarity between itch and pain pathways, we thought itching would respond to treatments used for neuropathic pain.

AIMS AND OBJECTIVIES

The aims and objectives of the study are:

To evaluate the effect of oral Gabapentin in the relief of itching due to wound healing and hypertrophic scars in burns patients.

To standardize a treatment protocol for post burn itching in our institute.

MATERIALS AND METHODS

This was a one year prospective study of role of Gabapentin in the treatment of itching causing by wound healing in the post burn hypertrophic scars in the Department of Plastic surgery, Christian Medical College, Vellore. The prospective study was conducted from July 1st 2008 to June 30th, 2009. The relief of itching is evaluated after administration of Gabapentin. The study group selected comprises of the patients who has sustained thermal, electrical, and chemical burns / healed burns atleast 4 weeks after the burn event to 2 years after the burn event were included. The dose of Gabapentin to be used is 100mg three times daily in adults and increased to the maximum 0f 300mg three times daily depending on the response and 5-10 mg per kilogram body weight in children. Patients are assessed once in every 7 days in person or through phone for a period of 3 months and once in 15 days for next 3 months after administration of Gabapentin for the relief of itching. Treatment success is determined by relief or reduction of itching after administration of above mentioned dose of Gabapentin.

Inclusion Criteria:

- Male and Female Patients between 5 years and 60 years of age.

  Patients with thermal, chemical and electrical burns between 4weeks to 2 years after complete healing.

Exclusion Criteria:

- Male and Female Patients below 5 years and above 60 years of age.

  Male and Female patients within 4 weeks of burn incident or after 2 years after the burn incident.

- Patients who are already on other medications which can cause sedation.

- Female patients with confirmed pregnancy or history of amenorrohea.

- Lactating mothers who are actively breast feeding.

- Itching caused by Keloids, or other dermatological conditions not related to burns.

- Patients with post burn scars on other modalities of treatment such as Silicon gel sheet or kenacort injection for the relief of itching.

- Burn patients who had psychological and behavioral problems before the course of treatment.

Patient Demographics:

The study comprised of 23 patients of burns with hypertrophic scars due to thermal, electrical and scald burns. Almost all the patients gave history of delayed healing of wounds [more than 3 weeks].

Out of 23 patients, 18 [78.2%] had sustained thermal burns, 3 [13.04%] sustained electrical burns with flash injuries, and 2 [8.6%] had sustained scald burns.

Out of 23 patients, 10 patients were adult males, 9 were females, and 4 were children.

Methods

The following statistical method has been applied.

Preliminary analysis was done for demographic variables like sex and Age. Frequencies of the above variables have been output and corresponding Pie charts has been produced.

Descriptive statistics like Mean, Median, Mode and Range, Minimum, Maximum has been produced for continuous variables like Pre GABA scores and Post GABA scores at different months.

Then the Hypothesis that change in GABA score over time (in months) with Pre GABA scores was tested using Repeated Measures ANOVA Technique.

Individual Comparisons has been done to see whether Pair wise (baseline with other

time points) were tested with Bonferroni Correction.

Their trend over time has produced with the line graph.

Measurement of itching

The Itch Severity Scale[9]

1. The itching from your post burn ulcers / hypertrophic scars :

a. Occasional [1]

b. Often [2]

c. Always [3]

2. The severity of itching from your post burn ulcers / hypertrophic scars:

a. To a small extent [1]

b. To a moderate extent [2]

c. To a great extent [3]

3. Disturbance of night sleep due to itching is:

a. To a small extent [1]

b. To a moderate extent [2]

c. To a great extent [3]

4. Change of mood due to itching is:

a. To a small extent [1]

b. To a moderate extent [2}

c. To a great extent [3]

5. Disturbence in work and physical activity due to itching is:

a. To a small extent [1]

b. To a moderate extent [2]

c. To a great extent [3]

6. Does it affect your concentration and studies?

a. To a small extent [1]

b. To a moderate extent [2]

c. To a great extent [3]

7. Disturbance of sexual function:

a. To a small extent [1]

b. To a moderate extent [2]

c. To a great extent [3]

8. You are suffering form itching since how many months?

a. 3 months

b. 6 months.

c. 1 year.

d. 2 years

9. What percentage of your itching has improved after starting Gabapentin tablets?

a.25%

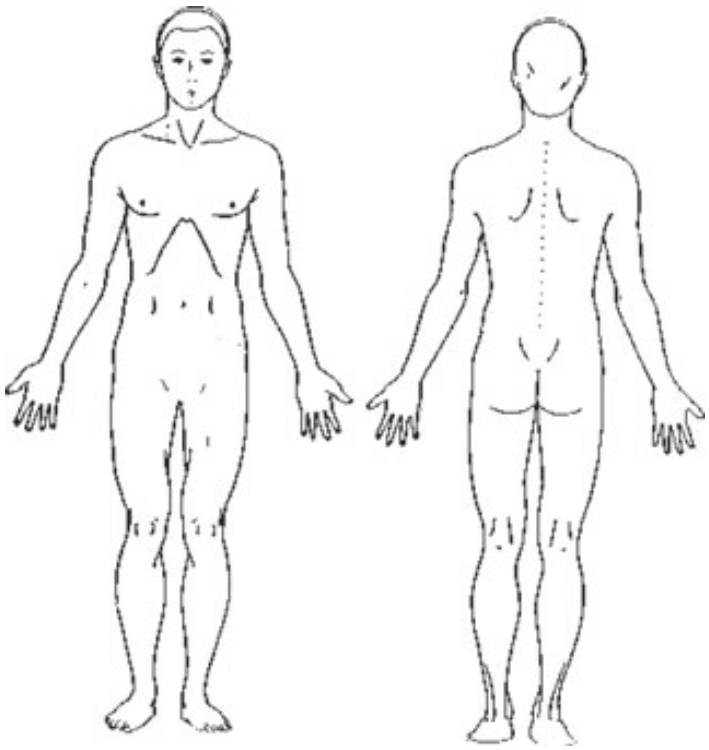
b.50%

c.75%

d. > 75%

f. No improvement.[9]

10. Please shade in the areas where you tend to be itchy



The results were considered as:

Good: 7-10 points.

Fair: 10-12 points.

Poor: >13 points.

REVIEW OF LITERATURE

ANATOMY OF SKIN

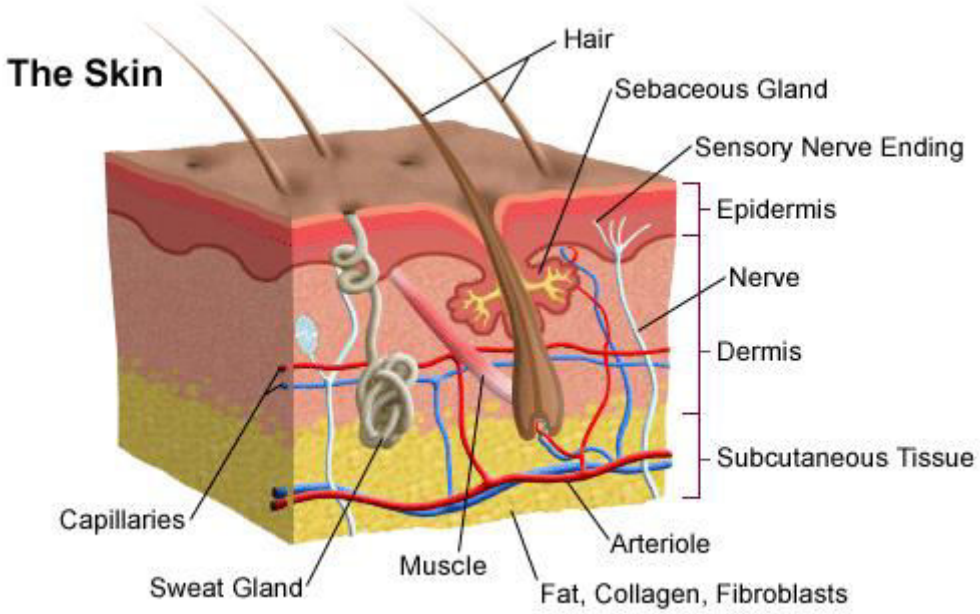


Diagram of Skin Layers

The skin is an ever-changing organ that contains many specialized cells and structures. The skin functions as a protective barrier that interfaces with a sometimes-hostile environment. It is also very involved in maintaining the proper temperature for the body to function well. It gathers sensory information from the environment, and plays an active role in the immune system protecting us from disease. Understanding how the skin can function in these many ways starts with understanding the structure of the 3 layers of skin - the epidermis, dermis, and subcutaneous tissue.

Epidermis

The epidermis is the outer layer of skin. The thickness of the epidermis varies in different types of skin. It is the thinnest on the eyelids at .05 mm and the thickest on the palms and soles at 1.5 mm.

The epidermis contains 5 layers. From bottom to top the layers are named:

Stratum basale

Stratum spinosum

Stratum granulosum

Stratum lucidum

Stratum corneum

The bottom layer, the stratum basale, has cells that are shaped like columns. In this layer the cells divide and push already formed cells into higher layers. As the cells move into the higher layers, they flatten and eventually die.

The top layer of the epidermis, the stratum corneum, is made of dead, flat skin cells that shed about every 2 weeks.

Specialized Epidermal Cells

There are three types of specialized cells in the epidermis.

The melanocyte produces pigment (melanin)

The Langerhan's cell is the frontline defense of the immune system in the skin[2]

Dermis

The dermis also varies in thickness depending on the location of the skin. It is .3 mm on the eyelid and 3.0 mm on the back. The dermis is composed of three types of tissue that are present throughout - not in layers. The types of tissue are:

Collagen

Elastic tissue

Reticular fibers

Layers of the Dermis

The two layers of the dermis are the papillary and reticular layers.

The upper, papillary layer contains a thin arrangement of collagen fibers.

The lower, reticular layer is thicker and made of thick collagen fibers that are arranged parallel to the surface of the skin.

Specialized Dermal Cells

The dermis contains many specialized cells and structures.

The hair follicles are situated here with the erector pili muscle that attaches to each follicle.[2]

Sebaceous (oil) glands and apocrine (scent) glands are associated with the follicle.

This layer also contains eccrine (sweat) glands, but they are not associated with hair follicles.

Blood vessels and nerves course through this layer. The nerves transmit sensations of pain, itch, and temperature.

There are also specialized nerve cells called Meissner's and Vater-Pacini corpuscles that transmit the sensations of touch and pressure.

Subcutaneous Tissue

The subcutaneous tissue is a layer of fat and connective tissue that houses larger blood vessels and nerves. This layer is important is the regulation of temperature of the skin itself and the body. The size of this layer varies throughout the body and from person to person.

Epidermal Appendages

Epidermal appendages are intradermal epithelial structures lined with epithelial cells with the potential for division and differentiation. These are important as a source of epithelial cells, which accomplish re-epithelialization should the overlying epidermis be removed or destroyed in situations such as partial thickness burns, abrasions, or split-thickness skin graft harvesting. Epidermal appendages include sebaceous glands, sweat glands, apocrine glands, mammary glands, and hair follicles. They often are found deep within the dermis,

and in the face may even lie in the subcutaneous fat beneath the dermis. This accounts for the remarkable ability of the face to re-epithelialize even the deepest cutaneous wounds.

Sebaceous glands.[2]

Sebaceous glands, or holocrine glands, are found over the entire surface of the body except the palms, soles, and dorsum of the feet. They are largest and most concentrated in the face and scalp where they are the sites of origin of acne. The normal function of sebaceous glands is to produce and secrete sebum, a group of complex oils including triglycerides and fatty acid breakdown products, wax esters, squalene, cholesterol esters, and cholesterol. Sebum lubricates the skin to protect against friction and makes it more impervious to moisture.

Sweat glands

Sweat glands, or eccrine glands, are found over the entire surface of the body except the vermillion border of the lips, external ear canal, the nail beds, labia minora, the glans penis, and the inner aspect of the prepuce. They are most concentrated in the palms and soles and the axillae. Each gland consists of a coiled secretory intradermal portion that connects to the epidermis via a relatively straight distal duct. The normal function of the sweat gland is to produce sweat, which cools the body by evaporation. The thermoregulatory center in the hypothalamus controls sweat gland activity through sympathetic nerve fibers that innervate the sweat glands. Sweat excretion is triggered when core body temperature reaches or exceeds a set point.

Apocrine glands

Apocrine glands are similar in structure but not identical to eccrine glands. They are found in the axillae, in the anogenital region, and, as modified glands, in the external ear canal (ceruminous glands), in the eyelid (Moll's glands), and in the breast (mammary glands).

Hair follicles

Hair follicles are complex structures formed by the epidermis and dermis. They are found over the entire surface of the body except the soles of the feet, palms, glans penis, clitoris, labia minora, mucocutaneous junction, and portions of the fingers and toes. Sebaceous glands often open into the hair follicle rather than directly onto the skin surface, and the entire complex is termed the pilosebaceous unit.

Blood Supply of the Skin

Cutaneous vessels ultimately arise from underlying named source vessels. Each source vessel supplies a 3-dimensional vascular territory from bone to skin termed an angiosome. Adjacent angiosomes have vascular connections via reduced caliber (choke) vessels or similar caliber (true) anastomotic vessels. The cutaneous vessels originate either directly from the source arteries (septocutaneous or fasciocutaneous perforators) or as terminal branches of muscular vessels (musculocutaneous perforators).

During their course to the skin, they travel within or adjacent to the connective tissue framework and supply branches to each tissue with which they come into close contact (bone, muscle, fascia, nerve, fat). They emerge from the deep fascia in the vicinity of the intermuscular or intramuscular septa or near tendons and travel toward the skin, where they form extensive subdermal and dermal plexuses. The dermis contains horizontally arranged superficial and deep plexuses, which are interconnected via communicating vessels oriented perpendicular to the skin surface. Cutaneous vessels ultimately anastomose with other cutaneous vessels to form a continuous vascular network within the skin.

In addition to the skin's natural heat conductivity and loss of heat from the evaporation of sweat, convection from cutaneous vessels is a vital component of thermoregulation. Cutaneous blood flow is 10-20 times that required for essential oxygenation and metabolism, and large amounts of heat can be exchanged through the regulation of cutaneous blood flow. The thermoregulatory center in the hypothalamus controls vasoconstriction and vasodilatation of cutaneous vessels through the sympathetic nervous system.[2]

Lymphatics

Skin lymphatics parallel the blood supply and function to conserve plasma proteins and scavenge foreign material, antigenic substances, and bacteria. Blind-ended lymphatic capillaries arise within the interstitial spaces of the dermal papillae. These unvalved superficial dermal vessels drain into valved deep dermal and subdermal plexuses. These then coalesce to form larger lymphatic channels, which course through numerous filtering lymph nodes on their way to

join the venous circulation near the subclavian vein-internal jugular vein junction bilaterally.[2]

Skin Innervation

Sensory perception is critically important in the avoidance of pressure, mechanical or traumatic forces, and extremes of temperature. Numerous specialized structures are present in the skin to detect various stimuli. As previously mentioned, Merkel cells of the epidermis detect light touch. Meissner corpuscles also detect light touch. These are found in the dermal papillae and are most concentrated in the fingertips. Pacini corpuscles are found deep within the dermis or even in the subcutaneous tissue. These structures are specialized to detect pressure.

Pain is transmitted through naked nerve endings located in the basal layer of the epidermis. Krause bulbs detect cold, whereas Raffini corpuscles detect heat. Heat, cold, and proprioception also are located in the superficial dermis. Cutaneous nerves follow the route of blood vessels to the skin. The area supplied by a single spinal nerve, or single segment of the spinal cord, is termed a dermatome. Adjacent dermatomes may overlap considerably, of importance to note when performing field blocks with local anesthesia.[2]

Wound healing

Wound healing, or wound repair, is an intricate process in which the skin repairs itself after injury. In normal skin, the epidermis and dermis exists in a steady-stated equilibrium, forming a protective barrier against the external environment. Once the protective barrier is broken, the physiologic process of wound healing is immediately set in motion. The classic model of wound healing is divided into three or four sequential, yet overlapping, phases: (1) hemostasis (not considered a phase by some authors), (2) inflammatory, (3) proliferative and (4) remodeling.

The proliferative phase.

The proliferative phase is characterized by angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction. In angiogenesis, new blood vessels are formed by vascular endothelial cells. In fibroplasia and granulation tissue formation, fibroblasts grow and form a new, provisional extracellular matrix (ECM) by excreting collagen and fibronectin. Concurrently, re-epithelialization of the epidermis occurs, in which epithelial cells proliferate and 'crawl' atop the wound bed, providing cover for the new tissue.

In contraction, the wound is made smaller by the action of myofibroblasts, which establish a grip on the wound edges and contract themselves using a mechanism similar to that in smooth muscle cells. When the cells' roles are close to complete, unneeded cells undergo apoptosis.

In the maturation and remodeling phase, collagen is remodeled and realigned along tension lines and cells that are no longer needed are removed by apoptosis.

However, this process is not only complex but fragile, and susceptible to interruption or failure leading to the formation of chronic non-healing wounds. Factors which may contribute to this include diabetes, venous or arterial disease, old age, and infection.

Inflammatory phase

In the inflammatory phase (lag phase/resting phase), clotting takes place in order to obtain hemostasis, or stop blood loss, and various factors are released to attract cells that phagocytise debris, bacteria, and damaged tissue and release factors that initiate the proliferative phase of wound healing.

Clotting cascade

Coagulation

When tissue is first wounded, blood comes in contact with collagen triggering blood platelets to begin secreting inflammatory factors. Platelets also express glycoproteins on their cell membranes that allow them to stick to one another and to aggregate forming a mass.

Fibrin and fibronectin cross-link together and form a plug that traps proteins and particles and prevents further blood loss. This fibrin-fibronectin plug is also the main structural support for the wound until collagen is deposited. Migratory cells

use this plug as a matrix to crawl across, and platelets adhere to it and secrete factors. The clot is eventually lysed and replaced with granulation tissue and then later with collagen.

Platelets

Platelets, the cells present in the highest numbers shortly after a wound occurs, release a number of things into the blood, including ECM proteins and cytokines, including growth factors. Growth factors stimulate cells to speed their rate of division. Platelets also release other proinflammatory factors like serotonin, bradykinin, prostaglandins, prostacyclins, thromboxane, and histamine, which serve a number of purposes, including to increase cell proliferation and migration to the area and to cause blood vessels to become dilated and porous..

Vasoconstriction and vasodilatation

Immediately after a blood vessel is breached, ruptured cell membranes release inflammatory factors like prostaglandins and thromboxanes that cause the vessel to spasm to prevent blood loss and to collect inflammatory cells and factors in the area. This vasoconstriction lasts five to ten minutes and is followed by vasodilation, a widening of blood vessels, which peaks at about 20 minutes post-wounding. Vasodilation is the result of factors released by platelets and other cells. The main factor involved in causing vasodilation is histamine. Histamine also causes blood vessels to become porous, allowing the tissue to become edematous because proteins from the bloodstream leak into the extravascular space, which increases its osmolar load and draws water into the area. Increased

porosity of blood vessels also facilitates the entry of inflammatory cells like leukocytes into the wound site from the bloodstream.

Polymorphonuclear neutrophils

Within an hour of wounding, polymorphonuclear neutrophils (PMNs) arrive at the wound site and become the predominant cells in the wound for the first two days after the injury occurs, with especially high numbers on the second day. They are attracted to the site by fibronectin, growth factors, and substances such as kinins. Neutrophils phagocytise debris and bacteria and also kill bacteria by releasing free radicals in what is called a 'respiratory burst'. They also cleanse the wound by secreting proteases that break down damaged tissue. Neutrophils usually undergo apoptosis once they have completed their tasks and are engulfed and degraded by macrophages.

Other leukocytes to enter the area include helper T cells, which secrete cytokines to cause more T cells to divide and to increase inflammation and enhance vasodilation and vessel permeability. T cells also increase the activity of macrophages.

Macrophages

Macrophages are essential to wound healing. They replace PMNs as the predominant cells in the wound by two days after injury. Attracted to the wound site by growth factors released by platelets and other cells, monocytes from the bloodstream enter the area through blood vessel walls. Numbers of monocytes in the wound peak one to one and a half days after the injury occurs. Once they are

in the wound site, monocytes mature into macrophages. Recently it has been found that the spleen contains half the body's monocytes in reserve ready to deployed to injured tissue.

The macrophage's main role is to phagocytise bacteria and damaged tissue, and it also debrides damaged tissue by releasing proteases. Macrophages also secrete a number of factors such as growth factors and other cytokines, especially during the third and fourth post-wounding days. These factors attract cells involved in the proliferation stage of healing to the area. Macrophages are stimulated by the low oxygen content of their surroundings to produce factors that induce and speed angiogenesis.] And they also stimulate cells that reepithelialize the wound, create granulation tissue, and lay down a new extracellular matrix.By secreting these factors, macrophages contributes in pushing the wound healing process into the next phase.

Decline of inflammatory phase

As inflammation dies down, fewer inflammatory factors are secreted, existing ones are broken down, and numbers of neutrophils and macrophages are reduced at the wound site. These changes indicate that the inflammatory phase is ending and the proliferative phase is underway.

Because inflammation plays roles in fighting infection, clearing debris and inducing the proliferation phase, it is a necessary part of healing. However, inflammation can lead to tissue damage if it lasts too long. Thus the reduction of inflammation is frequently a goal in therapeutic settings. Inflammation lasts as long as there is debris in the wound.

Proliferative phase

About two or three days after the wound occurs, fibroblasts begin to enter the wound site, marking the onset of the proliferative phase even before the inflammatory phase has ended. As in the other phases of wound healing, steps in the proliferative phase do not occur in a series but rather partially overlap in time. The proliferative phase is also called the reconstruction phase.

Angiogenesis

Also called neovascularization, the process of angiogenesis occurs concurrently with fibroblast proliferation when endothelial cells migrate to the area of the wound. Because the activity of fibroblasts and epithelial cells requires oxygen and nutrients, angiogenesis is imperative for other stages in wound healing, like epidermal and fibroblast migration. The tissue in which angiogenesis has occurred is erythematous due to the presence of capillaries.

Stem cells of endothelial cells, originating from parts of uninjured blood vessels, develop pseudopodia and push through the ECM into the wound site to establish new blood vessels. Endothelial cells are attracted to the wound area by fibronectin found on the fibrin scab and chemotactically by angiogenic factors released by other cells, e.g. from macrophages and platelets when in a low-oxygen environment. Endothelial growth and proliferation is also directly stimulated by hypoxia, and presence of lactic acid in the wound.

To migrate, endothelial cells need collagenases and plasminogen activator to degrade the clot and part of the ECM. Zinc-dependent metalloproteinases digest

basement membrane and ECM to allow cell migration, proliferation and angiogenesis. When macrophages and other growth factor-producing cells are no longer in a hypoxic, lactic acid-filled environment, they stop producing angiogenic factors. Thus, when tissue is adequately perfused, migration and proliferation of endothelial cells is reduced. Eventually blood vessels that are no longer needed die by apoptosis.

Fibroplasia and granulation tissue formation

Simultaneously with angiogenesis, fibroblasts begin accumulating in the wound site. Fibroblasts begin entering the wound site two to five days after wounding as the inflammatory phase is ending, and their numbers peak at one to two weeks post-wounding. By the end of the first week, fibroblasts are the main cells in the wound Fibroplasia ends two to four weeks after wounding.

In the first two or three days after injury, fibroblasts mainly proliferate and migrate, while later, they are the main cells that lay down the collagen matrix in the wound site. Fibroblasts from normal tissue migrate into the wound area from its margins. Initially fibroblasts use the fibrin scab formed in the inflammatory phase to migrate across, adhering to fibronectin. Fibroblasts then deposit ground substance into the wound bed, and later collagen, which they can adhere to for migration.

Granulation tissue functions as rudimentary tissue, and begins to appear in the wound already during the inflammatory phase, two to five days post wounding, and continues growing until the wound bed is covered. Granulation tissue consists of new blood vessels, fibroblasts, inflammatory cells, endothelial cells,

myofibroblasts, and the components of a new, provisional extracellular matrix (ECM). The provisional ECM is different in composition from the ECM in normal tissue and its components originate from fibroblasts. Such components include fibronectin, collagen, glycosaminoglycans, and proteoglycans. Its main components are fibronectin and hyaluronin, which create a very hydrated matrix and facilitate cell migration Later this provisional matrix is replaced with an ECM that more closely resembles that found in non-injured tissue.

Growth factors and fibronectin encourage proliferation, migration to the wound bed, and production of ECM molecules by fibroblasts. Fibroblasts also secrete growth factors that attract epithelial cells to the wound site.

HYPERTROPHIC SCARS[18]

Wound repair normally culminate in fine line scars, however the repair process may go awry and wounds may heal with large raised collagenous scars known as keloids or hypertrophic scars.Both lesions have the annoying clinical symptoms of itching, tenderness and pain.[18]

Hyperopic scars are often raised and red, remain within the confines of the wound and tend to regress over a period of time .The complications of these abnormal scar formations are often severe and their clinical management is frustrating.

Etiology: Keloids and hypertrophic scars are unique to man. Hypertrophic scars are fibroproliferative disorders of wound healing with excess healing. However

because there are no animal models there are few biochemical or molecular data that may indicate which factors may initiate hypertrophic scar formation.

Diagnosis: Hypertrophic scars appear to be self limiting type of over healing following injury. With time the raised, red hypertrophic scar becomes pale and flat. If there is a doubt biopsy is mandatory.

Treatment modalities: Several types of treatment modalities have been tried with varying degrees of success. The surgeon should ascertain whether the patient's objective is to eradicate the esthetic and /or functional deformity or to prevent recurrence by surgery or by pharmacological therapy or whether the objective is merely ameliorate physical discomfort and itching.

Pharmacologic: directed towards either decreasing protein production or enhancing collagen turnover. Steroids affect the former and lathyrogens and penicillamine are agents used to accomplish the latter. Steroids like Triamcinolone acetonide are best used in concentration of 40 mg per ml. Injections are usually given 6 to 8 weeks apart.

Mechanical: Mechanical pressure has been known to inhibit hypertrophic scar production by altering glycosaminoglycan content and blood vessel permeability of healing wounds and thus subsequently curtailed scar formation by altering normal collagen –GAG interaction during wound healing. Also it has been suggested that mechanical pressure increases collagenase activity which in turn prevents excessive collagen deposition..

Radiation: Radiation nonselectively destroys collagen producing fibroblasts in the lesions as well as surrounding connective tissue and cells.

Surgery:Mechanical factors of surgical wound closure affecting scar appearance;

Amount of scar tissue-Avoid use of large foreign body sutures,applying pressure and prevention of hematoma may decrease amount of scar.

Lines of minimal tension-Lines parallel to muscle pull resolve earlier and and remain finer.

Shape of scars-avoid semicircular scar as it may become puffy and raised(trap door scar)

Skin suture marks-closure with subcuticular sutures takes the burden of tension from the skin sutures and allows their early removal thus avoiding most risks of suture marks.

Location of scars-some areas of body (eg eyelids,forehead) heal with less noticeable scars than others.[18]

Incidence and Characteristics of itching in burn patients[22]

Itching in the healed burn patient is considered to be one of the most problematic and distressing issues that the patient experiences. Staff in any burn centre can attest to both the magnitude of the problem as well as the fact that no effective treatiment exists.[22]

The itch experienced by the burn survivor can be described by three criteria- incidence, severity, and duration.

The incidence of significant itching in burn survivors is approximately 50% for adults and close to 100% for children.

The severity has always been difficult to evaluate. However, studies using a 10 point linear visual analog scale, have demonstrated that itch ranges from 5 to 7 in patients already on standard antihistamine therapy.[22]

IMPACT OF ITCHINNG: [22]

>Impedes sleep

> Impedes work and play.

> Impedes therapy.

> Impedes eating.

> Creates depression and anxiety

> Impairs quality of life

THE INCIDENCE:

Despite using oral antihistamines, "severe itching" is reported to be present in :

*Approximately 70% of children.

*Approximately 50% of adults.

The characteristics of itch are:

-Starts during healing.

-most prominent with time of closure over 3 weeks.

-worse for partial thickness burns.

-Accentuated by healing, activity.

-Worse at night.

-Lasts months to years.

Pathophysiology of itching:[6]

ITCH AND PAIN: Itch is considered by many investigators to be a form of pain. The similarity is that itch shares with a peripheral group of C fibers, a group of dorsal horn interneurons and specific pathway in the anterolateral spinal cord to brain. Both itch and pain disappear when the pathway is cut. The C fibers carry both itch and pain stimuli. However, itch can only be produced, by superficial skin. Deep stimuli produce pain. Another similarity is that fact that histamine placed just beneath the epidermis leads to intense itching while histamine injected deeper in the skin produces pain. Another similarity is a strong itch stimulus to skin such as light touch, imitates the secondary hyperalgesia in which the surrounding painful focus is also painful to light touch. The mechanism is the spreading of hyperactivity of neurons in the cord following a C fiber volley. Pain

will override the itch sensation the itch sensation if a painful stimulation occurs in the area of the itch.[6]

Likely both use the same skin C-fibers for the pathway to the brain.

Itch is caused by stimulation of a restricted number of C fibers.[13]

A small afferent volley signals itch.

A larger activation of C fibers will cause pain.

Itch is only present on the surface of skin.

Pain can be present on the surface and deeper portion of skin

Morphine causes itch but stops pain.

HISTAMINE AND BURN ITCH: The most common hypothesis for the skin itch and in the healed wound is the stimulation of skin sensory nerve fibers by Histamine. The histamine produced in the skin and especially in the burn wound is by the increased number of mast cells. Secondly, Histamine applied in low concentrations to the epidermo-dermal junction causes intense itching. Third, histamine causes itch by binding to the H1 receptor, found in large concentrations in skin.

The healed partial thickness burn wound or donor site appears to be most prone to itch due to injury induced alteration in the superficial nerve fibers making them more sensitive to histamine and secondly, The presence of increased number of

histamine factories, namely the mast cells. A number of other agents, known to induce itch, appear to act indirectly through stimulation of histamine release or potentiation of the itching effect of histamines.

The mechanism of itching is not clearly defined, but increased histamine release from the wound is a likely etiological factor. The source of the histamine would be the increased mast cell population typically present in the chronically pruritic wound. Any wound manipulation or increase in wound temperature exacerbates the itching.

The mechanism of itch is considered to be the activation of the wound surface C nerve fibers. The C fibers are typically considered to be pain fibers, and itch has been categorized as a form of pain. Histamine also increases surface wound blood flow, which would explain the raised red surface usually present on the chronically itching wound.[22]

The current standard pharmacologic management of itch is the use of oral antihistamines with the frequent addition of sedatives. However, this approach is successful in less than half of the chronically itching burn patients.[14]

Doxepin, a tricyclic compound used for clinical depression, has been found to have very potent H1 and H2 histamine receptor blocking properties. Doxepin, which is available as 5% topical cream has been reported to be effective in controlling the itching and erythema of more acute pruritic burn wound up to three months from the time of healing.

Criteria for the use of Doxepin were: The burn wound must be healed. In addition, the pruritic wound could not exceed 20% of total body surfce, and the total initial burn could not exceed 35% of the body. Larger burn injuries usually have other causes of discomfort, which are hard to distinguish from itch. Doxepin could not used in acute post burn period or immedietly after debridment and skin grafting.[4]

Many of the treatments available to reduce itching can be used when the wounds are healed, these include colloid and oatmeal baths, local anaesthetic creams and massage therapy. 5% doxepin cream can be used only after the wound healing is complete. Doxepin is not recommended for children under 12 years. Drowsiness can be significant with this cream.

Antihistamines are the current mainstay of treatment. Vitale et al compared three different oral antihistamines and found that they provided complete relief of itch in only 20% of patients. Severe itching was still reported in more than 70% of patients. The side effect with the highest incidence and common to all antihistamines was sedation, and it may the sedation itself that relieves the itching.

Ondensetron is a 5HT-3 receptor antagonist used for prevention of nausea and vomiting in patients receiving chemotherapy/ radiation therapy. Serotonin [5HT], a central and peripheral acting substance implicated in other pruritogenic processes such as uraemia and cholestastis, could reasonably be implicated in the burn pruritis pathway as well.

Pain and itch are thought to be conducted via C-fibres that are influenced to a degree by serotonin. By inhibiting this influence at the 5HT3 receptor, pruritis may also be inhibited.

The comparative trial has been done between ondensetron and antihistamines has been done. 17 patients had participated in the drug study. Pretreatment itching scores were similar for both drugs 6 for dyphenhydramine and 6.35 for ondensetron. Post treatment scores were 3.41 for dyphenhydramine and 2.65 for ondensetron. The greater benefit in the ondensetron group was not dramatically better than dyphenhydramine .

Anticonvulsant drugs have been used for a considerable time in the management of neuropathic pain .

Pharmacology of Gabapentin[8]

Gabapentin is an anti-seizure drug that consists of a GABA molecule covalently bound to a lipophilic cyclohexane ring. Gabapentin was designed to be a centrally active GABA agonist, with its high lipid solubility aimed at facilitating its transfer across the blood- brain barrier.[8]

Pharmacological effects and mechanism of action

Gabapentin inhibits tonic hindlimb extension in the electroshock seizure model. Gabapentin also inhibits clonic seizures induced by pentylenetetrazol. Its efficacy in both these tests parallels that of valproic acid and distinguishes it from phenytoin and carbamazepine. The anticonvulsant effect of Gabapentin is

unknown. Gabapentin may promote nonvesicular release of GABA through a poorly understood mechanism. Gabapentin binds protein in cortical membranes with an amino acid sequence identical to that of the alpha2 delta subunit of the L type of voltage-sensitive calcium channel.[8]

Pharmacodynamics:

Gabapentin is absorbed after oral administration and is not metabolized in humans. It is not bound to plasma proteins. It is excreted unchanged, mainly in the urine. Its half-life, when used as a monotherpy, is is 4-6 hours.

Therapeutic uses: Gabapentin is effective for partial seizures, with or without secondary generalization, used in the treatment of neuropathic pain.

Toxicity: Overall, gabpentin is well tolerated with the most common adverse effects of somnolence, dizziness, ataxia, and fatigue. These effects usually are mild to moderate in severity but resolve within 2 weeks of onset during continued treatment.[8]

Precautions and Contraindications:

Patients who are allergic to gabapentin or other ingredients should not take gabapentin.

Gabapentin should be use with caution in patients with neurological disorders and pregnant ladies.

Dose modification of gabapentin may be required in patients with renal failure or patients with compromised renal function.

This drug may cause dizziness, caution should be taken before advising patients with involved in activities requiring alertness such as driving or using machinery

Caution is advised when using this drug in the elderly because they may be more sensitive to its effects.

Caution is advised when using this drug in children because they may be more sensitive to its effects, especially the mental/mood changes (e.g., hostility).

Results

Statistical Methods Used:

1. **Variable Explanations**:
   a. Age : Age of the Patients
   b. Pre : Pre GABA Score(Baseline)
   c. Post1 to Post7: Post GABA Scores(in Months)
2. **Hypothesis Tested** :
   a. Is there any change over time (Months) in Mean GABA scores from baseline? Refer to : Table 2
   b. If you wish to see at which time point (months) say whether there is any change over time in Mean GABA scores at Post1 and Post2? Refer to: Table 3
3. **Statistical Methods Applied**:
   a. Repeated Measures ANOVA

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
age	20	5	45	25.70	10.717
Pre	20	12	15	13.35	.875
post1	20	7.25	10.00	8.3625	.60413
post2	20	7.25	9.00	8.1000	.61985
post3	20	7.25	8.75	8.0000	.52566
post4	20	7.0	9.0	7.875	.5821
post5	20	7.0	9.0	8.000	.6689
post6	20	7.0	9.0	7.825	.7304
Valid N (listwise)	20				

Table 2:

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
score	**Pillai's Trace**	**.964**	**62.438[a]**	**6.000**	**14.000**	**.000**

Interpretation:

It answers the first hypothesis, we conclude from the above table that there is significant difference (i.e. decrease) over time in Mean GABA scores.

Table 3:
Pairwise Comparisons

Measure:MEASURE_1

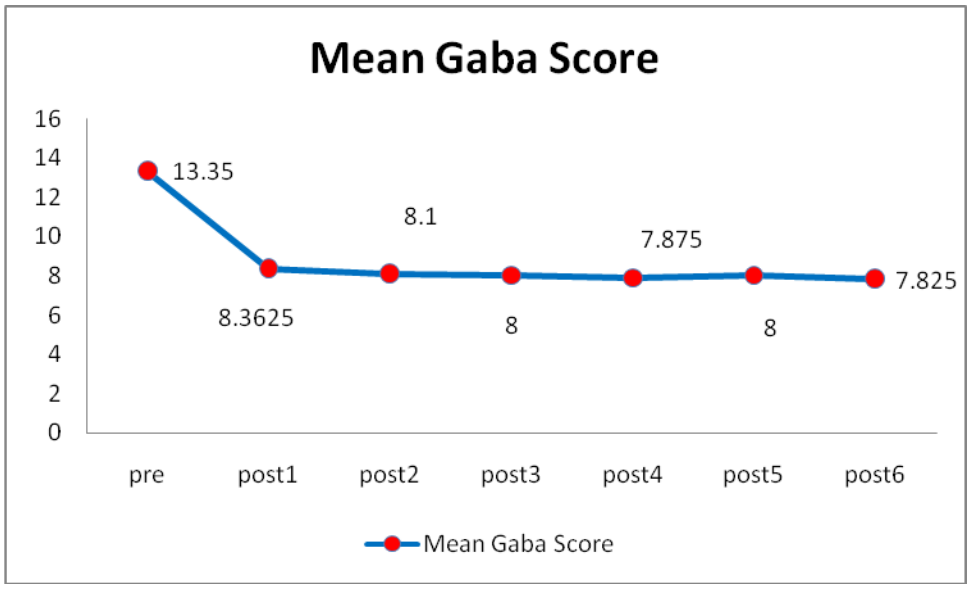
(I) score	(J) score	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	4.988*	.288	.000	3.978	5.997
	3	5.250*	.302	.000	4.191	6.309
	4	5.350*	.282	.000	4.361	6.339
	5	5.475*	.282	.000	4.487	6.463
	6	5.350*	.321	.000	4.227	6.473
	7	5.525*	.325	.000	4.385	6.665
2	1	-4.988*	.288	.000	-5.997	-3.978
	3	.263	.105	.455	-.105	.630
	4	.363*	.093	.021	.036	.689
	5	.488*	.090	.001	.173	.802
	6	.363	.120	.144	-.056	.781
	7	.538*	.148	.037	.020	1.055
3	1	-5.250*	.302	.000	-6.309	-4.191
	2	-.263	.105	.455	-.630	.105
	4	.100	.088	1.000	-.207	.407
	5	.225	.081	.250	-.058	.508
	6	.100	.097	1.000	-.239	.439
	7	.275	.081	.063	-.008	.558

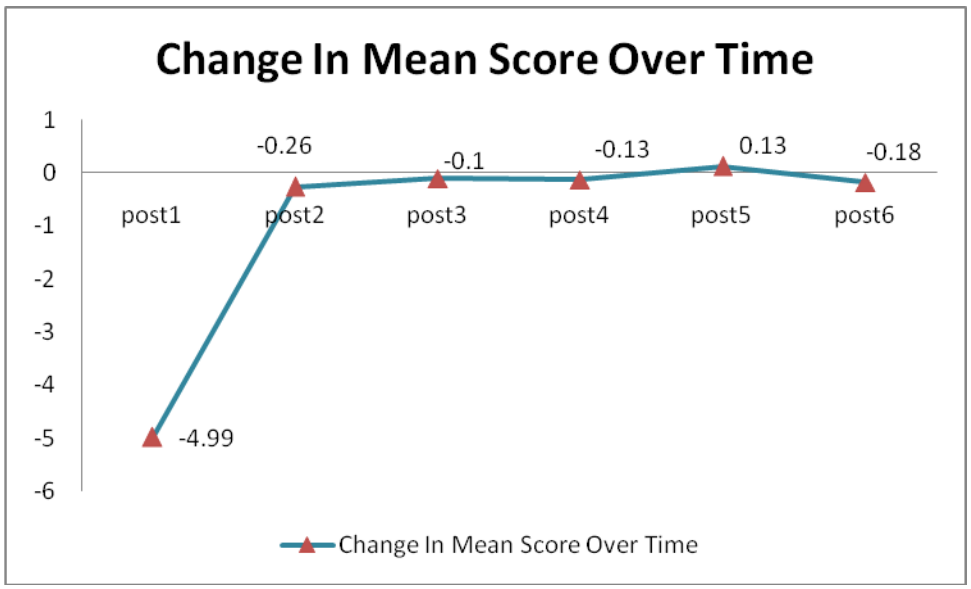
4	1	-5.350*	.282	.000	-6.339	-4.361
	2	-.363*	.093	.021	-.689	-.036
	3	-.100	.088	1.000	-.407	.207
	5	.125	.092	1.000	-.196	.446
	6	.000	.089	1.000	-.311	.311
	7	.175	.110	1.000	-.212	.562
5	1	-5.475*	.282	.000	-6.463	-4.487
	2	-.488*	.090	.001	-.802	-.173
	3	-.225	.081	.250	-.508	.058
	4	-.125	.092	1.000	-.446	.196
	6	-.125	.125	1.000	-.563	.313
	7	.050	.102	1.000	-.307	.407
6	1	-5.350*	.321	.000	-6.473	-4.227
	2	-.363	.120	.144	-.781	.056
	3	-.100	.097	1.000	-.439	.239
	4	.000	.089	1.000	-.311	.311
	5	.125	.125	1.000	-.313	.563
	7	.175	.122	1.000	-.252	.602
7	1	-5.525*	.325	.000	-6.665	-4.385
	2	-.538*	.148	.037	-1.055	-.020
	3	-.275	.081	.063	-.558	.008
	4	-.175	.110	1.000	-.562	.212
	5	-.050	.102	1.000	-.407	.307
	6	-.175	.122	1.000	-.602	.252

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.


Mean Gaba Score
16
14
12
10
8
6
4
2
0
13.35
8.3625
8.1
8
7.875
8
7.825
pre
post1
post2
post3
post4
post5
post6
Mean Gaba Score


Change In Mean Score Over Time
1
0
-1
-2
-3
-4
-5
-6
-4.99
-0.26
-0.1
-0.13
0.13
-0.18
post1
post2
post3
post4
post5
post6
Change In Mean Score Over Time

Descriptive Measures for Post GABA Scores at each Month:

Statistics

	N								
	Valid	Missing	Mean	Median	Mode	Std. Deviation	Range	Minimum	Maximum
Post GABA Score at Month1	20	0	8.3625	8.5000	8.50	.60413	2.75	7.25	10.00
Post GABA Score at Month2	20	0	8.1000	8.3750	7.50[a]	.61985	1.75	7.25	9.00
Post GABA Score at Month3	20	0	8.0000	7.8750	8.50	.52566	1.50	7.25	8.75
Post GABA Score at Month4	20	0	7.8750	8.0000	7.50	.58208	2.00	7.00	9.00
Post GABA Score at Month5	20	0	8.0000	8.0000	7.50	.66886	2.00	7.00	9.00
Post GABA Score at Month6	20	0	7.8250	7.7500	7.00	.73045	2.00	7.00	9.00

a. Multiple modes exist. The smallest value is shown

Descriptive Measures for Pre GABA Scores:

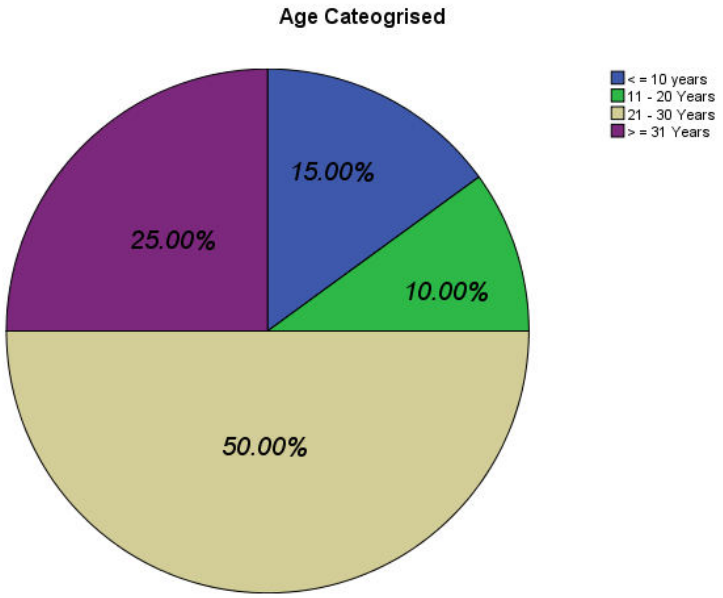
Statistics

Variables	N		Mean	Median	Mode	Std. Deviation	Range	Minimum	Maximum
	Valid	Missing							
PRE GABA SCORES	20	0	13.35	13.50	14	.875	3	12	15

Age Distribution :

Age Cateogrised

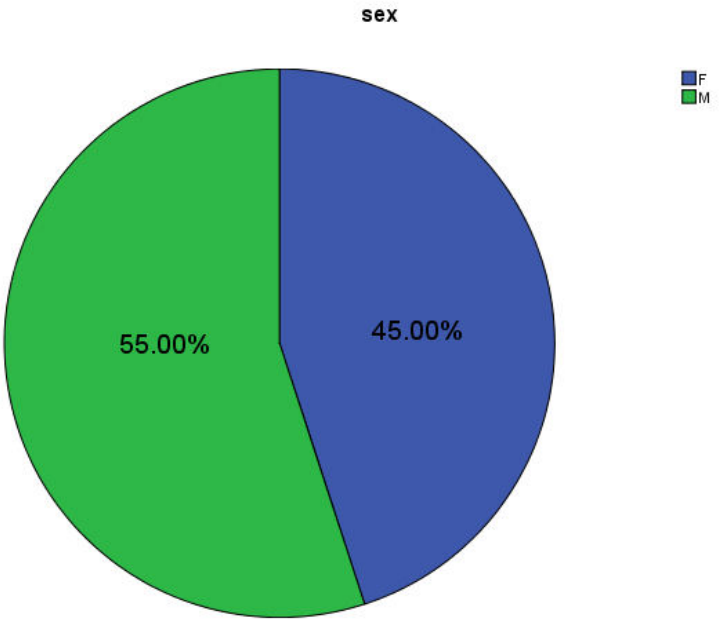
	Frequency	Percent	Valid Percent	Cumulative Percent
< = 10 years	3	15.0	15.0	15.0
11 - 20 Years	2	10.0	10.0	25.0
21 - 30 Years	10	50.0	50.0	75.0
> = 31 Years	5	25.0	25.0	100.0
Total	20	100.0	100.0	



Sex Distribution:

sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	F	9	45.0	45.0	45.0
	M	11	55.0	55.0	100.0
	Total	20	100.0	100.0	



DISCUSSION

Post burn itching is one of the common problems associated with hypertrophic scars. It causes many problems to the patient, continuous discomfort, lack of concentration in study and work, disturbance in sleep, difficulty in postoperative period and over all quality of life. Post burn itching should be properly investigated and treated instead of prescribing antihistaminic drugs or other placebo drugs.

The way in which itch is processed in the central nervous system is incompletely understood. Injection of histamine into the superficial layers of the skin stimulates itching in a dose dependent manner and it undoubtedly plays a role as increased histamine release in the healed burn wound is well documented. Prostaglandins lower the threshold for histamine to produce itching , and opioids, 5HT, substance P and many other neuropeptides may all be responsible for producing the itch sensation and .

Bickford in 1938 hypothesized that itchy skin is mediated by a peripheral neurogenic mechanism. The pathway for itch, like the pathway for pain, involves the spinothalamic tracts and C fibres. Both itch and pain disappear when this pathway is cut. Pain and itch, however, are dissociable – opiate administration relieves pain but causes itch. Itch can be inhibited by noxious stimuli, thus they are distinct sensations that interact. Since pain and itch have similar pathways and similar sensitization of neurons they may have similar chemical transmission and hence respond to the same treatment. Central inhibitory neurons must also play a part in the perception of itch .

The neural basis for itching is still unclear but itching most likely has a multitude of mechanisms that may depend on the primary cause.

Several reports show gabapentin can be used safely in children for treatment of epilepsy and neuropathic pain with minimal side effects. It seems now that it may also provide an alternative treatment to antihistamines for itching. The treatment has been so successful that it has now become standard treatment in our hospital. The drug should probably be used with care, if at all in children with behavioural difficulties as behaviour may deteriorate rapidly during treatment.[6]

At follow up, the patients have stopped taking the drug as soon as the itching has stopped. For some, this is about 4 months; others have been taking it for up to 12 months, especially if their wounds are hypertrophied.

We have shown that gabapentin is an effective treatment for post-burn pruritis. We hope that larger burns centers will be able to research further into this promising new therapy.

SUMMARY

The study comprised of 23 patients of burns with hypertrophic scars due to thermal, electrical and scald burns. Almost all the patients gave history of delayed healing of wounds [more than 3 weeks].

Out of 23 patients, 18 [78.2%] had sustained thermal burns, 3 [13.04%] sustained electrical burns with flash injuries, and 2 [8.6%] had sustained scald burns.

Out of 23 patients, 10 patients were adult males, 9 were females, and 4 were children.

We took detailed history of all these patients regarding the nature of burns, the type of treatment they received, time taken for burns to heal. Medical history of neurological and behavioral disorders, history of renal dysfunction, pregnancy was ruled out before stating the Gabapentin therapy. Any hypersensitivity to Gabapentin or other anticonvulsants was ruled out.

All the patients were thoroughly explained about the Gabapentin, its actions, side effects and precautions. Any doubt of the patient regarding the drug was properly clarified. The information and consent sheet was given to patient or the patient's parents if the patient was a minor. After the patients read and understood, the consent sheet was signed by them and they were enrolled in to the drug trial.

Most of the patients chosen were local patients who can come for regular follow up and dose adjustment, for patients who are from far away places, advise was

given to stay in the city for at least one week for assessing the side effects and dose adjustment.

Most of the patients were started with 100 mg of Gabapentin twice daily and gradually increased to 200 -300 mg thrice daily depending on the improvement of relief from itching and tolerance to the drug. Most of the patients had minimal side effects like headache, dizziness, and nausea most of which subsided with continuation of treatment, dose adjustment or addition of symptomatic drugs like paracetamol, and domperidone.

No patients experienced any serious side effects after starting Gabapentin. All the patients were advised to come back after a week for dose adjustments.

A itch score questionnaire was given to them before starting the therapy and same questions were asked at weekly interval for 3 months and once in fortnight for another 6 months through telephone. Patients were called to O.P.D only in case of problems. All the scores were tabulated in a file and assessed about their improvement.

More 80% of patients showed fairly good relief from itching within one month of starting the treatment and continued the treatment for 6 months to 1 year depending upon the severity of their burns. All patients were relieved form discomfort of itching, were able to concentrate in work and school. House wives could do work better at home. Patients could sleep well without itching in the night times. Overall the quality of life was improved considerably.

Only 3 patients showed moderate or little improvement from gabapentin. They had long history of burns and extensive area of burns.

Exact reason why these patients were not relieved from itching was not known. These 2 patients were lost for long term follow up.

Especially children showed remarkable improvement from itching after starting gabapentin. They showed improved performance in studies and extra-curricular activities. We have started gabapentin as a protocol for most of the patients with hypertrophic scars in our hospital.

CONCLUSIONS

1. Gabapentin effectively combats post burn itching in patients with hypertrophic scars.

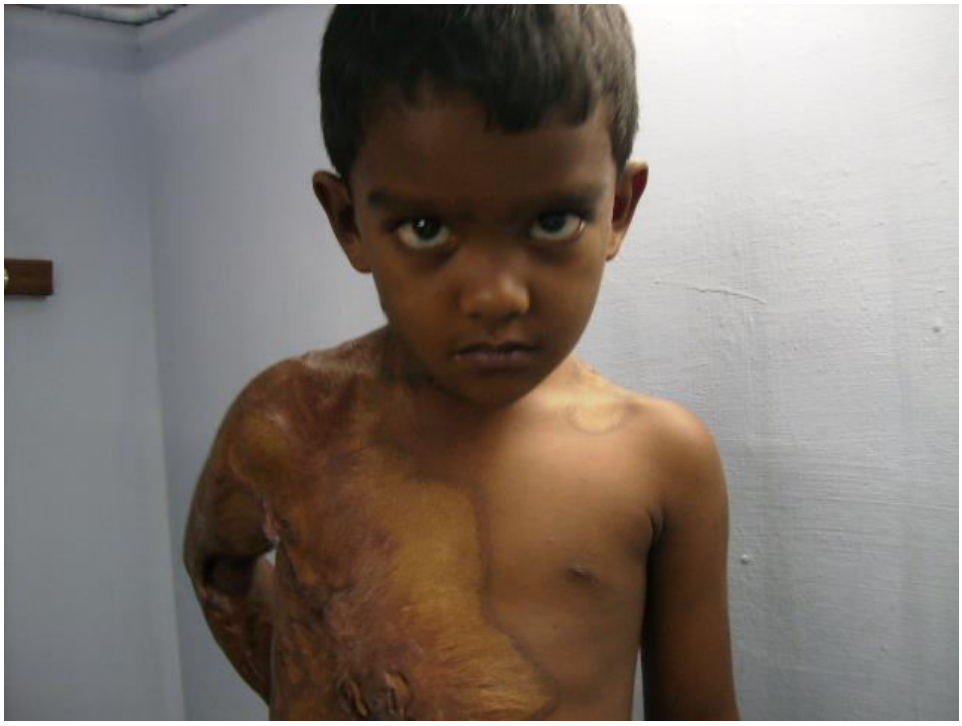
2. Gabapentin showed improvement in work & play, improvement in quality of sleep.

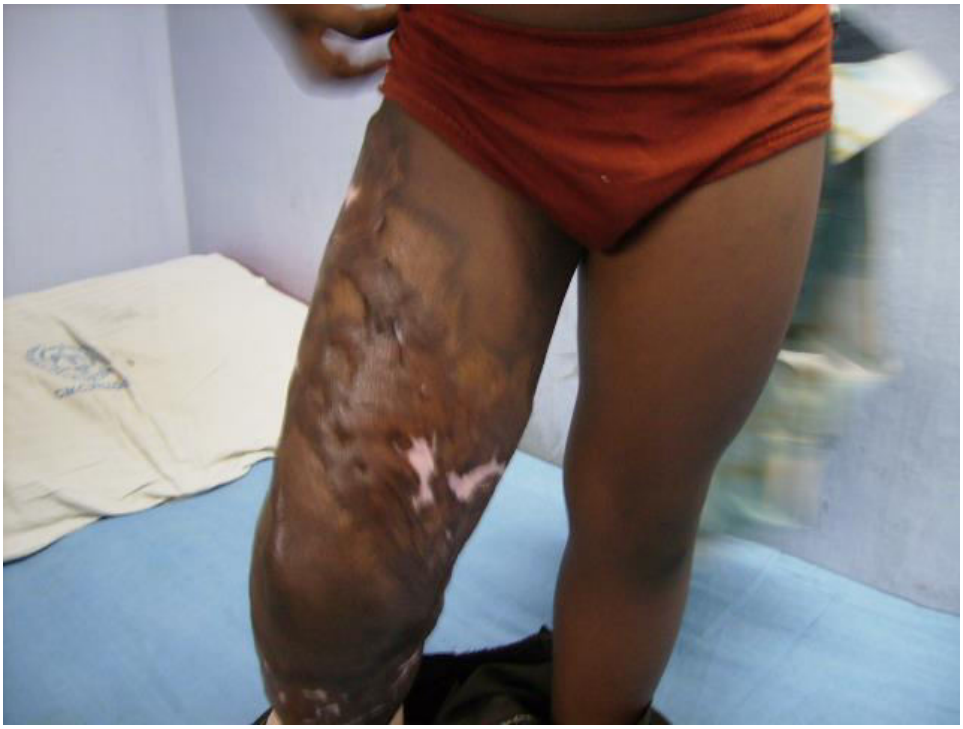
3. Gabapentin showed marked co-operation of patients to therapy during post operative period.

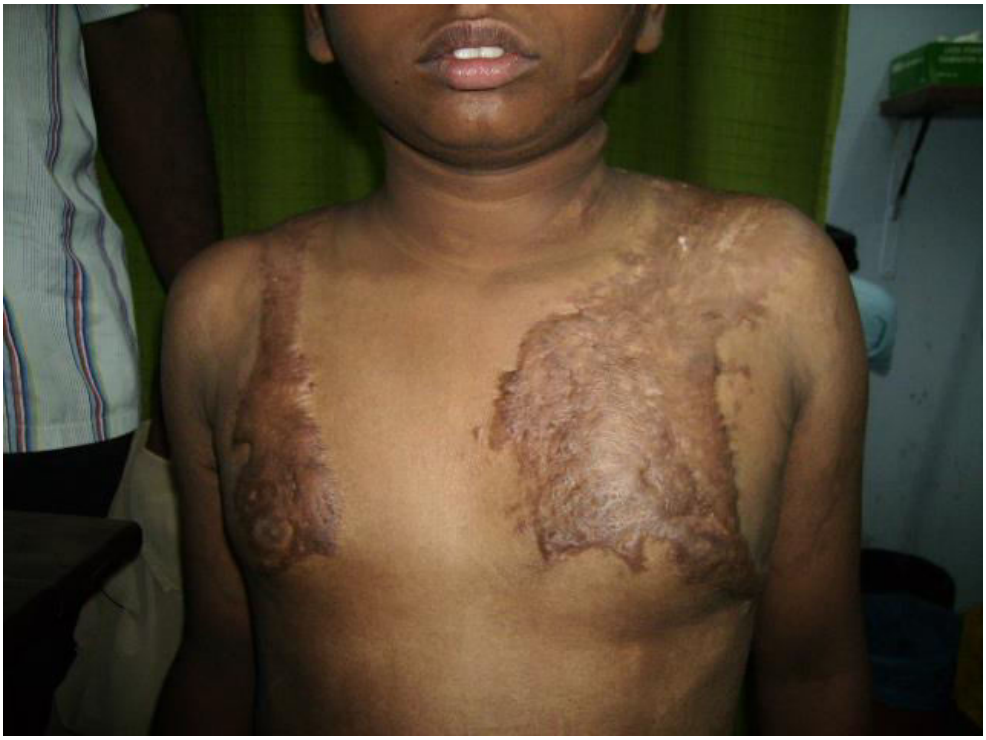
4. It reduced depression and anxiety in post burn patients with itching.

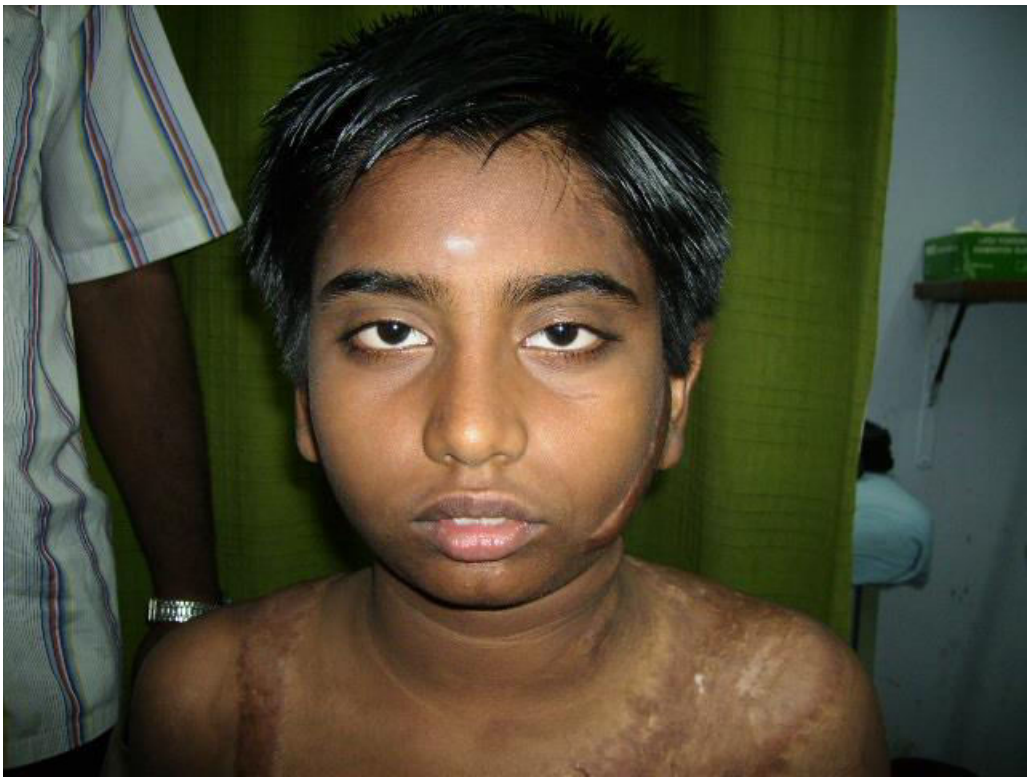
5. Gabapentin brought about an overall improvement in the quality of life in patients with post burn itching.

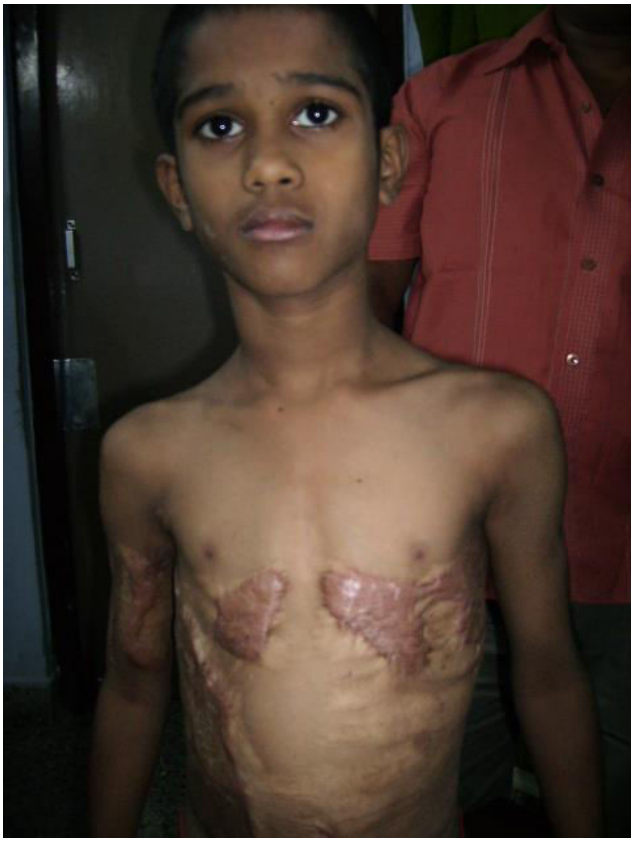
PATIENT PHOTOGRAPHS

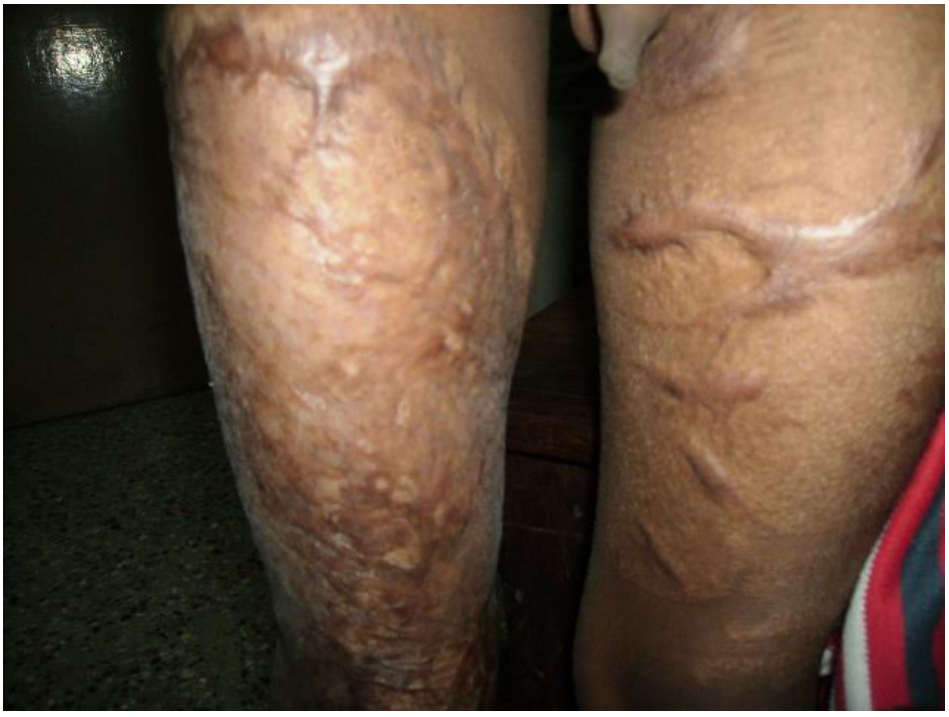


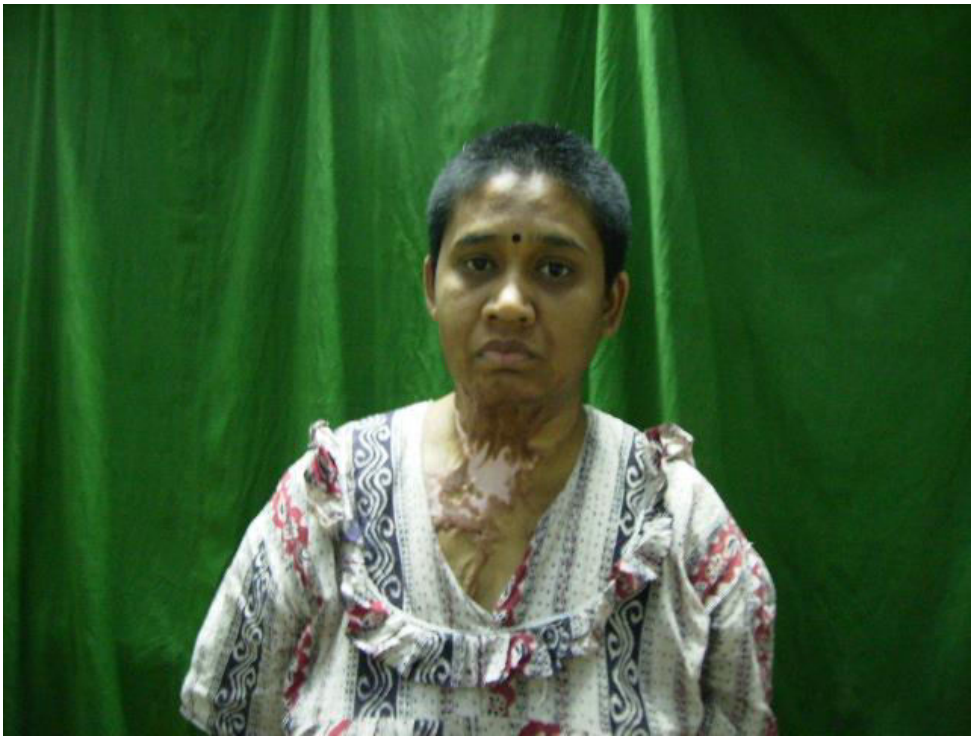












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ANNEXURE-1 PROFORMA

Christian Medical College, Vellore
Department of Plastic Surgery

Study of role of Gabapentin in post burn itching.
Information sheet

You are being requested to participate in a study to see if a drug called *Gabapentin* can help you with post burn itching . We hope to include about 40 people from this hospital in this study.

What type of drug is Gabapentin?
Gabapentin is an anti epileptic drug used in the treatment of seizures. It has been shown to reduce itching after burns.

Does *Gabapentin* have any side effects?
The side effects are minimal as you will be taking low dose of Gabapentin. However, side effects are nausea, vomiting, fatigue, headache, hyperkinesis, emotional lability, and behavioral problems.

If you take part what will you have to do?
If you agree to participate in this study, you will be given the tablet Gabapentin, to be taken three times a day.
All other treatments that you are already on will be continued and your regular treatment will not be changed during this study. You will be expected to come for a review to the hospital 2 weeks after starting the tablet and again after 4 more weeks and finally after a further 4 weeks. Before starting the study and at each visit you will be asked questions about your sleep. No additional procedures or blood tests will be conducted routinely for this study.
If at any time you experience any problems, you will be expected to report this to the doctor. You will also be contacted by telephone at least once in between the monthly visits by the doctors in this study who will ask you about any side effects you are experiencing.

Can you withdraw from this study after it starts?
Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. In addition, if you experience any serious side effects or your condition worsens, the study tablets will be stopped and you may be given additional treatment.

What will happen if you develop any study related injury?
We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will you have to pay for the study tablets?
Yes. You need to buy these tablets. The cost of tablets per day will be around 10 rupees.

How long I should take these tablets?
You are expected to take tab. Gabapentin for 2 months.

What happens after the study is over?
You may or may not benefit from the study drug that you are given. Once the study is over, If Gabapentin has helped you and you wish to continue, then your doctor may prescribe it for you.

Will your personal details be kept confidential?
The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

1. **If you have any further questions, please ask**: **Dr. Aravind Lakshmanarao Department of Plastic Surgery, CMC, Vellore. Ph.04164212017.** email id : aravindlakshmanaro@gmail.com **or: Dr. M. Kingsly Paul, Associate Professor, Department of Plastic Surgery, CMC, Vellore. . Ph.04164212017.**

CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: ***Role of Gabapentin for the treatment of itching produced by acute burns and hypertrophic scars.***

Study Number:
Participant's name:
Date of Birth / Age (in years):

I_____
_____, son/daughter of _____

(Please tick boxes)
Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]
I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
I am aware that I have to take the tablet called Gabapentin for the period of three months.
I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]
I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
I understand that my identity will not be revealed in any information released to third parties or published [ ]
I voluntarily agree to take part in this study [ ]

Name:
Signature:
Date:

Name of witness:
Relation to participant:
Date:

ANNEXURE-2 MASTER CHART

NO	Sl.	NAME	HOSP.NO	AGE/SEX	STARTED ON	PRE GABA SCORES	POST GABA SCORES -- WEEKLY									POST GABA SCORES -- FORTNIGHT										REMARKS
							1st MONTH				2nd MONTH					3rd MONTH			4th MONTH		5th MONTH		6th MONTH			
	1	CHITRA	006629D	29 / F	07/10/2008	14	9	8	9	8	10	9	8	8	8	9	8	9	8	9	8	8	8	8		Trial given after 3 months. Total duration 9 months.
	2	BHARAT	323006D	12 / M	26/09/2008	14	9	9	8	10	8	7	9	8	8	8	9	9	8	8	7	8	7	8		Trial given after 3 months. Total duration of course 8 months
	3	DHARUN	422440	5 / M	10/03/2008	13	8	7	8	8	7	7	8	8	9	8	7	7	8	7	8	7	7	7		Trial given after 3 months. Total duration 9 months.
	4	GOMATHY	432440	18 / F	08/06/2008	14	9	8	7	7	7	7	8	7	7	8	8	7	7	7	8	7	7	7		Trial given after 3 months. Total duration 9 months.
	5	MOHAN.G	346721D	28 / M	17/09/2008	13	8	8	8	8	9	7	7	7	8	8	8	7	7	7	8	8	7	7		Trial given after 3 months. Total duration 9 months.
	6	PALANIYAPPAN	401752D	36 / M	12/10/2008	14	8	7	7	7	7	7	7	8	7	7	8	7	7	7	7	8	7	7		Trial given after 3 months. Total duration 9 months.
	7	LAKSHMI	198957D	23 / F	16/12/2008	12	10	9	8	9	9	8	9	9	9	8	8	9	9	9	8	9	9	9		Trial given for 3 months. Total duration 6 months.
	8	JAYABALAN	432456D	43 /M	14/10/2008	13	12																			Lost to follow up
	9	SARASWATHI	474292D	22 / F	12/06/2009	12	11	11	10	8	9	10	9	8	9	9	8	8	9	8	9	9	8	8		Trial given after 3 months. Still on therapy
	10	PUTUL TIWARI	542376d	36 /M	08/02/2009	14	12																			Lost to follow up
	11	JAYANTHI	160532D	30 / F	25/06/2008	14	9	8	8	9	10	9	8	7	8	8	9	9	8	8	8	9	8	9		Trial given after 3 months. Total duration 7 months.
	12	SARAVANAN	240849C	35 / M	10/05/2009	13	10	9	8	8	8	9	8	9	9	9	8	8	8	8	9	9	8	8		Trial given after 3 months. Total duration 6 months.
	13	SAKTHI	519689D	37 / M	11/06/2009	13	9	8	9	8	9	9	8	8	8	9	9	8	8	8	9	9	8	9		Trial given after 3 months. Total duration 7 months.
	14	JOSEPH	603732C	28 / M	10/02/2009	13	8	8	9	8	7	8	9	9	8	8	8	7	7	8	8	8	7	8		Trial given after 3 months. Total duration 8 months.
	15	VALARMATHI	401654D	39 / F	14/12/2008	12	9	9	8	8	9	9	9	8	9	8	8	9	9	8	8	9	9	9		Trial given after 3 months. Total duration 6 months.
	16	SANGEETHA	291202D	25 / F	16/08/2008	13	8	7	8	8	9	8	8	9	8	7	8	8	7	8	7	8	9	8		Trial given after 3 months. Total duration 9 months.
	17	SHANKAR	543245d	35 /M	12/08/2008	14	13																			Lost to follow up
	18	RAMESH	402578D	9 / M	12/01/2009	14	9	8	9	8	9	9	8	8	7	8	8	7	8	9	8	8	8	8		Trial given after 3 months ,total duration 5 months
	19	CHONG BALAMA	404087D	45 / M	10/11/2009	12	8	9	9	9	8	10	9	8	9	9	8	9	9	8	9	9	9	9		Trial given after 3 months. Total duration 9 months.
	20	RAHUL	260571D	9 / M	21/01/2009	14	9	8	9	8	8	7	7	8	7	8	8	9	8	8	7	8	8	7		Trial given after 3 months. Total duration 8 months.
	21	TANDRA DAS	584481D	27 / F	14/01/2009	14	8	8	7	9	8	7	7	7	8	7	8	7	8	7	7	8	7	7		Trial given after 3 months. Total duration 8 months.
	22	SWAPNA	512547D	29 / F	22/12/2008	15	9	8	7	7	8	7	8	7	7	7	8	7	7	8	7	7	7	7		Trial given after 3 months. Total duration 8 months.
	23	SANJAY GORAI	557197D	28 / M	20/02/2009	14	10	8	7	8	7	7	9	7	7	8	7	7	7	8	7	7	8	7		Trial given after 3 months. Total duration 8 months.