A COMPARISON OF TOPICAL DIPHENYLHYDANTOIN WITH A STANDARD THERAPY IN BURN WOUNDS AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM, TANZANIA.

BY

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CERTIFICATION

The Undersigned certifies that he has read and hereby recommend for acceptance by the University of Dar es Salaam a dissertation entitled: *A comparison of topical diphenylhydantoin with a standard therapy in burn wounds at Muhimbili National Hospital, Dar es Salaam, Tanzania.* in partial fulfillment of the requirements for the degree of Master of Medicine (Surgery).

Prof. C. Mkony, MD, M MED

Supervisor.

DECLARATION & COPYRIGHT

I declare that, this dissertation is my own work and that it has not been submitted to any other University or academic institution for a similar or any other academic award.

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DEDICATION

To my parents: my father Josephat who did not survive to see the achievement of a son, my mother Maria Nyebilwechi who encouraged and supported me all the way through.

ABSTRACT

A prospective randomized controlled study was done at Muhimbili National hospital in adult and paediatric surgical wards to compare topically applied diphenylhydantoin (phenytoin) with a standard therapy (silverex) in the treatment of small to moderate 2^0 burn wounds.

Comparison was made in terms of rate of healing, effect on burn wound pain, elimination of burn wound infections, hospitalization period and the outcome of wounds.

Sixty four patients were enrolled in the study between July 2000 and February 2001. Daily cleaning of wounds was done with normal saline and then either diphenylhydantoin powder or silverex powder was sprinkled on the wounds. Parameters for observation included pus discharge, smell, pain, wound size reduction and, wound swab cultures on three occasions. Manual data analysis and Epi Info 2000 computer Programme was used for statistical testing of results.

The majority of patients in the study were children under five (67.2%), 51.6% of patients were males and 48.4% were females. Pus discharge was noted in 59.4% of patients on diphenylhydantoin and in 75% of patients on the standard therapy during the study. This difference was

not statistically significant. Significant reduction in bacterial contamination of wounds was noted in diphenylhydantoin-treated wounds (P=0.001). Also significant relief of pain was noted in patients managed with diphenylhydantoin (P=0.01).Diphenylhydantoin showed faster wound healing, better wound outcome and, a shorter period of hospitalization when compared to standard therapy.

The findings indicate that the treatment of small to moderate burn wounds can be improved with the use of topical diphenylhydantoin powder. Diphenylhydantoin reduces wound pain and produces a highly significant reduction in positive bacterial cultures of treated wounds, reducing the need for analgesics and antibiotics in these patients. There were no adverse effects due to diphenylhydantoin noted during the study. This drug is cheap and easy to use, and making it widely available countrywide for treatment of burn wounds may prove highly beneficial

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LIST OF ABBREVIATIONS

A.D	Anno Domino
B.C	Before Christ
TBSA	Total Body Surface Area

1. INTRODUCTION:

Burn injury is a common surgical problem and leads to a loss of many working hours, prolonged hospitalization, permanent disability and mortality among burn victims in Tanzania and around the world.

Every year in the United States more than 1.25 million people sustain burns[1]. In the United Kingdom, about 700-800 deaths in a year result from burns and scalds- related conditions[2]. Muniu et al observed that burn injury was the leading cause of mortality following non-transport injuries in Nairobi[3].

The incidence of burns in Tanzania has not been documented. Some of the factors contributing to the incidence of burn injury in the developing world include poor architectural design of cooking places with open fires at floor level and sometimes in the open[4,5,6].

In a study done in 1974, Kimati put burns in the 3rd rank among the causes of childhood accidents in Dar es Salaam[7]. Also a high proportion was reported by Shija et al of 33% among the causes of paediatric trauma in a review of paediatric surgical admissions at the then Muhimbili Medical Centre, Dar es Salaam[8] for the period from 1972-1979.

Burn is a leading cause of death in the paediatric surgical unit at Muhimbili National Hospital where children up to the age of 10 years with surgical problems, including burns, are admitted. An average of 10 new burn cases are admitted every month and approximately two of them (20%) die (morbidity and mortality report 2000, Department of Surgery).

While major burns are a specific entity requiring specialized, intensive care, the more common small- to -moderate sized second degree burns are a major source of patient morbidity and suffering and have enormous economic impact in medical cost and loss of time from school and work.

Most deaths from extensive burns are related to fluid- electrolyte imbalances and other systemic effects of severe burns, but a great deal of morbidity and even mortality is related to the local complications of the burn wound itself.

The care of the burn wound is therefore important and has a strong influence on the outcome of the patient. Various ways have been recommended to manage a burn wound in order to avoid or minimize

bacterial invasion and proliferation. Exposure or closed methods can be used in the management of burn wounds. Exposure and drying of the surface may be regarded as the natural way to treat a wound.

Various products are now available in the market for burn wound dressing. However, most of these products are expensive and may not be available in developing countries like Tanzania.

Available data indicate that topical application of diphenylhydantoin sodium (phenytoin) is beneficial in the management of burn wounds[9,10,11]. A prospective, randomized controlled study to assess the effect of topical diphenylhydantoin on the rate of wound healing, effect on burn wound pain, suppression of infection and period of hospitalization when compared to standard topical therapy alone in the treatment of small to moderate second degree burn wounds was conducted during the period from July 2000 to February 2001 in the Department of Surgery, Muhimbili National Hospital, Dar es Salaam.

2. LITERATURE REVIEW:

2.1.Historical Background.

Leaves, feathers, honey, tree bark, rags and paper have all played a part in wound treatment through the ages. Dried goats' dung, honey boiled in vinegar, heads of soldier ants and boiled puppies have also been used through the ages in the management of wounds[12].

The Egyptians treated burns by incantations and a mixture of gum, goats' hair, and milk from a woman who had given birth to a son[13]. Neanderthal man treated burns with extracts of plants. Between the sixth and fifth centuries B.C, the Chinese and Japanese used tinctures and extracts made from tea leaves[13]. Around 430 B.C., Hipocrates[13] proposed the use of warm vinegar- soaked dressings to relieve the pain, and he later treated burns by tanning with solutions of oak bark.

Three methods were used in ancient Rome;

1. Celsus described treatment with a mixture of honey and bran, and then cork and ashes.
2. Pliny the Elder wondered if it would not be better to allow burns to remain exposed to the open air rather than covering them with grease.
3. Galen prescribed vinegar or wine.

Paulus of Aegina, a Byrantine of the seventh century A.D. used various emollient preparations. The famous Arabian physician, Rhazes, around the ninth century A.D. used ice-cold water.

In 1827 Syme proposed the use of dry cotton wool dressing applied with firm pressure onto the burn wounds. Lizfrank, in 1835 recommended wet dressings containing sodium and calcium chloride and later in 1858, Passavant promoted the use of saline baths. Exposure method used in the management of burn wounds, was suggested by Sneve in 1905.

Several local medicaments have been in use on the burn wounds since the 20th century. Edward Clark Davidson initiated the use of tannic acid spray in 1925[13]. However, it was abandoned in 1944 because of liver toxicity. In 1942 the use of petrolatum gauze pressure dressings with strict immobilization was introduced. However, it was immediately abandoned because it did not limit fluid loss. It was in the twentieth century that many dressing materials in the market were introduced. Moyer's historic use of Silver nitrate soaks and Moncrief's introduction of mafenide (Sulfamylon) ushered in a new era of local antibacterial agents[13].

It has been a long road from mud and dung dressings to aerosol sprays, a road with many blind alleys and double bends. One wonders how much tetanus and anthrax was caused in this way over the centuries !

2.2. Skin anatomy and function:

The skin is the organ commonly affected by burns. Anatomically, the surface of the body is covered by the skin integument together with certain specialized derivatives of the skin[14].

The skin is composed of two layers[14], the outer layer or epidermis, and beneath this, the dermis or corium of vascular dense connective tissue. These two layers adhere firmly to each other and form a membrane that varies in thickness from 0.5 to 4mm or more in different parts of the body. Skin is also classified as thick or thin. Thick skin is found on the palms of the hands and soles of the feet: thin skin covers the remainder of the body.

The primary function of the skin is to serve as a protective barrier against the environment[15]. Loss of the integrity of large portions of the

skin as a result of injury or illness may lead to major disability or even death. The skin protects the organisms from injurious substances and influences; it provides a barrier to invasion by microorganisms, it helps to regulate the temperature of the body, by sweating it excretes water and various waste products of catabolism; it is the most extensive sense organ of the body for the reception of tactile, thermal and painful stimuli.

2.3. Aetiology of burns:

Burns are caused by the application of heat on the body surface. Open flame and hot liquids are the most common heat sources[16]. Of all burns, scalds are the most common. They are often of limited extent and depth, and heal quickly with insignificant scarring, but may be extensive and deep[17]. In adults, the most common thermal burns are those due to flame (40 -45%), while in children, thermal injuries are most commonly caused by scalding by hot liquids[17]. Similar views were shared by Kalayi[18] when he reported that scalds was the leading cause of burn injury in children. However he noted that on the whole, open flame was the predominant injury. Other investigators put scalds on the top among the cause of burn injury in children[8,19].

Flame burns tend to destroy the full thickness of part of the burn area. Conduction burns from electrical domestic appliances are always full thickness. Other causes of burns are explosion of inflammable gases or vapours or the discharge of electricity and chemical burns resulting from industrial accidents or assault (non-accidental injuries).

2.4. Burn wound classification

Guilhelmus Fabricius Hildanus in 1607 recognised three degrees of burns. L. Heister classified burns into four degrees rather than three and later, in 1832, Baron Guillaume Dupuytren classified burn lesions into six degrees of injury[13]. Classification of a burn wound is related to its extent and depth. While the extent is estimated as percentage of total body surface area (TBSA), the burn depth can be classified as first, second or third degree burn injury[20].

The extent of burn injury in adults is determined by using the Wallace's rule of nines, whereby anatomical regions of the body are considered to represent 9 percent of TBSA; each upper limb, 9%; each lower limb, 18%; anterior and posterior trunk, each 18%; head and neck, 9%; and perineum and genitalia, 1%[17,21,22]. The Lund and Browder Burn Diagram is used when calculating the body surface area burnt in children[17,22]. In the Lund and Browder Burn Diagram, the burn shape is

drawn on the chart and the proportion of each area included in the drawing is entered in a table and added up to give the total percentage of burn surface area. Another way of estimation in adults is by the use of the patient's hand: this method uses the palmar surface of the patients' hand to represent 1% of body surface area. The general consensus is that the whole of the open palmar surface, including fingers, is about 0.8 to 0.9% of total body surface area so this method will usually over-estimate the burn size[22].

Different classifications of depth of burn wound exist. Here a three-degree category is described. In first-degree burn, there is thermal damage to the superficial cells of the epidermis. The skin is dry, hyperaemic, erythematous, painful and usually without bullae. Healing typically occurs within 3 -6 days, often associated with a peeling off of the non- viable superficial epidermis[20,21].

A second degree or partial thickness burn is either superficial or deep dermal burn. Superficial second-degree burns involve the epidermis and also upper layer of dermis[17]. There is formation of blisters and exudation of serum. The wound has a mottled appearance, moist and extremely sensitive to pain. It heals spontaneously within 3 weeks from local epidermal elements, from hair follicles, and sebaceous glands with very little, if any scarring[21].

Deep dermal burn involves the deeper dermal elements. The wound is cherry -red or yellow white (pale) in appearance. The burn surface feels indurated, or boggy, and does not blanch on pressure. Some areas may be insensitive or anaesthetic to pinprick. Deep pressure sensation remains intact. These wounds require over 3 weeks to heal and often do so with significant scarring.

In third degree burn wounds there is complete destruction of the whole thickness of the skin, including all of its appendages. The wounds are pearly white or charred in appearance and often have thrombosed visible superficial veins. These wounds are insensitive to pain. The wounds if small, can heal from the edges by scar formation, but for the most part must be repaired by skin grafting[21].

Assessment of area and depth of a large burn is not easy and is complicated by the fact that burn wounds may change in size and depth with time and different parts of a burn wound may be of different depths. However, this differentiation is of great consequence in terms of subsequent wound care and the ultimate prognosis and outcome of healing.

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2.5. Wound Healing:

The primary goals of the treatment of wounds are rapid wound closure and a functional and anaesthetically satisfactory healed wound. Wound healing is a dynamic, interactive process involving soluble mediators, blood cells, extra cellular matrix, and parenchymal cells[15]. Wound healing has three phases; inflammatory, tissue formation and tissue remodeling:

2.5.1. Inflammation

Tissue injury causes the disruption of blood vessels and extravasation of blood constituents. The blood clot re-establishes haemostasis and provides a provisional extra cellular matrix for cell migration. Platelets facilitate the formation of a haemostatic plug and secrete several mediators of wound healing e.g. Platelet-derived growth factors, which attract and activate macrophages and fibroblasts[23]. The coagulation and activated-complement pathways generate numerous vasoactive mediators and chemotactic factors.

Infiltrating neutrophils cleanse the injured area of foreign particles and bacteria, which are extruded within the eschar or phagocytosed by macrophages[15].

In response to specific chemoattractants, monocytes also infiltrate the wound site and become activated macrophages that release growth factors such as platelet - derived growth factor and vascular endothelial growth factor, which initiate the formation of granulation tissue. The monocyte and macrophage - derived growth factors are almost certainly necessary for the initiation and propagation of new tissue formation in wounds, because macrophage-depleted animals have defective wound repair[24].

2.5.2. Epithelialisation

Skin has a covering of squamous epithelium cells, which are constantly being shed and replaced from below. When a defect is made in the squamous covering, the cells at the wound edge multiply, flatten and migrate towards the area of cell deficit. Re-epithelialisation of wound begins within hours after injury[15].

Extensive superficial injuries such as 2^0 burns epithelialise not only from the wound edge, but also from hair follicles and other deep dermal appendages that supply live squamous cells. Epidermal and dermal cells cease to adhere to one another because of the dissolution of hemidesmosomal links between the epidermis and the basement

membrane, this allows the lateral movement of epidermal cells. The migrating epidermal cells dissect the wound, separating desiccated eschar from viable tissue.

The degradation of the extra-cellular matrix depends on the production of collagenase by epidermal cells[25] and the activation of plasmin by plasminogen activator produced by the epidermal cells. One to two days after injury, epidermal cells at the wound margin begin to proliferate behind the actively migrating cells[15]. As re-epithelialisation ensues, basement membrane protein reappears in a very ordered sequence from the margin of the wound inward, in a zipper like fashion.

2.5.3. Formation of Granulation Tissue

Granulation tissue begins to invade the wound space approximately four days after injury. Macrophages, fibroblasts and blood vessels move into the wound space at the same time. The macrophages provide a continuing source of growth factor necessary to stimulate fibroplasia and angiogenesis.

Growth factors, especially platelet-derived growth factor and transforming growth factor β_1 stimulate fibroblasts of the tissue around the wound to proliferate, express appropriate intergrin receptors and

migrate into the wound space. The fibroblasts are responsible for the synthesis, deposition and remodeling of the extra-cellular matrix. Once they have migrated into the wound, fibroblasts commence the synthesis of extra cellular matrix[26,27] which is replaced by a collagenous matrix. Once an abundant collagen matrix has been deposited in the wound, the fibroblasts stop producing collagen, and the fibroblast-rich granulation tissue is replaced by a relatively acellular scar.

2.5.4. Neovascularization

The formation of new blood vessels is necessary to sustain the newly formed granulation tissue. Many molecules like vascular endothelial growth factors, transforming growth factor β_1, angiogenin, angiotropin among others, appear to induce angiogenesis by stimulating the production of basic fibroblast growth factor and vascular endothelial growth factor by macrophages and endothelial cells[15]. Appropriate extracellular matrix and endothelial receptors for the provisional matrix are necessary for angiogenesis.

2.6. Burn Wound Management

In treating a burn wound the aim remains to make the healing process as comfortable as possible and to produce the best quality scar.

Unfortunately, the healed area may consist of poor skin that may break down or scar. More superficial 2^0 burns heal in two weeks. In the acute phase, pain control, prevention of infection and promotion of healing are critical therapeutic goals. Infection delays healing and may transform a partial thickness injury into a full thickness one. The management of the wound should neither retard nor inhibit any part of the healing process. The procedure used and the dressing applied must therefore contribute to the production and maintenance of an environment as close to the optimum as possible.

Current burn wound treatments range from debridement, cleaning with normal saline and exposure treatment or simple dressing with use of topical antimicrobials, use of artificial and other skin substitutes, and when necessary, skin grafting. A dressing should be comfortable when applied, worn or removed. A non-irritating and non-toxic agent should be applied in the dressing to deter infection. The most commonly used antimicrobial agents are silver sulphadiazine, silver nitrate, povidone-Iodine and chlorhexidine cream.

Silver sulfadiazine is a poorly soluble compound readily synthesized by reacting silver nitrate with sodium sulfadiazine[28]. The in vitro antimicrobial spectrum of silver sulfadiazine is appropriately wide and

includes S. aureas, Enterobacteriacae, E.coli and Candida albicans. Sulfadiazine is a well-known competitive inhibitor of para-aminobenzoic acid. It has a highly efficient prophylactic value, particularly against gram-negative bacteria.

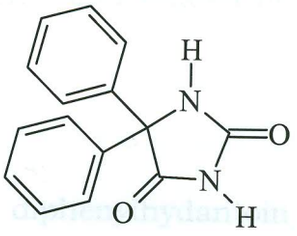
Recently there has been a potential emergence of sulfadiazine resistance. Some absorption of sulfadiazine occurs depending on the size of the burn and the interval post injury. Transient leukopenia typically occurring after the first few days of application in about 5% of patients and cutaneous sensitivity reactions to silver sulfadiazine occurs in 5% or less of patients[28].

When selecting a topical agent some criteria are important like in vitro and clinical efficacy, toxicity, super infection rate, ease and flexibility of use. Other considerations are costs, patient acceptance and side effects.

2. 7. Diphenylhydantoin (Phenytoin)

Biltz first synthesized phenytoin in 1908, but its anticonvulsant activity was not discovered until 1938. It was introduced for the symptomatic treatment of epilepsy in the same year[29].

Diphenylhydantoin has the following biochemical structure[29] ;



It is a weak acid with a Pka of about 8.3. Absorption of diphenylhydantoin after oral ingestion is slow, sometimes variable, and occasionally incomplete. Diphenylhydantoin is extensively (about 90%) bound to plasma protein, mainly albumin. Approximately 2% of phenytoin is excreted unchanged in the urine. Primarily the hepatic microsomal enzymes metabolize the remainder. The toxic effects of diphenylhydantoin depend upon the route of administration and duration of exposure as well as dosage. First observation was gingival hypertrophy in patients on diphenylhydantoin[29,30]. Gingival hyperplasia occurs in about 20% of all patients during chronic therapy[29]. Since then diphenylhydantoin sodium has been reported to promote wound

healing when applied as a topical agent[11]. Earlier studies report no transwound absorption of diphenylhydantoin[9,11].

Apart from treatment of epilepsy, diphenylhydantoin a hydantoin derivative, is a pharmacological agent that has been employed in the treatment of many medical conditions including cardiac arrhythmias, muscle disorders, trigeminal and related neuralgias and other types of pain.

Used topically or orally diphenylhydantoin has been reported to be efficacious in the treatment of skin and soft tissue wounds and ulcers of various types. Shapiro noted the effects of diphenylhydantoin on the healing of gingival wounds in 1958[30].

Recently, there has been increasing evidence supporting earlier observation, that diphenylhydantoin has a distinct beneficial role in the biology of wound repair. Evidence indicates that diphenylhydantoin stimulates collagen formation, a phenomenon noted clinically as gingival hyperplasia also described as increased bulk of dense collagen fibres[29,31].

The tensile strength of skin wound in operated rats pretreated with diphenylhydantoin has been shown to be significantly greater when the rats are sacrificed as early as three to four days after surgery[31]. Kolbert[32] noted that oral diphenylhydantoin induced increased wound strength in the early stage of wound healing.

Muthukumarasamy et al in their prospective controlled trial found that the use of diphenylhydantoin topically promotes healing of diabetic ulcers and that it is both effective and safe. Its use reduced patient morbidity and hospitalization[33].

Examining effects of topical diphenylhydantoin on the general process of wound healing, laboratory investigations have demonstrated dramatic increases in tensile wound strength in primarily closed skin wounds[31,34]. Other laboratory studies have revealed diphenylhydantoin's stimulation of fibroblast growth in tissue culture[35], inhibition of collagenase and collagen peptidase activity in vitro[36], increase in collagen content and maturation in granulation tissue[37], increase in collagen with concomitant decrease in dermal water and fat in rat skin[38] and diminution of the catabolic effect of cortisol in skin[39].

Several more studies have shown that there is a marked reduction in the degradation of older collagen in tissue culture, inhibition of release of both β-glucuronidase and lactate dehydrogenase, inhibition of extracellular enzymatic degradation of proteoglycans and inhibition of release of lysosomal enzymes[40,41,42,43].

Its ability to reduce pain as well as to promote healing suggests that it should be useful in the treatment of burns. Clinical studies with topical diphenylhydantoin have demonstrated significant improvement and healing of both chronic cutaneous ulcers and acute burn wounds[9,44]. Biopsies of the diphenylhydantoin-treated burns showed increased fibroblast proliferation, increased neovascularisation and capillary patency and increased collagen content. Decreased wound water loss and bacterial contamination and infection were also noted. No adverse reactions (including contact dermatitis, other manifestations of hypersensitivity or chemical toxicity) have been reported in the published studies when used topically. There is strong laboratory[11,31,34,36,37,45] and clinical[9,11,43] evidence that diphenylhydantoin not only enhances the process of wound healing including burns, but also reduces or eliminates associated pain. A clinical trial of diphenylhydantoin's usefulness in second degree burns

in our ethnic, climatic and socio-cultural environment is clearly indicated.

3. STUDY RATIONALE

Various methods are applied in the management of burn wounds in the different wards of the surgical department, Muhimbili National Hospital. No documented comparison has been made on the effectiveness of these methods.

Available literature indicates that diphenylhydantoin is very effective in the treatment of burn wounds. Evidence indicates it reduces the period of hospital stay, minimises wound infection, increases rate of epithelialisation and has got a local analgesic effect. This drug is not expensive. Minimal adverse reactions have been reported from the various studies done in some areas. There are no studies documented in Tanzania or our region on the use of diphenylhydantoin in the treatment of wounds.

Therefore the study was designed to evaluate the effectiveness of diphenylhydantoin in acute 2^0 burn wounds. The results to be presented and discussed are expected to influence positively the management of burn wounds in Tanzania and other countries with a similar resource-scarce situation.

4. OBJECTIVES:

4.1 BROAD OBJECTIVE.

To compare topical diphenylhydantoin with silverex in the treatment of small to moderate second-degree burn wounds.

4.2 SPECIFIC OBJECTIVES;

1. To determine the aetiology of 2^0 burn wounds in patients admitted at Muhimbili National Hospital surgical wards.
2. To determine the rate of decrease in wound size in 2^0 burn wounds treated with diphenylhydantoin powder compared to silverex powder treatment.
3. To compare the effect of diphenylhydantoin and silverex on burn wound pain in patients with 2^0 burns.
4. To compare the bacterial suppression activity of diphenylhydantoin and silverex in 2^0 burn wounds.
5. To determine the period of hospitalization of 2^0 burn patients treated with diphenylhydantoin compared with silverex treatment.

5. PATIENTS AND METHODS

5.1 TYPE OF STUDY

This is a randomized controlled prospective study. The cases were those patients with 2^0 burn wounds who were dressed with diphenylhydantoin (Phenytoin) and the controls were those patients with 2^0 burn wounds dressed with silverex.

Silverex is a common antimicrobial topical agent used in burn and other wounds. It is a preparation of silver sulfadiazine and chlorhexidine hydrochloride. It is marketed in a powder form or as a cream. Silverex was used as a standard therapy in a powder form.

5.2 STUDY AREA

The study was conducted in the surgical wards (adult and paediatric) at Muhimbili National Hospital from July, 2000 to February, 2001. Muhimbili National Hospital has 1500 bed capacity. It is the main consultant referral hospital in Tanzania but it also serves about 3 million or so inhabitants of Dar es Salaam city and its surroundings. The hospital has inpatient wards for all major clinical disciplines including Surgery.

The Department of Surgery has 5 adult wards and one ward for children up to the age of 10 years, making a total bed capacity of 290.

5.3 STUDY POPULATION

Both children and adults were enrolled in the study.

5.3.1 Inclusion criteria

Male and female patients who were clinically assessed to have 2^0 burn injury with extent of 30% total body surface area or less for adults and 20% total body surface area or less for children. More extensive burns were excluded to avoid dealing with the systemic effects arising from such extensive burns. The extent of burn injury in adults was determined by the use of Wallace's rule of 9 (appendix II), while the Lund and Browder burn diagram (appendix III) was used to determine the extent of burn injury in children. Assessment of the extent of burn injury was done by the author.

5.3.2 Exclusion criteria

1. Hypersensitivity to diphenylhydantoin
2. Patients on oral diphenylhydantoin

3. Subjects with any other condition or therapy which in the opinion of the investigator might pose a risk to the subject should he/she be entered into the study.
4. Patients on immunosuppressive or steroid therapy.
5. Pregnant mothers.

5.4 SAMPLE SIZE AND STUDY DESIGN

5.4.1 Sample size

After establishing eligibility, 64 patients were entered in the study and randomly assigned in sequence using a service of sealed envelopes to either the topical diphenylhydantoin or standard treatment therapy.

The sample size was determined by the following formula (Analytical study):

.

$$n = \frac{(Z\alpha/2 + Z\beta)^2 [(P_1(1-P_1) + P_2(1-P_2)]}{(P_1-P_2)^2}$$

Where; n = sample size per group.

$Z_{\alpha/2}$ = point on standard normal distribution.

α = Significance level.

$1-\beta$ = power of the study.

β = type II error rate.

P_1 = proportion (estimated) of patients recovering with standard therapy[10].

P_2 = proportion (estimated) of patients recovering with diphenylhydantoin therapy[10].

The significance level $\alpha = 0.05$

Hence $Z\alpha/_2 = 1.96$.

Power of the study; $1-\beta = 1-0.15 = 0.85 = 85\%$.

Hence $Z_\beta = 1.64$

$P_1 = 50\% = 0.5$

$P_2 = 50\% + 35\% = 85\% = 0.85$.

$$n = \frac{(1.96 \times 1.64)^2 \, (0.5 \, (1 - 0.5) + 0.85 \, (1- 0.85)}{(0.5 - 0.85)^2}$$

= 31.81 appro. 32 Patients per group.

A total of 64 patients were enrolled in the study.

5.4.2 Treatment 1

Cleaning of burn wounds was done with normal saline and the wounds were debrided as needed once daily. Dry thin uniform layer of diphenylhydantoin powder was then sprinkled topically onto the burn wound which was then left open.

Diphenylhydantoin was applied to the burn until uniform healing took place or granulation tissue appeared. It would then be stopped to prevent hypergranulation. The end point of the study was appropriate subsequent therapy (grafting) or complete healing .

5.4.3 Treatment 2

Cleaning of burn wounds was done with normal saline and the wounds were debrided as needed once daily. A thin uniform layer of Silverex powder was sprinkled topically onto the wound which was then left open.

Also the end point of the study was appropriate subsequent therapy (grafting) or complete healing.

5.5 PARAMETERS OF OBSERVATION

Wound swabs were taken from the burn wounds on admission and on days 5 and 10. These swabs were put in Stuart's transport media and delivered to the Microbiology laboratory immediately for culture and sensitivity. Only aerobic cultures were performed as it was impractical to perform anaerobic cultures.

The wounds were inspected daily by the author. The following were assessed:

- **5.5.1 Pus discharge from the wounds.**

  Wounds were inspected daily before debridement and cleaning for presence of pus. Notification of pus at any occasion on a patient's wound was regarded as pus.

- **5.5.2 Wound Pain.**

  Assessment of pain was done three times: on the 2nd, 4th and the 6th days of treatment. This was done at 10 minutes after sprinkling a powder onto the burn wound.

  Adults were asked to report subjectively how they felt in terms of pain after the drug has been applied. They would report it as mild, moderate or severe pain.

  For children who could not express themselves, parents were requested to report how comfortable the child was after

the application of the powder. This was graded as mild, moderate or severe pain. Then these were scored;

Mild pain scored 1, moderate pain scored 2 and severe pain scored 3. A total of 6 or more score points from the three assessments was regarded as pain. A total of less than 6 points was regarded as no pain.

- **5.5.3 Wound size.**

  The wound surface area was also determined. Sterile plain gauzes were applied to exactly cover the burn wound and then using a tape measure the longest vertical and horizontal dimensions were determined. From these measurements the approximate area of the burn wound was calculated by multiplying the 2 dimensions.

  Determination of wound area was done at admission (baseline), day 3, day 7, day 10 and day 14. Measurements were made in centimetres.

- **5.5.4 Odor/smell.**

  During wound review the smell of the wound was determined and recorded as foul or no smell. This observation was done daily.

5.6 DATA ANALYSIS

All data were gathered in a questionnaire (appendix I).Manual analysis of data was done. Statistical testing of data for comparison purposes was done in a computer with the help of Epi Info 2000 computer programme. Statistical significance was assessed using Chi-Square test for categorical variables and Student's t-test for means. The statistical significance level of P-Value less than 5% ($P<0.05$) was used for all comparisons.

5.7 ETHICAL CONSIDERATIONS

The study was submitted to the hospital ethical committee for clearance, which was granted. The whole exercises was conducted after obtaining consent from the patient. For children, the consent was obtained from a parent or a guardian. Relevant information was given to the patient /guardian about the study before he/she gave verbal consent.

The results are presented in the following section:-

6. RESULTS

Patients characteristics

During the study period, July 2000 to February 2001, 64 patients were enrolled in the study, 32 patients in each group.

The majority of patients in this study, 43(68.7%) were children under five. (Table I).

Of the studied patients, 33 (51,56%) were males and 31 (48.44%) were female patients (Table II).

Table I: Characteristics of patients by age

Age groups (years)	Dephenylhydantoin	Standard therapy	Total	
			N	(%)
0 – 4	21	23	44	(68.7)
5 – 9	5	4	9	(I4.I)
10 – 14	2	1	3	(4.7)
15-19	1	1	2	(3.1)
≥ 20	3	3	6	(9.4)
Total	32	32	64	(100)

$\chi^2 = 0.29$, p=0.59

Table II: Characteristics of patients by sex

	Diphenylhydantoin		Standard therapy		Total	
	N	(%)	N	(%)	N	(%)
Males	14	(43.8)	19	(59.4)	33	(51.6)
Females	18	(56.2)	13	(40.6)	31	(48.4)
Total	32	(100)	32	(100)	64	(100)

χ^2 = 1.56, p = 0.21

Table III: Aetiology of burn injury among patients in the study

Aetiology	Diphenylhydantoin		Standard therapy		Total	
	N	(%)	N	(%)	N	(%)
Scalds (Hot liquids	21	(65.6)	30	(93.8)	51	(79.7)
Open flame	11	(34.4)	2	(6.2)	13	(20.3)
Total	32	(100)	32	(100)	64	(100)

χ^2 = 7.82; P = 0.005

In this study there were only two aetiologies causing burns, namely scalds and open flames.

Scalds constituted the aetiology in the majority of patients, 51 (79.7%) and those due to open flame were 13 (20.3%). *(χ^2 = 7.82; P = 0.005).*

Table IV: Circumstances of injury

Circumstance	Diphenylhydantoin		Standard therapy		Total	
	N	(%)	N	(%)	N	(%)
Domestic accident	31	(96.9)	31	(96.9)	62	(96.9)
Assault	1	(3.1)	1	(3.1)	2	(3.1)
Total	32	(100)	32	(100)	64	(100)

χ^2 = 0.50, P=0.48

The majority of patients 62(96.9%) in this study, sustained injury accidentally mainly in domestic accidents. Only two patients sustained non-accidental injuries by being assaulted (Table IV). There was no statistical difference between the two groups (χ^2 = *0.50, P=0.48)*

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Initial topical therapy on the burn wounds.

Immediately after burn injury 42.2% of the patients had honey applied on their wounds prior to coming to hospital. Patients who had their

wounds washed with cold water constituted 21.9%. Ten patients (15.6%) had sugar applied on their wounds. Other substances frequently applied were burn cream and raw eggs (Table V).

In 21.9% of patients nothing was applied on their wounds immediately after the burn injury and prior to coming to hospital.

Table V: Topical therapy applied on the wounds immediately after the burn injury

Agent applied	Diphyeylhydatoin	Standard therapy	Total	
			N	(%)
Honey	13	14	27	(42.2)
Cold water	8	6	14	(21.9)
Sugar	7	3	10	(15.6)
Burn cream	4	4	7	(12.5)
Raw eggs	3	4	7	(10.9)
Sufratulle	4	2	6	(9.4)
Cooking oil	2	-	2	(3.1)
Eusol	2	-	2	(3.1)
Local herbs	1	-	1	(1.6)
Oxy-cort spray	-	1	1	(1.6)
N/Saline	-	1	1	(1.6)
Table salt	-	1	1	(1.6)
Sand/dust	1	-	1	(1.6)
Vaseline	-	1	1	(1.6)
Nil	7	7	14	(21.9)

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Table VI: Chronic underlying illness

Illness	Diphenylhydantoin	Standard therapy	Total	
	N	N	N	(%)
None	30	30	60	(93.7)
Epilepsy	1	1	2	(3.1)
Sickle cell disease	1	-	1	(1.6)
Bronchial asthma	-	1	1	(1.6)

Majority of the patients (93.8%) had no chronic underlying illness. Two patients were suffering from epilepsy but had never been treated with oral diphenylhydantoin.

Table VII: Site of burn wounds

Site	Dephynyhydantoin		Standard therapy		Total	
	N	(%)	N	(%)	N	(%)
Trunk	14	(43.8)	18	(56.3)	32	(50.0)
Upper limbs	10	(31.3)	15	(46.9)	25	(39.1)
Lower limbs	12	(37.5)	10	(31.3)	22	(34.4)
Face	6	(18.8)	10	(31.3)	16	(25.0)
Buttocks	5	(15.6)	5	(15.6)	10	(15.6)
Shoulders	3	(9.4)	1	(3.1)	4	(6.3)
Neck	2	(6.3)	1	(3.1)	3	(4.7)

Half of the patients 32 (50%) had burn injuries on their trunks. Other parts of the body which were commonly injured were found to be upper and lower limbs, 39.1% and 34.4% respectively.

No significant difference between the two groups.

Table VIII: Extent of burn injury

TBSA (%)	Diphenylhydantoin		Standard therapy		Total	
	N	(%)	N	(%)	N	(%)
10– 14	19	(59.4)	14	(43.8)	33	(51.6)
15 - 19	10	(31.2)	10	(31.2)	20	(31.2)
20 – 24	3	(9.4)	8	(25.0)	11	(17.2)
Total	32	(100)	32	(100)	64	(100)

χ^2 = 3.03, P=0.22.

More than half of the patients, 33 (51.6%) patients in the study had burn of less than 15%. Twenty (31.2%) patients had burn in the range of 15-19%. 11 (17.2%) patients had burn surface area in the range of 20-24%. There was no patient with burn surface area of more than 24%.

Patients in both treatment groups were comparable as far as extent of burn injury is concerned *(P = 0.22).*

Status of the wounds.

Table IX: Pus discharge from the burn wounds.

Pus discharge	Diphenylhydatoin		Standard therapy		Total	
	N	(%)	N	(%)	N	(%)
Yes	19	(59.4)	24	(75.0)	43	(67.2)
No	13	(40.6)	8	(25.0)	21	(32.8)
Total	32	(100)	32	(100)	64	(100)

χ^2 = 1.77, P=0.18.

While 59.4% of burn wounds in the Diphenylhydantoin group showed sign of pus discharge, 75% in the standard therapy group showed signs of pus discharge.

Pus discharge was seen in 67.2% of all patients.

There was no significant difference between the two groups *(P=0.18).*

Table X: Presence of foul smell.

Foul smell	Diphenylhydantoin		Standard Therapy		Total	
	N	(%)	N	(%)	N	(%)
Yes	6	(18.8)	10	(31.2)	16	(25.0)
No	26	(81.2)	22	(68.8)	48	(75.0)
Total	32	(100)	32	(100)	64	(100)

χ^2=1.33, P=0.25

In 25% of patients the wounds had foul smell during follow-up. In 75% of patients there was no smell though some had signs of sepsis

There is no statistically significant difference between the two groups *(p=0.25).*

Table XI: Burn wound bacterial cultures

Period on treatment	Diphenylhydantoin		Standard treatment	
	Positive	Negative	Positive	Negative
	N (%)	N (%)	N (%)	N (%)
Pre-treatment (day 0) **(χ^2=0.06,P=0.8)**	13 (40.6)	19 (59.4)	14 (43.8)	18 (56.3)
On day 5 of treatment **(χ^2=7.63,P=0.006)**	12 (37.5)	20 (62.5)	23 (71.9)	9 (28.1)
On day 10 of treatment **(χ^2=16.0,P=0.001)**	3 (10.0)	27 (90.0)	15 (48.4)	16 (51.6)

Burn wound cultures revealed that in the Diphenylhydantoin-treated group, 19 patients (59.4%) had no bacterial growth in pre-treatment cultures and in subsequent cultures, day 5 and 10, 62.5% and 90% had no bacterial growth respectively.

In the standard treatment pre-treatment cultures revealed 56.3% of patients with no growth and the subsequent cultures, day 5 and 10 revealed 28.1% and 51.6% of patients with no bacterial growth respectively. The difference in wound bacterial cultures between the treatment and control groups was highly significant, p=0.006 and p=0.001 on day 5 and day 10 respectively.

Note: Two patients in the diphenylhydantoin group and one patient in the standard therapy were already discharged on the 10th day of treatment i.e their wounds were already healed.

Table XII: Presence of wound pain

Pain	Diphenylhydantoin		Standard Therapy		Total	
	N	(%)	N	(%)	N	(%)
Yes	7	(21.9)	17	(53.1)	24	(37.5)
No	25	(78.1)	15	(46.9)	40	(62.5)
Total	32	(100)	32	(100)	64	(100)

(χ^2=6.67, P=0.01)

Twenty five patients (78.1%) in the Diphenylhydantoin group reported no pain compared to 15 patients (46.9%) in the standard treatment group.

The difference is statistically significant *(P=0.01)*

Table XIII: Average reduction rate in surface area of the burn wounds.

Period (duration)	Reduction in wound area (%)		
	Diphenylhydantoin	Standard therapy	
Day 3	27.2	13.8	***χ^2=24, P=0.12***
Day 7	64.9	41.1	***χ^2=4.02, P=0.45***
Day 10	81.0	62.5	***χ^2=2.78, P=0.10***
Day 14	90.3	75.9	***χ^2=2.74, P=0.10***

The results indicate faster healing in the Diphenylhydatoin-treated group over a period of two weeks of observation when compared to the standard treatment over the same period. However, there is no statistically significant difference between the two groups.

Table XIV: Treatment outcome of burn wounds.

Outcome	Diphenylhydantoin		Standard therapy		Total	
	N	(%)	N	(%)	N	(%)
Complete healing	29	(90.6)	24	(75.0)	53	(82.8)
Skin grafting	2	(6.3)	1	(3.1)	3	(4.7)
Poor healing, treatment changed	1	(3.1)	7	(21.9)	8	(12.5)
Total	32	(100)	32	(100)	64	(100)

χ^2=2.74, P=0.10

Complete healing was observed in 90.6% of the patients treated with diphenylhydantoin and 75% of patients in the standard treatment. Overall there was no statistically significant difference between the two groups as far as the outcome of wounds is concerned (P=0.10).

In the standard group, in 7 patients (21.9%) their wound progressed poorly hence the treatment was changed. This occurred in 1 patient (3.1%) in the diphenylyhydantoin group. This outcome is not statistically significant *(χ^2=3.77, P=0.05).*

Hospitalization Period.

Average hospitalisation period for study cases was found to be 14.2 days, while in the standard therapy was 16.25 days. No statistically significant difference between the two groups *(p=0.33).*

7.0 DISCUSSION

7.1 Demographic characteristics

7.1.1 Age

In this study the majority of patients who sustained burn injury were found to be children under five (Table I). The study recruited patients with small to moderate 2^0 burn wounds. This factor probably contributed to the majority of patients being children under five. Adults tend to get severe and deep burns following open flames mostly happening at work or during fire accident. However, these findings are consistent with findings from several other investigators[7,8,46] who reported more cases of burns involving children.

7.1.2 Sex

Of the patients who where studied 51.6% were males and 48.4% were females. The difference in sex distribution of the patients between the two groups was not statistically significant, hence avoiding sexual bias contributing to outcome of study.

7.2 Aetiology

In this study two aetiologies were noted, scalds (hot liquids) and open flames (Table III). Scalds and open flame cause most of burn injuries world wide[16] as was seen in this study. Over all scalds remain the most common. The majority of patients in both groups were children. The major aetiology of burn in children is scalds[8,17,18,19]. Therefore, the fact that the majority of the patients in the study were children dictates the main aetiology to be scalds. Furthermore, only 2^0 burn injuries were enrolled in the study. Scalds tend to cause 2^0 burn wounds; open flames, chemical and electrical injuries tends to cause deep burn wounds of 3^0 , while sun burn causes first degree burn wounds and are generally not admitted in hospital. Adults are likely to get 3^0 burn wounds from open flames, chemical or electrical injuries. The difference between the two groups with regard to aetiology is statistically significant ($p=0.005$). However, this is not considered to cause bias in this study as much emphasis and patients recruitment was based on the depth (degree) of burn wounds.

Other aetiologies like chemical, electrical and other injuries did not appear here, not because they were not admitted, but it was a matter of exclusion criteria as they tended to have extensive and

frequently deep wounds of 3^0 . Observation made by Wang et al[47] was that the majority of burns occurred in the home and were largely caused by hot liquids.

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7.3 Circumstances of injury

In this study it was observed that almost all injuries were due to domestic accidents (96.9%) (Table IV). Two thirds or more of burn injuries occur in a domestic environment[22].

Children and females are the victims in most of domestic burn accidents. Ideally, children should be excluded from areas where food is cooked. Our resource-scarce environment makes it comparatively difficult to keep children away from hazardous situations that may lead to burns.

7.4 Initial topical agents

Immediately after burn injury, topical agents are applied onto the wounds as a first aid measure. The practice of applying topical agents on wounds immediately after burn injury as a first aid measure is a well-known practice through the ages[12]. In this study honey was the most common topical agent applied on the wounds (42.2%). Other agents like sugar, burn cream and raw

eggs were applied frequently. Applications of these agents may contaminate the wounds and lead to infection, hence prolonging treatment with possible complications. The application to fresh burn wounds of things like unsterilised local herbs, dust and animal dung are particularly hazardous and may lead to serious infections, including tetanus. Fortunately, no complication related to the previous applied local agents on the wounds was noted during this study. The two groups were comparable in terms of substances applied to the wound immediately after injury.

7.5 **Status of the wounds.**

7.5.1 Pus discharge:

During follow up, 59.4% of patients in the diphenylhydantoin group developed pus discharge in their wounds. This was observed in 75% of the patients in the standard treatment. This difference is not statistically significant (P = 0.18). (Table IX).

Pus discharge is one of the signs in infection but bacteria are not always cultured from pus-discharging wounds.

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7.5.2 Smell

When smell (odour) of the wounds was determined only 6 patients (18.8%) in the diphenylhydantoin group and 10 (31.2%) in the standard treatment had foul smelling wounds. Again the results are comparable between the two groups. Wound cleaning and debridement was done daily, and this may have contributed to the lower percentage of patients with foul odour.

7.5.3 Wound infection

In this study wound swabs were taken for culture before treatment, on the 5th day and 10th day on treatment. The baseline results showed that 40.6% in the study group had bacterial growth. In the

standard therapy, 43.8% of patients' wounds had bacterial growth.

Wound cultures done on the 5th and 10th days showed a highly significant difference between the study cases and patients on standard therapy (P value 0.006 and 0.001 respectively) Table XI. The significant reduction in wound infection by diphenylhydantoin seen in this study has also been reported in other series[11,33,44,48,49,50,51,52].

A topically applied agent should have the benefit of preventing/reducing the rate of infection. It is known that, infection can lead to sepsis, septiceamia, endotoxic shock and death. Also, infection can change a 2^0 burn wound to a 3^0 burn wound.

Burn patients at Muhimbili National Hospital are nursed in an open general ward with a constant flow of visitors. The rate of infection is likely to be high. Therefore periodic bacteriological culture is used to

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monitor the efficacy of the topical therapy employed with regards to bacterial contamination.

Bacterial cultures before treatment showed similar rates of bacterial contamination in both groups. After 5 and 10 days of treatment, wounds on topical diphenylhydantoin had much lower rates of positive bacterial culture. This demonstrates a strong bacterial suppression by diphenylhydantoin in burn wounds. Mendiola-Gonzalez et al[9] had similar findings where the surface cultures were negative after 5 to 10 days of treatment with diphenylhydantoin.

The mechanism of reduction of wound contamination by diphenylhydantoin is thought to be the result of a change in wound P^H and improvement in local circulation[49]. However, Lodha et al[51] reported a possibility of direct antibacterial effect. But, he also stresses on local P^H changes, improved local circulation and/or immune function in the wounds

treated with diphenylhydantoin as an explanation for this effect.

7.6 Wound Pain.

Pain remains one of the major complaints of patients with partial thickness burns, mostly during and soon after dressing of burn wounds.

Because of intact skin appendages and nerve endings in 2^0 burn wounds, these patients experience severe pain. The reduction of pain by diphenylhydantoin was found to be statistically significant (P=0.01) (Table XII) when compared to silverex. Studies done earlier reported the same[44]. Lodha[10] had similar observations where, diphenylhydantoin – treated patients appeared more comfortable and reported less pain. Modaghegh et al[48] also, reported local pain relief following topical application of diphenylhydantoin.

The local analgesic property of topical diphenylhydantoin is thought to be consistent with its selective depression of repetitive neuronal activity and synaptic transmission[53]. Other studies done indicate that diphenylhydantoin has local analgesic

properties due to its membrane stabilizing actions, including modulation of ion flux and selective depression of repetitive neuronal activity[49].

With this effect of local pain relief diphenylhydantoin reduces the use of analgesics especially in burn patients who may require strong analgesics like pethidine or anaesthetic agents like ketamine during and after dressing of burn wounds.

7.7 Rate of healing

Since its discovery in 1908[29], diphenylhydantoin was noted to promote healing. Diphenylhydantoin stimulates collagen formation and maturation in granulation tissue[37].

In this study, it was observed that healing was faster in patients treated with diphenylhydantoin compared to patients on a standard treatment (Table XIII).

In the first week of treatment, the average reduction rate of the burn wounds in patients managed with diphyenylhydantoin was 64.9% compared to 41.1% of the standard therapy group. After 2

weeks the difference in healing rate was even more convincing where reduction of 90.3% of burn wounds in patients treated with diphenylhydantoin was achieved. Though diphenylhydantoin produced faster healing rate, the difference was not statistically significant when compared to silverex. Acceleration of wound healing in several studies with the use of diphenylhydantoin has been observed[33,54]. Acceleration of healing in a wide variety of ulcers of skin and soft tissues and burn wounds has been demonstrated with both topical and oral diphenylhydantoin[54].

Diphenylhydantoin enhances wound healing at several levels. One is its ability to enhance the formation of granulation tissue[48,55].

Studies also show it has the ability of reducing oedema and inflammation, increasing fibroblast proliferation and collagen production and accelerating growth of healthy granulation tissue[10]. It also has ability of stabilizing cell membrane and reducing calcium dependent release of various cellular products[9,10,44,49].

Similar results of burn wound reduction was reported by Lodha[10] where at 20 days the reduction was 89.6% for the diphenylhydantoin while for the standard teatment it was 56.9% during the same duration of observation, the difference being statistically significant

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7.8 Outcome of burn wounds

Faster healing observed in diphenylhydantoin-treated group would correlate with better outcome of burn wounds. There was, however, no statistically significant difference in outcome of burn wounds in the two groups.

In this study 90.6% of patients in the diphenylhydantoin group had their wounds completely healed before discharge. In the control 75% had complete healing. There was no statistically significant difference between the two groups. Of interest is the number of patients whose wounds progressed poorly hence the treatment had to be changed to other treatment such as Eusol or sofratulle dressings. This was because the patients seemed not to

benefit from the previous treatment and the wounds had more infection, sloughs and even turned to 3^0 burn wounds.

Only 1 patient in the diphenylhydantoin group had to have a change of treatment while in 7 patients (21.9%) in the standard treatment their wounds showed poor progress hence an alternative way of management was started for the benefit of the patients in the study. Treatment was changed to soflatulle or honey dressing. These findings are not statistically significant (P=0.05).

The reduction in bacterial colonization of the wound and promotion of growth of granulation tissue can be expected to enhance and accelerate wound healing.

7.9 Hospitalization

This aspect depends on the outcome of wounds. The duration of hospitalization is determined by the wound size reduction rate or the healing process. The faster the healing the shorter the duration of hospital stay. In this study average hospitalization

period was 14.2 days for diphenylhydantoin treated patients and 16.25 days for the standard treatment group.

Observation of a mean healing time of 15.7days of burn patients treated with Diphenylhydantoin was reported in one study[50]. In another study a mean healing time of 18.2days in patient treated with diphenylhydantoin against 20 days for those treated with silver sulfadiazine in patients with superficial 2^0 burns was reported[50].

The difference in period of hospitalisation is not that much different from the standard therapy though the phenytoin group had a shorter hospitalisation by 2 days thereby minimising the hospital costs. There was no statistically significant difference between the two groups *(p=0.33)*.

8.0 CONCLUSION.

Burn injury constitutes a very important clinical problem in the practice of surgery in Tanzania. It is a common condition, and in Paediatric surgery it is the commonest cause of death among paediatric surgical admissions. In addition, burns is associated with a high morbidity, the most serious being that related to early haemodynamic derangements, but also important are the wound-related complications, including infections and subsequent disabilities. At Muhimbili burns are admitted in the general surgical ward, and no specialized care is available. Research findings that hold the promise of improving the care rendered to burn patients will therefore be highly valued.

This randomized prospective controlled study has demonstrated a high degree of effectiveness of diphenylhydantoin in suppressing burn wound bacteria compared to a standard treatment. This finding may prove to be very valuable, considering the fact that wound sepsis delays wound healing, may convert superficial wounds into deep ones, and can lead to bacteraemia, septicaemia and subsequent life-threatening complications. The results from this study suggest advocating wider use of diphenylhydantoin in moderate-sized 2^0 burn wounds, a practice which may bring about a real improvement in the management of burn

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wounds in Tanzania. This cheap drug may make it unnecessary to use expensive antibiotics and various costly topical applications in the burn wound.

Diphenylhydantoin has been shown in this study to be effective in relieving pain in the wound in 2^0 burns of small or moderate size. Use of topical diphenylhydantoin may therefore make it unnecessary to use systemic analgesics or reduce their use significantly.

Small to moderate burns are very common in domestic accidents. If they cover less than 15% of TBSA in adults or 10% TBSA in children and do not involve special areas of the body, they do not warrant hospitalization. Patients or relatives can be instructed in cleaning the wound and applying diphenylhydantoin at home, and patients seen at the clinic for weekly follow up.

The study results also suggest beneficial effects in the use of topical diphenylhydantoin in decreasing pus discharge from the wound, decreasing wound surface area and time to complete healing enabling patient to be discharged home. These results require further study.
There were no adverse effects noted with the use of diphenylhydantoin for topical treatment of small to moderate 2^0 burns.

9.0 RECOMMENDATIONS

1.More studies should be done to clearly ascertain the safety and effectiveness of this drug and the dosage.

2.Effort should be made that the drug is available in the country.

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