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A Study of Topical Phenytoin Sodium in Diabetic Foot Ulcer Healing

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Abstract

Diabetic foot ulcers are associated with high financial cost, long term morbidity and sometimes ever mortality. Diabetic foot ulcers are associated with slow wound healing and increased susceptibility to infection. The development of wound granulation is important for successive healing. Pheny to in sodium has been studied in the healing of pressure ulcers, venous stasis ulcers, diabetic ulcers, traumatic wounds and burns. Topical pheny to in sodium appears to enhance healing by promoting fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism and antibacterial activity. Pheny to in sodium increases gene expression of Platelet derived growth factor PGDF-b chain in macrophages and monocytes hence increases the formation of granulation formation.

AIM AND OBJECTIVE

To promote early wound healing in non-healing trophic foot ulcer in diabetic patients, to promote wound bed preparation with phenytoin sodium powder dressing for early Skin graft and to prevent long hospital stay and to reduce distress and disturbance to the patient.

MATERIALS AND METHODOLOGY

The study is made in 100 patients who attend Karpagam Faculty of Medical Sciences and Research Hospital, Coimbatore were selected for the study with 50 patients as control. Selection of patients was made based on Wagner's classification – grade-II, grade-III and Grade-IV who underwent adequate debridement, glycemic control, selective sensitive antibiotic coverage, no peripheral vascular disease or osteomyelitis. Monitoring of granulation tissue formation, hemoglobin status and any untoward reaction were done. Glycemic control is monitored every alternate days. The following method was carried out for 2-8 weeks based on the extension of the ulcer raw area. On achieving required ulcer bed SSG was planned.

RESULTS

The study including no age limit. Among 50, 43 subjects responded well to whom the granulation formation was rapid and subjected to early coverage of the wound area. Among the remaining 7 subjects , 4 of them did not have proper glycemic control due to non co-operative for the diabetic treatment, 1 subject did not respond to insulin therapy and wound was progressive, 2 subjects did not respond to the therapy. Only 8 among 50 patients required 8 weeks hospital stay, other patients were discharged at the earliest. The 50 subjects as control , only 5 of them showed better results with betadine application. Remaining 45 were requiring repeated debridement and even few were subjected to limited amputations following prolonged hospital stay.

CONCLUSION

Observation during this study among 50 patients for a period of 6 months and 9 days gives an encouragement in the topical application of phenytoin sodium not only on diabetic foot raw areas but also on all types of long standing ulcers of venous, arterial and other systemic disease etiology.Since phenytoin sodium is cheaper and easily available drug than any other newer forms of application. Hospital stay is also rationally reducedbased on the present day financial situation.

Keywords-Topical Phenytoin Sodium, Gene expression of PGDF-b, Fibroblast proliferation, Collagen deposition, Glucocorticoid antagonism, Increases granulation formation

INTRODUCTION

DIABETIC FOOT –The human foot is a remarkable mirror in systemic diseases, the earliest manifestation of diabetis, perinicious anemia, polycythemia, metabolic disorders including gout as well as brain and spinal disorders are often first seen in the foot. The risk factors of diabetic foot ulcer are long term diabetes, peripheral neuropathy[9] and peripheral vascular disease. Prior to foot ulcer and amputation prevalence of neuropathy in diabetes is 23% and peripheral vascular disease is 15%. Patient with diabetes are at increased risk for foot ulceration. The prevalence of foot ulcers among patients with diabetes mellitus is 12%. These ulcers are associated with high financial cost, long term morbidity and sometimes ever mortality. Diabetic foot ulcers are associated with slow wound healing and increased susceptibility to infection where primary closure of ulcer is often difficult. Wound closure by SSG is often simple and most versatile method of wound management. The development of wound granulation is important for successive healing, SSG . This degree of vascularity enables granulation tissue to accept skin grafts.

Pathogenesis of diabetic foot ulcer - Patients with uncontrolled diabetes mellitus experience more serious complications earlier in disease process than do those with systemic control. Two major groups of long term complications of diabetes are macrovascular and microvascular effects.

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Macrovascular complications which involve the large blood vessels of the body contribute to the development of the coronary artery disease , cerebrovascular disease and peripheral vascular disease resulting in poor circulation to the extremities. Microvascular disease which affects the small blood vessels of the body is responsible for renal diseases, retinopathy and neuropathy. The extent of neuropathic complications due to poor glycemic control increases proportionally to the length of time a person has been diabetic.

Nerve fibre degeneration and neuropathy associated with diabetis effects 60-70% of diabetic patients are among the earliest detectable signs of long term glucotoxity. Neuropathies are categorized as either sensory motor or autonomic sensory motor neuropathies. Typically affects the pain sensation in the extremities and manifest as numbness, tickling or burning sensation in the foot and hands. Neuropathies affecting the autonomic or vegetative nervous system include gastroparesis, impotence , urinary bladder incontinence and impair cardiovascular reflexes. Foot ulcers are caused by both sensory and autonomic neuropathies as well as peripheral vascular disease. Surgeons and Physicians caring for diabetic patients have the oppurtinity held to prevent delay or even arrest the process of neuropathy and to offer treatments for symptoms of existing neuropathic complications.

The various mechanisms that explain how hyperglycemia causes the vascular and neuropathic complications of diabetis leading to trophic ulcer formation.

1,Aldolase reductase pathway
2,reactive oxygen species
3,Advanced glycation end products theory
4,Protein kinase theory

Microbiology-Many studies have shown the polymicrobial nature of diabetic foot with an average of 5.8 bacterial species (3.2 aerobes and 2.6 anaerobes) per specimen. One common finding in diabetic patients is presence of gas in deeper tissues of the foot ulcer due to non-clostridial gas forming organisms like anaerobes streptococci and bacteriodes. Poor vascularity also aggravates the situation . Staphylococcus Aureus, Bacteriodes, Proteus, Enterococcus, Clostridium, Escherichia

coli and fungal infection lead to skin breakout and secondary ulceration.

PHENYTOIN SODIUM –Phenytoin sodium is the oldest non sedative antiepileptic drug, introduced in 1938 by Meritt and Putnam following a systematic evaluation of compounds such as phenobarbital that altered electrically induced seizures in laboratory animals. Phenytoin sodium is a Diphenyl substituted Hydantoin[11] which is most effective drug against partial seizures and generalized tonic-clonic siezures.

Phenytoin Sodium has been studied in the healing of pressure ulcers, venous stasis ulcers, diabetic ulcers[3,4] , traumatic wounds and burns[2]. Topical phenytoin sodium appears to enhance healing by promoting fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism and antibacterial activity[5]. Phenytoin sodium increases gene expression of Platelet derived growth factor PGDF-b[1,10]chain in macrophages and monocytes hence increases the formation of granulation formation.

AIM AND OBJECTIVE

- To promote early wound healing in non healing trophic foot ulcer in diabetic patients
- To promote wound bed preparation with phenytoin sodium powder dressing for early wound closure
- To prevent long hospital stay and to reduce distress and disturbance to the patient.

MATERIALS AND METHODOLOGY

The study is made in 100 patients who attended Karpagam Faculty of Medical Sciences and Research Hospital, Coimbatore, were selected for the study with 50 patients as control. Selection of patients was made based on Wagner's classification – grade-II, grade-III and Grade-IV.

Wagner's classification of diabetic foot ulcers –

- Grade 0 – High risk foot, no ulcer
- Grade 1 – Foot with no open lesion with intact skin with bunions, hammer toes, Charcot's deformity, prominent metatarsal heads
- Grade 2 – lesions with superficial ulcers with cellulitis not below subcutaneous adipose tissue
- Grade 3 – Ulcer with penetration into joints, forming deep abcess, forming osteolmyelitis, tendon sheath infections and necrotizing fasciitis
- Grade 4- lesion with gangrene of parts of foot, toes, forefoot and heal
- Grade 5 – lesion with extensive gangrene and necrosis.

On day – 1, Wound swab and pus for culture and sensitivity were sent for Microbiology lab, X- ray of the local parts were taken, random blood sugar and glycosylated blood sugar were assessed. On day – 2, fasting and post prandial blood sugar were assessed and strict diabetic treatment protocol were started. The team of patientssubjected to adequate wound debridement based on the principles of debridement,

Principles of debridement –

- All dead tissue removal
- Margination until it bleeds freely
- Draining of abcess or any collections
- Opening up of cavities

The principles of diabetic foot ulcer treatment were followed strictly throughout the study.

Principles of diabetic foot ulcer treatment

- Control of Diabetes with subcutaneous insulin and oral hypoglycemic drugs and diabetic diet
- Wound care with proper evaluation, pressure relief
- Infection control with proper sensitive antibiotic therapy
- Prevention of recurrences with appropriate wound management

The patients with peripheral vascular disease, severe neuropathy and osteomyelitis with sinus formation were eliminated from this study.

Phenytoin sodium in the form of 100mg tablet is available, powdered into fine particles, is sprayed on the subjected wound surface. Sterile gause and gonge pad bandaged dressing was applied. Monitoring of granulation tissue formation was done daily on a chart, hemoglobin status and any untoward reaction were noted. Glycemic control was monitored on alternate days. The following method was carried out for 2-8 weeks based on the extension of the ulcer raw area. On achieving required ulcer bed SSG was planned.

REVIEW OF LITERATURE

Phenytoin sodium in cutaneous Medicine – Phenytoin sodium has been investigated to treat ulcers, epidermolysis bullosa and inflammatory conditions, numerous allergic and cutaneous side effects .

Phenytoin sodium in ulcers – Phenytoin sodium has been studied in healing of pressure ulcers, venous stasis ulcers, diabetic ulcers, traumatic wounds and burns. It appears to enhance healing without any side effects. It has been used in treatment of buruli ulcer of mycobacterium ulcerens8.

Topical phenytoin sodium was used with good effect during the Iran-Iraq war12,13. In Iran , it was reported to have a role in treating 19 wounds caused by missiles and 6 refractory ulcers in civilians. In Iraq it was reported that topical Phenytoin sodium in treatment of war- related ulcers resulted in prompt pain relief, decreased wound exudates and bacterial contamination and

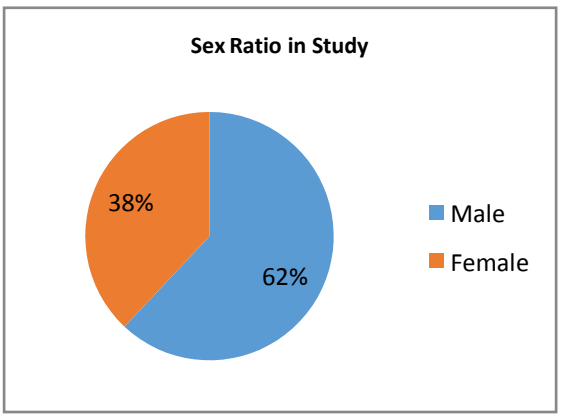
enhancing granulation tissue formation and more rapid healing.
Phenytoin sodium in Orthopedics – Phenytoin sodium is reported to be used locally in tendon repair site to increase the rate and strength of healing. Local percutaneous injection of phenytoin solution resulted in improving fracture healing

MECHANISM OF PHENYTOIN SODIUM TOPICALLY ON WOUND BED

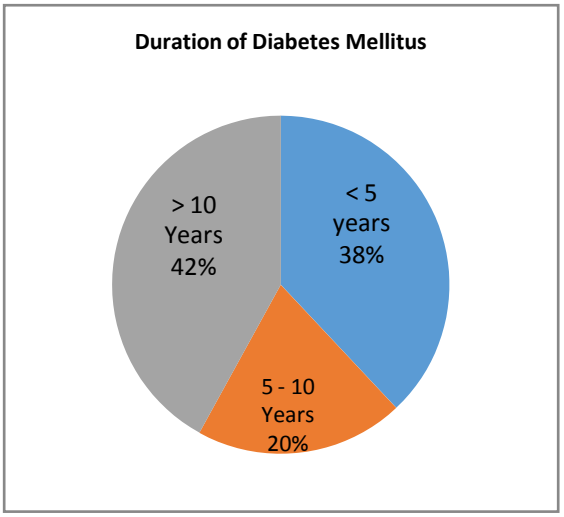
Diabetic foot ulcers are associated with slow wound healing and increased susceptibility to infection. Development of granulation tissue is important requirement for successful skin grafting. Phenytoin sodium enhances formation of granulation tissue which has a high level of vascularity resulting in abundance of new capillary formation7.
Topical phenytoin sodium has wound healing promoting effects attributed to the following mechanisms:
increased fibroblast proliferation
inhibition of collagenase activity
promotes collagen disposition
enhances granulation tissue formation
decreases bacterial contamination
reduces wound exudate formation
up-regulates growth factor receptors
Phenytoin sodium stimulates the development of granulation tissue formation within 2-7 days after beginning the treatment and disassociation with non-detectable serum phenytoin levels6.

RESULTS

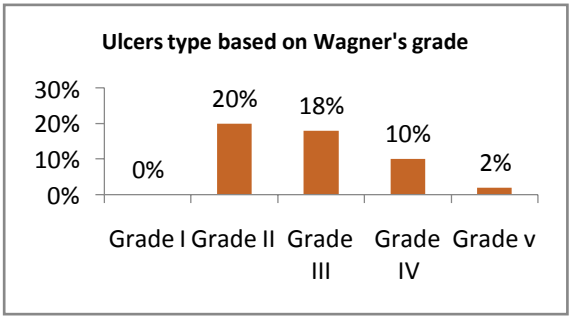
During the period between august 2016 – February 2017, a total of 50 patients against 50 patients as control were enrolled and included in this study. The study including no age limit.
Sex ratio – M:F 62:38



Type of DM – Type I: Type II 92:8
Duration of Diabetes mellitus - < 5yrs – 38%
5-10yrs – 20%
>10yrs – 42%



Based on Wagner's classification of wound –
Grade I – 0%
Grade II- 20%
Grade III- 18%
Grade IV – 10%
Grade V – 2 %



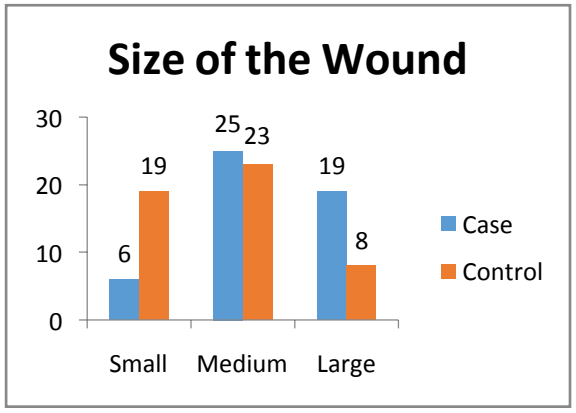
Wound status and response to Topical Phenytoin sodium

S.No	Treatment method	Size of the wound			Response of wound to Topical phenytoin sodium By granulation formation				Further Response of wound following Topical phenytoin sodium application		
		Small	Medium	Large	0-1 wk	1-2 wks	2-3 wks	>3 wks	Repeated debridement	SSG	Progressive necrosis
1	Topical Phenytoin-study	6	25	19	3	21	22	4	8	43	7
2	Povidone Iodine -control	19	23	8	-	7	17	26	22	16	12

Size of the wound–
Small – AP: Axial –(5cms to 10cms)

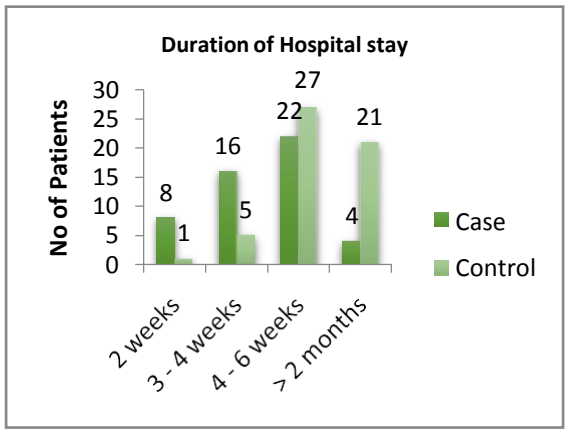
Medium – AP: Axial –(10cms to 15cms)
Large – AP: Axial –(15cms and above)

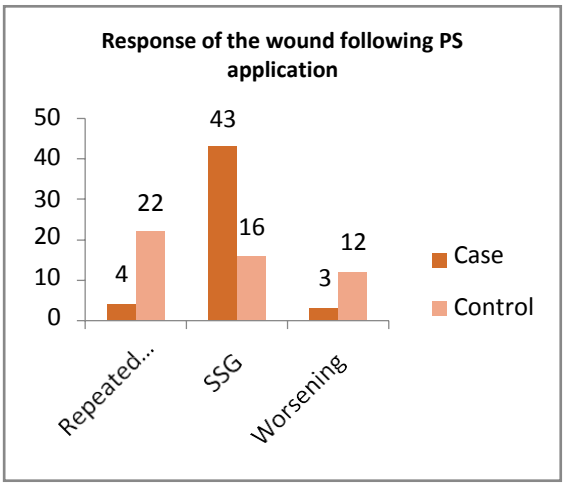
Small: Medium: Large = 6:25:19



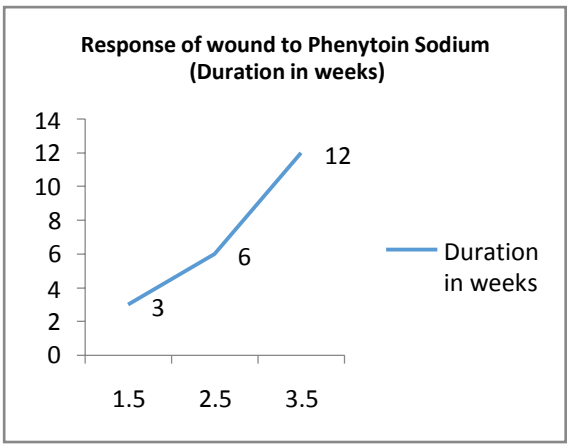
Response to Topical phenytoin sodium Vs Hospital stay

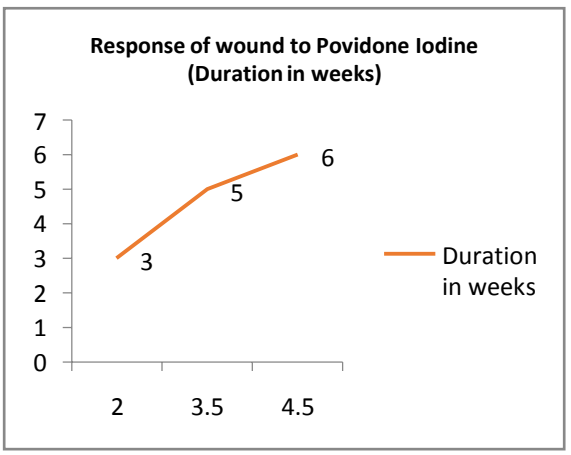
S No.	Treatment method	Required repeated debridement	SSG	Progressive necrosis	Hospital stay			
					2 wks	3 wks	4-6 wks	>2 months
1	Topical Phenytoin - study	4	43	3	8	16	22	4
2	Povidone Iodine - control	22	16	12	1	5	27	21





Duration Vs Wound response





Skin graft response following wound treatment with Topical Phenytoin sodium

S NO.	Treatment method	No. of patient underwent SSG	100% Take	75% take	50% take	Total loss (requiring re-grafting)
1	Topical Phenytoin - study	43	32	4	3	4
2	Povidone Iodine - control	16	10	-	1	5

Therefore, among 50 subjects 43 of them responded well to whom the granulation formation was rapid and subjected to early coverage of the wound area, among the remaining 7 subjects , 4 of them did not have proper glycemic control due to non-co-operative to the diabetic treatment, 1 subject did not respond to insulin therapy and the wound was progressive, 2 subjects did not respond to the therapy inspite of good glycemic control. 0nly 8 among 50 patients required 3 weeks hospital stay. The patients underwent SSG at the earliest and the wound healed completely. The 50 subjects as control also subjected to SSG but required more than 8 weeks and recurrence of the ulcers.

CONCLUSION

Observation during the 6 months and 9 days period on topical application of Phenytoin sodium powder on non-healing diabetic ulcers among 50 subjects shows better results which is an encouragement in its use not only on diabetic foot raw areas but also on all types of long standing non-healing ulcers of venous, arterial and other systemic disease etiologies. Since phenytoin sodium is cheaper and easily available drug than any other newer forms of application. Phenytoin sodium has nil side effects when topically used over the wounds and serum level of phenytoin is been in safer levels throughout the study in these subjects. The rationale of this study is reached based on early granulation tissue formation, wound closure, decreased hospital stay duration. Present day financial situation, psychological depression are all targeted in view of this study which is very supportive for the diabetic subjects developing long standing non-healing ulcers. Most of the patients developing ulcers are subjected to limited amputations of parts in view of Save the limb or Save the life mission. Present day recent advances in the medicine are including collagen powder, collagen sheet, epidermal growth factor gel, silicon gel, vacuum dressing, antibiotic pack, topical enzymes preparation, plant extract application dressing are also on upgrading the following study. But our study is based on the most easily available, cheaper, acceptable by all type of subjects and low risk causing factors and gives the best outcome.

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