Comparison of Efficacy - Phenytoin Vs. Conventional Dressing (Povidone Iodine) Vs. Local Sucralfate Vs. L-Lysine as Wound Dressing Following Surgical Debridement of Diabetic Foot Gangrene

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ABSTRACT

BACKGROUND

Diabetes is a cause of many complications, one of them being foot ulcer and gangrene. Control of diabetes and wound healing should be the aim of treatment. Wound healing requires formation of healthy granulation tissue after wound debridement. Topical phenytoin helps in the formation of granulation tissue, reduces the slough and bacterial load, and promotes wound healing in diabetic foot. It is cheap and easily available. We wanted to compare the efficacy of phenytoin with conventional dressing (povidone iodine), local sucralfate, and L-lysine in management of diabetic foot gangrene after surgical debridement.

METHODS

This single blind multi-arm randomised controlled trial was carried out at a tertiary care teaching hospital in Kolkata over a period of one year. Data was recorded in a pre-designed proforma, with special emphasis on the number of days required for the development of healthy granulation tissue and hospital stay (in days).

RESULTS

A total of 160 cases were studied. The mean age of the patients was 59.6813 ± 8.7007 years with range of 38 - 81 years and the median age was 59.0 years. Male to female ratio was 1.9:1. The duration of diabetes varied from 2 to 23 years. In 90 (56.3 %) patients, diabetes was controlled but it was uncontrolled in 70 (43.8 %) patients. The most common organism isolated in pus culture growth was staphylococcus. In phenytoin group, healthy granulation tissue formed earlier in comparison to conventional dressing with povidone-iodine or dressing with sucralfate or L-lysine. Hospital stay period was less in case of phenytoin treated group in comparison to other three groups.

CONCLUSIONS

In our study we found that phenytoin dressing forms healthy granulation tissue faster; so, it can be considered as an alternative to other forms of dressing. Hospital stay is also reduced which is beneficial for the patient.

KEYWORDS

Diabetic Foot Gangrene, Phenytoin, Povidone Iodine, Sucralfate, L-Lysine

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BACKGROUND

Diabetic foot disease occurs due to peripheral arterial disease, sensory neuropathy or a combination of both. Phenytoin is an agent which improves wound healing. It was synthesized by German chemist Heinrich Biltz in 1908.[1] Foot ulcers and gangrene require frequent treatment which is a financial burden to patients in a developing country.[2] Due to advancement in the knowledge and treatment of diabetes, people with this disease are now surviving for a longer time. This is a cause for an increase in the different complications of diabetes like diabetic foot disease.[3]

Long standing and neglected diabetic foot disease ultimately lead to amputation which is preventable. Any agent that helps in the formation of granulation tissue for early skin grafting will reduce the hospital stay of the patient. Phenytoin causes hyperplasia of the connective tissues of the gums and this effect is the basis behind its use in wound healing.[3]

Objectives

The specific objective of this study was to assess the efficacy of topical phenytoin dressing and compare it with other wound dressings in the management of diabetic foot gangrene after surgical debridement. Other objectives were to study the bacteriology and pathophysiology of diabetic foot.

METHODS

This single blind multi-arm randomised controlled trial was carried out at a tertiary care teaching hospital in Kolkata over a period of one year from February 2014 to January 2015. A total of 160 cases were studied. From previous records and experience it was agreed that we may get about 180 patients in the stipulated time period, so a sample size of 160 patients was decided upon. Random allocation was done by asking the patient to pick up a piece of folded paper from a box. The papers had the name of the method written on it. Single blinding was ensured as the doctor who observed the granulation tissue formation was unaware of the method of treatment. Inclusion criteria were all patients of diabetic foot gangrene admitted in the Department of General Surgery. Exclusion criteria included diabetic foot problem without gangrene which needed no surgical debridement, dry gangrene of foot and atherosclerotic gangrene of the foot.

A detailed history was taken from the patients and they were all clinically examined. Baseline blood investigations were done, and diabetic status was evaluated and treated. X-ray of the foot was done for exclusion of any evidence of suspected osteomyelitis or to detect bony deformity. In some cases, colour Doppler study was done to detect any evidence of ischemia. During discharge some patients were advised to attend plastic surgery department for wound coverage and others were advised to review for follow up.

The patients were randomly allocated into four groups, P (phenytoin), C (conventional), S (sucralfate) and L (lysine). The wounds were thoroughly debrided. Initially broad-spectrum antibiotics were started. Later, as per culture and sensitivity report antibiotic was changed, if necessary. Under anaesthesia surgical debridement of diabetic foot gangrene was done at the operation theatre. Wound swab was taken and sent for culture and antibiotic sensitivity. Debridement was repeated, if found necessary.

In case of topical phenytoin, gauze soaked in phenytoin suspension was applied over the wound. In conventional dressing, dressing was done with 5 % w / v povidone-iodine solution. In case of local sucralfate, commercially available sucralfate cream was used for dressing. L-Lysine ointment, available commercially, was used as dressing for group allocated for L-Lysine. Daily dressing was done till the development of healthy granulation tissue was observed, thereafter, dressing was done on every alternate day.

Data was recorded in a pre-designed proforma, with special emphasis to the number of days required for development of healthy granulation tissue and hospital stay (in days).

Statistical Analysis

For statistical analysis data was entered in a Microsoft Excel spreadsheet and then analysed by SPSS 10.0.1 and Graph Pad Prism version 5. Data has been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables. The median and the interquartile range have been stated for numerical variables that are not normally distributed. Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups, unpaired proportions were compared by chi-square test or Fischer's exact test, as appropriate.

RESULTS

One hundred and sixty patients were randomly allocated into four groups. The mean age (mean ± SD) of the patients was 59.6813 ± 8.7007 years with range of 38 - 81 years and the median age was 59.0 years. Test of proportion showed that proportion of patients in the age group of 51 - 60 years (41.9 %) was significantly higher than the other age groups (Z = 2.82; P = 0.00048). Out of total 160 cases, males were 105 and females were 55 in number. The sex distribution of the four groups is given in Table 1. The age distribution of the four groups is given in Chart 2 and it was statistically not significant (P = 0.6147).

	Group				
Sex	**C**	**S**	**P**	**L**	**Total**
Female	16	11	15	13	55
Row %	29.1	20.0	27.3	23.6	100.0
Col %	40.0	27.5	37.5	32.5	34.4
Male	24	29	25	27	105
Row %	22.9	27.6	23.8	25.7	100.0
Col %	60.0	72.5	62.5	67.5	65.6
Total	**40**	**40**	**40**	**40**	**160**
Row %	25.0	25.0	25.0	25.0	100.0
Col %	100.0	100.0	100.0	100.0	100.0

Table 1. Sex Distribution of the Four Groups

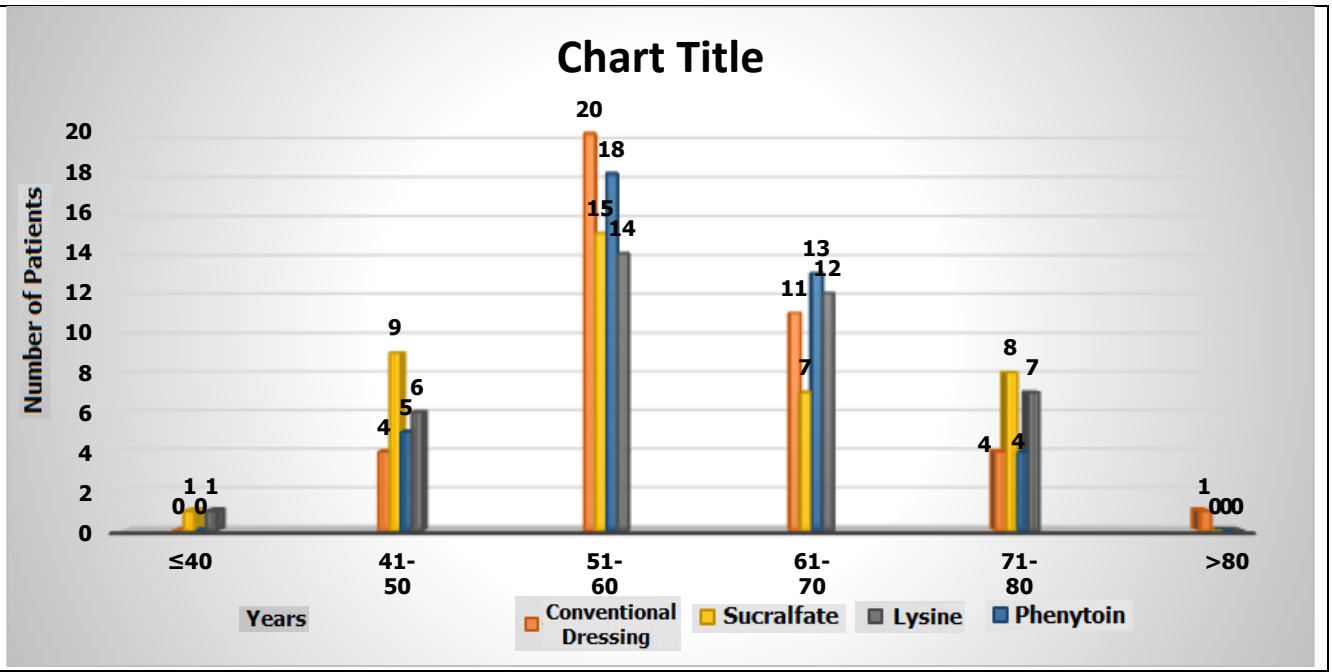

Chart 2. Age Group Distribution of the Four Groups

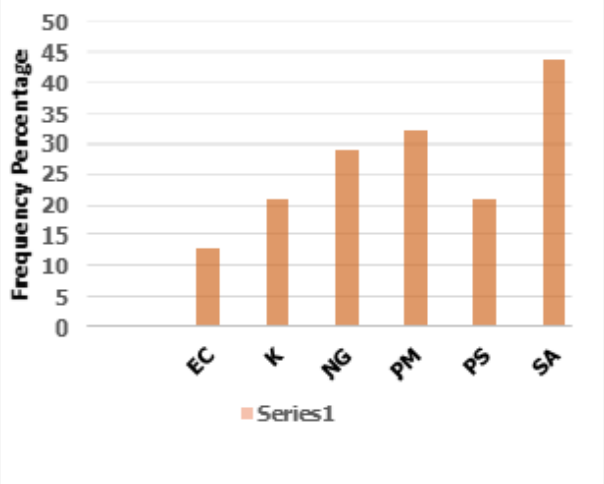

Chart 3. Distribution of Culture and Sensitivity Report of All Patients

EC - *E. coli,*
K - Klebsiella Sp.,
NG - No Growth
PM - Polymicrobial
SA- *Staph. aureus*
PS - Pseudomonas

		Sum of Squares	df	Mean Square	F	Sig.
Development of healthy granulation tissue (in days)	Between groups	1826.925	3	608.975	15.689	.000
	Within groups	6055.050	156	38.814		
	Total	**7881.975**	**159**			
Hospital stay (in days)	Between groups	2161.550	3	720.517	15.449	.000
	Within groups	7275.550	156	46.638		
	Total	**9437.100**	**159**			

Table 2. Development of Healthy Granulation Tissue (in Days) and Mean Hospital Stay in Days of the Four Groups

The sex distribution (P = 0.6516) and the mean duration of diabetes (P = 0.7646) between the four groups were also not statistically significant. The duration of diabetes varied from 2 to 23 years. In 90 (56.3 %) patients the diabetes was controlled and uncontrolled in 70 (43.8 %) patients. Among the uncontrolled cases some had stopped medication, and some were unaware of their diabetic condition. The most common organism isolated in pus culture growth was staphylococcus. The culture report is shown in Chart 3. Foot deformity was present in 9.4 % and neuropathy in 55.6 % of the patients. Uncontrolled diabetes was present in 43.8 % patients in our study.

Figure 1. Diabetic Foot before Debridement

Figure 2. Formation of Healthy Granulation Tissue

In phenytoin group (Fig 1 & 2), healthy granulation tissue was formed earlier in comparison to conventional dressing with povidone-iodine or dressing with sucralfate or L-lysine. Healthy granulation was formed after more or less

same time in cases of conventional dressing (povidone-iodine) and dressing with sucralfate or L-lysine. Period of hospital stay was less in case of phenytoin treated group in comparison to other three groups. Hospital stay periods were more or less same in cases of conventional dressing (povidone-iodine), sucralfate and L-lysine groups.

Multiple Comparisons

Dependent Variable	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95 % Confidence Interval	
					Lower Bound	Upper Bound
Development of healthy granulation tissue (in days)	C VS S	1.125	1.393	.851	- 2.49	4.74
	C VS P	7.775*	1.393	.000	4.16	11.39
	C VS L	- .750	1.393	.950	- 4.37	2.87
	S VS C	- 1.125	1.393	.851	- 4.74	2.49
	S VS P	6.650*	1.393	.000	3.03	10.27
	S VS L	- 1.875	1.393	.535	- 5.49	1.74
	P VS C	- 7.775*	1.393	.000	- 11.39	- 4.16
	P VS S	- 6.650*	1.393	.000	- 10.27	- 3.03
	P VS L	- 8.525*	1.393	.000	- 12.14	- 4.91
	L VS C	.750	1.393	.950	- 2.87	4.37
	L VS S	1.875	1.393	.535	- 1.74	5.49
	L VS P	8.525*	1.393	.000	4.91	12.14
Hospital stay (in days)	C VS S	1.475	1.527	.769	- 2.49	5.44
	C VS P	8.575*	1.527	.000	4.61	12.54
	C VS L	- .650	1.527	.974	- 4.62	3.32
	S VS C	- 1.475	1.527	.769	- 5.44	2.49
	S VS P	7.100*	1.527	.000	3.13	11.07
	S VS L	- 2.125	1.527	.507	- 6.09	1.84
	P VS C	- 8.575*	1.527	.000	- 12.54	- 4.61
	P VS S	- 7.100*	1.527	.000	- 11.07	- 3.13
	P VS L	- 9.225*	1.527	.000	- 13.19	- 5.26
	L VS C	.650	1.527	.974	- 3.32	4.62
	L VS S	2.125	1.527	.507	- 1.84	6.09
	L VS P	9.225*	1.527	.000	5.26	13.19

Table 3. Multiple Comparisons

During development of healthy granulation tissue (in days), mean difference of phenytoin (P) VS conventional dressing group (C) was - 7.775 with 95 % confidence interval [-11.39 – -4.16, P < 0.0001]. Development of healthy granulation tissue (in days), mean difference of P vs. S was - 6.650 with 95 % confidence interval [-10.27 – -3.03, P < 0.0001]. It was found that in development of healthy granulation tissue (in days), mean difference of P vs. L was - 8.525 with 95 % confidence interval [-12.14 – -4.91, P < 0.0001]. All the above were statistically significant.

On observing the hospital stay (in days), mean difference of P VS C was - 8.575 with 95 % confidence interval [-12.54 – -4.61, P < 0.0001]. Hospital stay (in days), mean difference of P vs. S was - 7.100 with 95 % confidence interval [-11.07 – -3.13, P < 0.0001]. Hospital stay (in days), mean difference of P vs. L was - 9.225 with 95 % confidence interval [-13.19 – -5.26, P < 0.0001]. All the above were statistically significant.

DISCUSSION

Peripheral vascular disease and neuropathy are complications of long-standing diabetes. Peripheral vascular disease involving large blood vessels decrease the blood supply to the extremities. Neuropathy occurs due to small vessel disease. Both peripheral vascular disease and neuropathy are responsible for the pathogenesis of diabetic foot ulcer and gangrene.[2] Pain sensation is lost due to the neuropathy leading to cuts from minor trauma. This combined with the poor blood supply leads to the development of ulcer. Diabetic foot syndrome is a combination of pathologies such as infection, foot ulcer and neuropathic osteoarthropathy. The hot and humid climate in our country, excessive sweating, malnourishment, poverty and lack of awareness regarding hygiene and sanitation have increased the problem.[3] In our study the male to female ratio was 1.9: 1. The incidence among males was higher probably because they often work barefoot outdoors due to which they are more exposed to dirt and trauma.

Phenytoin (diphenylhydantoin) was initially introduced into the therapy for the effective treatment of convulsive disorder. A common side effect of systemic phenytoin therapy is the development of fibrous overgrowth of gingiva. This apparent stimulatory effect of phenytoin on connective tissue suggested an encouraging possibility for its use in wound healing. Phenytoin helps in wound healing by stimulation of fibroblast proliferation, enhancing the formation of granulation tissue, decreasing collagenase activity, inhibition of glucocorticoid activity and up regulation of gene expression of the platelet derived growth factor β in macrophages and monocytes.

Sulphated saccharides, such as sucralfate, have previously been indicated for the treatment of gastric and duodenal ulcers in radio-labelled form. It has been found that sucralfate exerts an anti-inflammatory effect when applied topically to the skin and to mucosal surfaces, and that sucralfate exerts a beneficial effect on wounds when applied topically on epithelial surfaces outside the digestive tract.

Lysine is an essential α-amino acid with the chemical formula HO2CCH (NH2) (CH2) 4NH2. L-Lysine hydrochloride has shown improvement in both the rate and quality of wound healing. Another feature of this molecule is its ability to support healing process in long standing wounds. L-Lysine has been shown to promote therapeutic angiogenesis in wound healing

Debridement of all necrotic tissue is the mainstay of treatment in diabetic foot ulcer and gangrene.[3,4,5] Foot ulcers in diabetic patients are prone to infection and wound healing is very slow. Development of granulation tissue is important requirement for successful skin grafting. Phenytoin sodium enhances formation of granulation tissue.[6] The mechanism of wound healing with phenytoin is multifactorial. They are formation of granulation tissue, reducing the slough and bacterial load, reducing the wound size.[1] Various studies have shown that phenytoin is a useful topical agent in promoting wound healing in diabetic foot.[1,2,3,7]

In a study by Vijaya Patil,[7] phenytoin was shown to be a useful topical agent in promoting wound healing and control of infection in diabetic foot ulcers. The study was conducted on 100 patients and it showed significant reduction of discharge and slough in wound within 14 days in the phenytoin group and 21 days in the control group. The mean duration of stay in hospital was 20 days in the phenytoin group and 26 days in the control group. In another study conducted by Leo F Tauro[8] in 2013, a total of 200 patients

were observed among whom 100 patients underwent phenytoin dressing and 100 patients received conventional dressing. The wounds were inspected after 14 days. It was seen that the mean rate of granulation tissue formation in study group was 87 + _ 7.33 % and control group was 74.64 + _8.04 %. The mean hospital stay was 36.26 + _ 2.64 (SD) in study group and 40.97 + _ 3.31 (SD) in control group. The bacterial load was reduced in 70 % of study group and 54 % of control group. The results were analysed by unpaired students 't' test which showed highly significant ($P < 0.0001$) difference.

Our study shows a prevalence of 9.4 % cases of associated deformity of the limb among the admitted patients with diabetic foot gangrene. This is higher than in the developed countries which may be due to the higher percentage of neurogenic ulcers present in our part of the world. Our country has a poor socio-economic and poor awareness (late presentation with neurogenic ulcer) background.

In our study, 90 (56.3 %) patients had controlled diabetes and uncontrolled in 70 (43.8 %) patients. Among the uncontrolled cases some had stopped medication, and some were unaware of their diabetic condition. In our country many cases go undetected until they present with a complication. More awareness programs are required emphasizing on the complications of this disease. Many studies have shown the polymicrobial nature of diabetic foot. 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 bacteroides. Poor vascularity also aggravates the situation. *Staphylococcus aureus*, bacteroides, proteus, enterococcus, clostridium, *Escherichia coli* and fungal infection lead to skin breakout and secondary ulceration.[2] Our study also showed polymicrobial growth.

In our study development of healthy granulation tissue was earlier in case of phenytoin dressing and this was found to be statistically significant. Healthy granulation tissue developed in 33.65 days in the phenytoin group compared to 41.43 days in the conventional dressing group. Other studies also showed similar results.[1,3,8]

Tauro LF[8] in his study showed that at the end of the study period, the rate of granulation tissue formation was more in the study group than in the control group. The total hospital stay in the study group was also shorter. Another study by Bhardva et al.[9] showed the rate of healthy granulation at the end of the study period to be 60.71 % in case of phenytoin dressing and 11 % in case of conventional dressing. The hospital stay was 23.96 days in the phenytoin group compared to 35 days in the conventional dressing group. Our study also showed significant reduction in duration of hospital stay. It was 40.95 days in the phenytoin group compared to 49.53 days in the conventional dressing group. Similar findings were observed in another study[1] where the group for which phenytoin dressing was done underwent SSG or secondary suturing in less than 2 weeks compared to the conventional dressing group which took more than 3 weeks.

Topical phenytoin used in wound treatment is usually well tolerated. Mild adverse effects have been reported. In this study, no complications occurred during the application of dressings. A generalised rash that resolved when treatment was stopped has been reported by Rhodes et al.[10] in his study. Systemic absorption of topical phenytoin is not significant. Most studies that have monitored serum phenytoin levels during topical application have shown the levels to be undetectable.[9] No complications were reported in our study.

CONCLUSIONS

Phenytoin dressing forms healthy granulation tissue faster; so, it can be considered as an alternative to other forms of dressing. It is safe, easily available and cheap.[2,3] Phenytoin is cost effective because of lesser time required for wound to granulate, and low cost of phenytoin as compared to other conventional dressing material[9]. Hospital stay is also reduced which is beneficial to the patient.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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