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Dr. Sudhir S
Professor and Unit Chief
Dept of General Surgery
JSS Hospital and medical college
JSS Academy of higher education
and research Mysore, Karnataka,
India

Dr. Ganashree MH
Post graduate,
Dept of General Surgery,
JSS Hospital and medical college
JSS Academy of higher education
and research, Mysuru, Karnataka,
India

Dr. Deepak Naik
Assistant Professor,
Dept of General Surgery
JSS Hospital and medical college
JSS Academy of higher education
and research, Mysuru, Karnataka,
India

Dr. Dilip DK
Senior resident,
Dept of General Surgery
JSS Hospital and medical college
JSS Academy of higher education
and research, Mysuru, Karnataka,
India

Corresponding Author:
Dr. Deepak Naik
Assistant Professor,
Dept of General Surgery
JSS Hospital and medical college
JSS Academy of higher education
and research, Mysuru, Karnataka,
India

To compare the efficacy of topical phenytoin over conventional wound care (5% povidone-iodine) in diabetic ulcer

Dr. Sudhir S, Dr. Ganashree MH, Dr. Deepak Naik, and Dr. Dilip DK

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Abstract

Background: Diabetic foot ulcers is one of the common complication of diabetes mellitus. It has become a significant health care problem affecting 15%. In this study Phenytoin is used for diabetic foot ulcers comparing its efficacy over conventional dressing.

Methodology: This is a prospective study of 70 patients admitted in JSS hospital, with diagnosis of Diabetic foot ulcer between 2017-2019. They were divided into two group after a detailed clinical examination, and appropriate work up satisfying inclusion and exclusion criteria. One group underwent phenytoin dressing and other group conventional dressing and were assessed on 14th day.

Results: This study observed that group for which Phenytoin dressing was done underwent SSG or secondary suturing in <2 week, whereas the other group took more than 3weeks.

Conclusion: Wound healing was faster with Phenytoin dressing compared to conventional, hence reducing the duration of hospital stay in turn being cost effective. Thus this method can be implied.

Keywords: Diabetic foot, phenytoin, conventional dressing

1. Introduction

Diabetes is group of metabolic disorder characterised with hyperglycemia. Diabetic foot ulcers is one of the common complication of diabetes mellitus. It has become a significant health care problem by affecting 15% of all diabetics during their lifetime of which 15%-20% can lead to amputation. In India approximately 40,000 legs are amputated every year of which 75% are neuropathic with secondary infection which is potentially preventable. For many decades various technique have been tried like sucralfate dressing, mupirocin dressing, hemocoagulase dressing, oxum solution etc. Despite extensive effort to improve wound healing, the outcome of existing method are far from optimal. One such agent that has been tried in wound healing is Phenytoin. It was introduced in 1937 for effective control of convulsive disorder. A common side effect with phenytoin is development of fibrous overgrowth of gingiva. This apparent stimulatory effect of phenytoin on connective tissue suggest an existing possibility for its use in wound healing.

2. Method

This is a prospective comparative study conducted on 70 patients admitted in JSS hospital between 2017-2019 with the diagnosis of diabetic foot ulcers after taking the consent. They were randomly allocated into two groups and one group underwent Topical Phenytoin dressing and the other group underwent conventional dressing after taking thorough history, general physical, local and loco regional examination. Baseline blood investigation, Doppler, x ray was taken, diabetic status was evaluated and treated. Pus culture sensitivity was done on admission, 7th day and 14th day. Wound size was measured using surgical gauze-measuring tape using Walker's Formula and progress evaluation was done in terms of slough, discharge and appearance of granulation tissue at the end of 14th day.

2.1 Inclusion criteria

Patient aged >18yrs
Duration of ulcer >2 weeks

Wound surface area <10cm²
 In patients in JSS hospital

2.2 Exclusion criteria

Non healing ulcers of other etiologies like varicose vein, arterial disease, burns.
 Grade 3, 4, 5 of Wagner's classification
 Renal failure
 Generalised debility
 Anaemia

2.3 Data analysis

The study population was divided into two groups by random method. Group A underwent phenytoin dressing and Group B underwent conventional dressing i.e; 5% povidone iodine daily. Wound contracture is measured using Walker's formula. Topical phenytoin dressing was done by giving normal saline wash followed by placing sterile gauze soaked in phenytoin suspension (phenytoin dissolved in 5ml NS).
 Dosage used
 0 to 5cm²-100mg,
 5.1 to 9cm²-150mg,
 9.1 to 15cm²-200mg.

Conventional dressing is done with 5% povidone iodine solution and hydrogen peroxide wash followed by povidone iodine dressing.

Efficacy of phenytoin over conventional dressing were studied using statistical methods.

Progress evaluation was done in terms of appearance of granulation tissue, reduction of slough, discharge and wound contracture.

Statistical method that was used were:

1. Phi

2. Cramer's v
3. Mean
4. Standard deviation
5. Standard error mean
6. P value of <0.05

3. Result

3.1 Age and gender distribution

Table 1: Comparing the age distribution in each group

	Group	N	Mean	Std. deviation	Std. error mean
Age	Conventional	35	56.8571	11.74519	1.98530
	Phenytoin	35	58.6286	10.88465	1.83984

Mean age in each group is comparable
 Mean age in conventional group is 56.8671 yrs
 Mean age in Phenytoin group is 58.6286yrs
 The difference in mean age is statistically insignificant

Table 2: Statistics of the gender in each group

"Symmetric Measures"			
		Value	Approx. Sig.
Nominal by Nominal	Phi	.174	.145
	Cramer's V	.174	.145
N of Valid Cases		70	

"a. Not assuming the null hypothesis".

"b. Using the asymptotic standard error assuming the null hypothesis"

In this study though it is male predominant, the male female ratio in each group is comparable and is statistically insignificant with p=0.14

3.2 Microbiological consideration

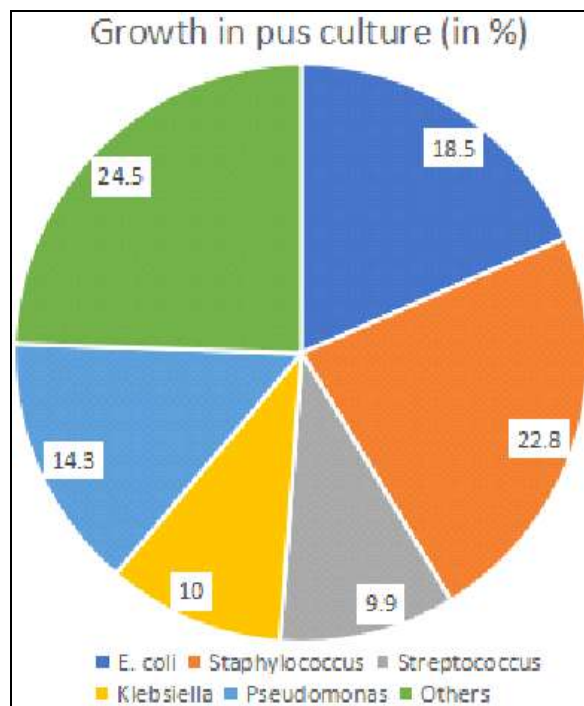


Fig 1: Pie chart of organisms in pus culture taken from wound

The most common organism isolated in pus culture growth was Staphylococcus >E. Coli >pseudomonas, which were not seen in repeat pus culture in patient who underwent Phenytoin dressing.

3.3 Progress evaluation in terms of slough, discharge and granulation Slough

Table 3: Comparing the progress evaluation in terms of reduction of slough

Groups			1Day	14 Day	Total	
Conventional	Progress_Evaluation_Slough	Yes	Count	35	14	70
			% within Session	100.0%	40.0%	66.7%
		No	Count	0	21	35
			% within Session	0.0%	60.0%	33.3%
	Total		Count	35	35	105
			% within Session	100.0%	100.0%	100.0%
Phenytoin	Progress_Evaluation_Slough	Yes	Count	32	3	38
			% within Session	91.4%	8.6%	36.2%
		No	Count	3	32	67
			% within Session	8.6%	91.4%	63.8%
	Total		Count	35	35	105
			% within Session	100.0%	100.0%	100.0%

Table 4: Statistics of reduction of slough in each group

“Symmetric Measures”				
GRPS			Value	Approx. Sig.
Conventional	Nominal by Nominal	Phi	.529	.000
		Cramer's V	.529	.000
	N of Valid Cases		105	
	Phenytoin	Nominal by Nominal	Phi	.813
Cramer's V			.813	.000
N of Valid Cases		105		

“a. Not assuming the null hypothesis”.

“b. Using the asymptotic standard error assuming the null hypothesis”.

Discharge

Table 5: Comparing the progress evaluation in terms of reduction in discharge

Groups			1Day	14 Day	Total	
Conventional	Day_1_Discharge	Yes	Count	35	32	102
			% within Session	100.0%	91.4%	97.1%
		No	Count	0	3	3
			% within Session	0.0%	8.6%	2.9%
	Total		Count	35	35	105
			% within Session	100.0%	100.0%	100.0%
Phenytoin	Day_1_Discharge	Yes	Count	35	34	104
			% within Session	100.0%	97.1%	99.0%
		No	Count	0	1	1
			% within Session	0.0%	2.9%	1.0%
	Total		Count	35	35	105
			% within Session	100.0%	100.0%	100.0%

Table 6: Statistics of reduction of discharge in each group

“Symmetric Measures”				
GRPS			Value	Approx. Sig.
Conventional	Nominal by Nominal	Phi	.243	.046
		Cramer's V	.243	.046
	N of Valid Cases		105	
	Phenytoin	Nominal by Nominal	Phi	.139
Cramer's V			.139	.364
N of Valid Cases		105		

“a. Not assuming the null hypothesis”.

“b. Using the asymptotic standard error assuming the null hypothesis”.

Granulation

Table 7: Comparing the progress evaluation in terms of granulation tissue appearance

Groups			1Day	14 Day	Total	
Conventional	Day_1_Granulation	Yes	Count	0	26	39
			% within Session	0.0%	74.3%	37.1%
		No	Count	35	9	66
			% within Session	100.0%	25.7%	62.9%
	Total		Count	35	35	105

		% within Session	100.0%	100.0%	100.0%	
Phenytoin	Day_1_Granulation	Yes	Count	3	34	57
			% within Session	8.6%	97.1%	54.3%
		No	Count	32	1	48
			% within Session	91.4%	2.9%	45.7%
	Total		Count	35	35	105
			% within Session	100.0%	100.0%	100.0%

Table 8: Statistics of appearance of granulation tissue in each group

“Symmetric Measures”				
GRPS			Value	Approx. Sig.
Conventional	Nominal by Nominal	Phi	.628	.000
		Cramer's V	.628	.000
	N of Valid Cases		105	
Phenytoin	Nominal by Nominal	Phi	.727	.000
		Cramer's V	.727	.000
	N of Valid Cases		105	

“a. Not assuming the null hypothesis”.

“b. Using the asymptotic standard error assuming the null hypothesis”.

Progress evaluation of wounds in each group was compared in terms of reduction of slough, discharge and time taken for appearance of granulation tissue and when both the groups were compared, Phenytoin was found to be more efficacious in each

parameter and was statistically significant with p value of 0.0001.

3.4 Reduction in area

Table 9: Comparing the area of the wound on day 1 and 7

	Group	N	Mean	Std. deviation	Std. error mean
Ulcer_Area_Day_1	Conventional	35	28.9771	24.09505	4.07281
	Phenytoin	35	28.7714	24.84669	4.19986
Ulcer_Area_Day_7	Conventional	35	27.5911	23.46914	3.96701
	Phenytoin	35	20.7549	19.91622	3.36646
Difference_Week_1	Conventional	35	1.3860	1.95978	.33126
	Phenytoin	35	8.0166	5.17724	.87511
Percent_area_Day_7	Conventional	35	93.8734	8.89887	1.50418
	Phenytoin	35	64.4932	10.94864	1.85066

Table 10: Statistics of reduction in wound area on day 1 and 7

“Independent Samples Test”					
	t-test for Equality of Means				
	t	df	Sig. (2-tailed)	Mean difference	Std. error difference
Ulcer_Area_Day_1	.035	68	.972	.20571	5.85035
Ulcer_Area_Day_7	1.314	68	.193	6.83629	5.20290
Difference_Week_1	-7.086	68	.000	-6.63057	.93571
Percent_area_Day_7	12.320	68	.000	29.38019	2.38485

T-Test

Table 11: Comparing the wound contracture on day 14

“Group Statistics”					
	Group	N	Mean	Std. deviation	Std. error mean
Ulcer_Area_Day_14	Conventional	35	25.1017	22.13608	3.74168
	Phenytoin	35	13.9083	14.11358	2.38563
Difference_Week_2	Conventional	35	2.4666	2.15928	.36499
	Phenytoin	35	6.8466	5.86349	.99111
Percent_area_Day_14	Conventional	35	83.0784	13.09719	2.21383
	Phenytoin	35	40.7781	10.43439	1.76373
Area_Reduction	Conventional	35	3.8754	3.37199	.56997
	Phenytoin	35	14.8631	10.93201	1.84785

Table 12: Statistics of wound contracture on day 14

“Independent Samples Test”					
	t-test for Equality of Means				
	t	df	Sig. (2-tailed)	Mean difference	Std. error difference
Ulcer_Area_Day_14	2.522	68	.014	11.19343	4.43750
Difference_Week_2	-4.147	68	.000	-4.38000	1.05618
Percent_area_Day_14	14.944	68	.000	42.30037	2.83051
Area_Reduction	-5.682	68	.000	-10.98771	1.93375

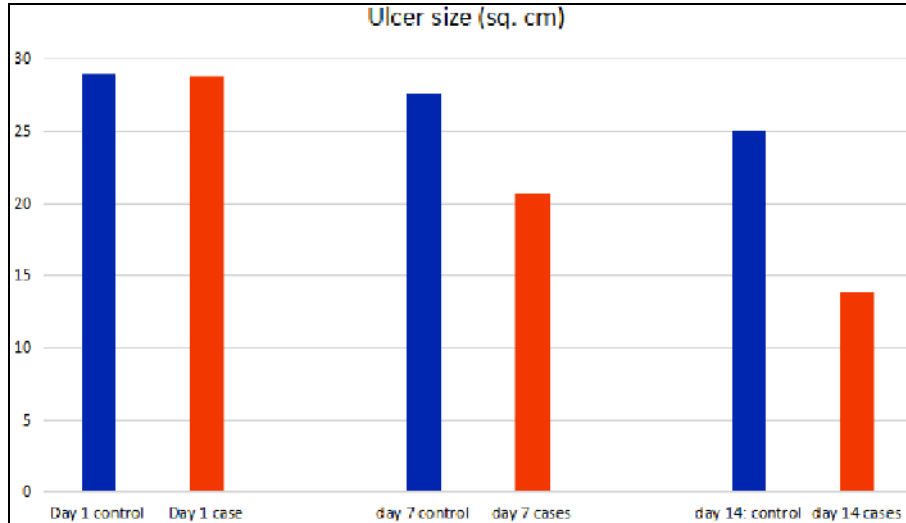


Fig 2: Wound contracture on day 1, 7 and 14

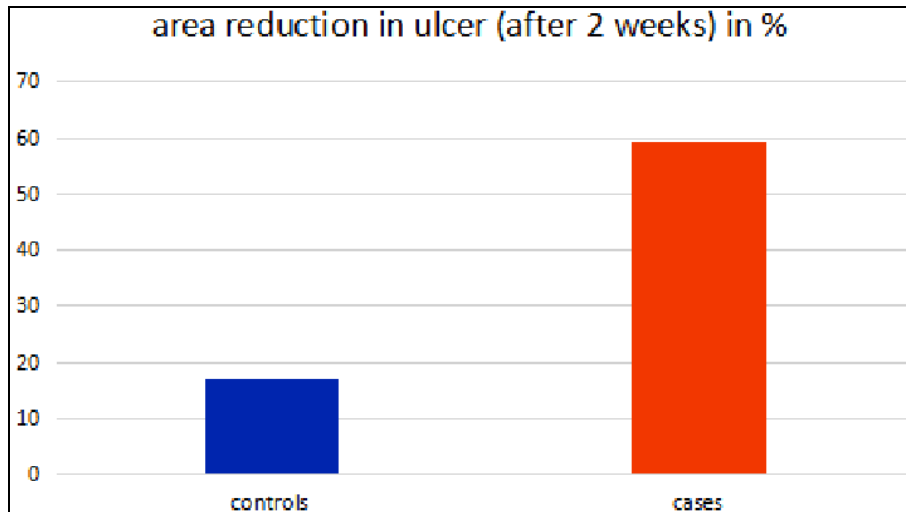


Fig 3: Percentage of area reduction after 2 weeks

Wound contracture is one of the most important parameters in determining the efficacy of phenytoin over conventional dressing. In this study, the area of reduction in phenytoin is better than conventional dressing by the end of 14th day, and it is

also statistically significant with p value of < 0.0001.

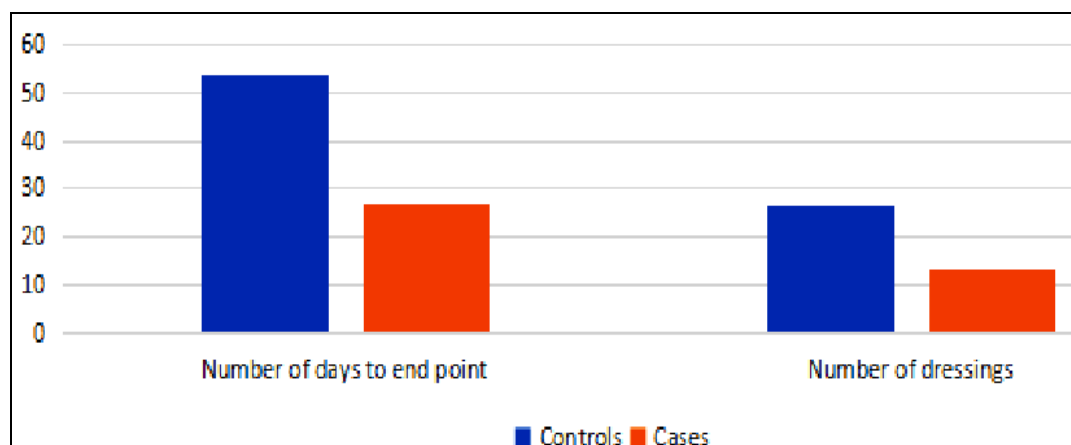
3.5 Duration of stay and average number of dressings

Table 13: Comparing the percentage of wound contracture and duration of hospital stay

“Group Statistics”					
	Group	N	Mean	Std. deviation	Std. error mean
Percentage_Reduction	Conventional	35	17.1359	12.99742	2.19696
	Phenytoin	35	59.2219	10.43439	1.76373
Number_of_days_to_end_point	Conventional	35	53.7143	31.60749	5.34264
	Phenytoin	35	26.5714	13.81663	2.33544
No_of_dressings	Conventional	35	26.9143	15.81766	2.67367
	Phenytoin	35	13.5714	6.78357	1.14663

Table 14: Statistics of percentage of wound contracture and duration of hospital stay

“Independent Samples Test”					
	t-test for Equality of Means				
	t	df	Sig. (2-tailed)	Mean difference	Std. error difference
Percentage Reduction	-14.938	68	.000	-42.08608	2.81734
Number of days to end point	4.655	68	.000	27.14286	5.83079
No of dressings	4.586	68	.000	13.34286	2.90917

**Fig 4:** Duration of hospital stay and no of dressings done for patients

In this study the duration of stay in hospital is significantly lesser in phenytoin dressing over conventional dressing and also the number of dressings is also lesser in case of phenytoin dressing, hence indirectly being cost effective for the patient. It is also statistically significant with p value of <0.0001.

4. Discussion

“Wound healing is a mechanism whereby the body attempts to restore the integrity of the injured part”. There are lot of factors that influence wound healing like site, structure, mechanism of wounding, contamination, loss of tissue, vascular insufficiency, malnutrition, immune deficiencies etc.

Normal wound healing occurs in three phases, they are:

1. “The inflammatory phase
2. The proliferative phase
3. The remodelling phase”.

These acute wounds are managed with “cleansing, exploration and diagnosis, debridement, repair of structures, replacement of loss of tissue, skin cover/closure”. These wound healing is of important concern to surgeons and there are various method incorporated, but there is not a single method that is ideal. Phenytoin is one such agent which improves the wound healing. Phenytoin-it was synthesized by German Chemist Heinrich Biltz in 1908. The usefulness of this in controlling of seizures was discovered by H. Houston Meritt and Tracy Putnam

One of the side effect of phenytoin is hyperplasia of gum which prompted its assessment in wound healing.

The mechanism of wound healing with phenytoin is multifactorial. They are formation of granulation tissue, reducing the slough, bacterial load/reducing the wound size. “In a study by Vijaya Patil, Rashmi Patil; phenytoin has been proved to be useful topical agent in promoting wound healing and control of infection in diabetic ulcers, study was conducted on 100 patients and results were-significant reduction of discharge and slough in wound by 14days in phenytoin group and 21days in control group, mean duration of stay in hospital was 20days in phenytoin group and 26days in control group”.

“A study conducted by Leo F Tauro in 2013, total of 200 patients

were taken, 100 patients underwent phenytoin dressing, 100 patients were subjected to conventional dressing, at the end of 14 days wounds were inspected, the mean rate of granulation tissue formation in study group was 87+7.33% and control group was 74.64+8.04%, mean hospital stay was 36.26+2.64(SD) in study group and 40.97+3.31(SD) in control group and bacterial load was reduced (negative culture sensitivity) 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”.

In this study the phenytoin hastens the wound healing by increasing the granulation tissue, decreasing the slough/bacterial load/area of the wound which is statistically significant.

5. Conclusion

According to this study, Topical phenytoin significantly hasten the wound healing by formation of granulation tissue, reducing the slough, Discharge from wound, bacterial load/reducing the wound size. Phenytoin dressing efficacy over conventional dressing in terms of requirement of dressing is less. The duration of stay in hospital is decreased, hence being cost effective for the patient. Now a days where time is essence, the patient can resume to their daily activities early with phenytoin dressing.

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