East African Medical Journal Vol. 80 No. 3 March 2003
TOPICAL PHENYTOIN VERSUS EUSOL IN THE TREATMENT OF NON-MALIGNANT CHRONIC LEG ULCERS
P.M.R. Carneiro, MD, MMed, Dipl. (Paed. Surg.) and E.T.M. Nyawawa, MD, Department of Surgery, Faculty of Medicine, Muhimbili University College of Health Sciences, P.O. Box 65451, Dar es Salaam, Tanzania

Request for reprints to: Prof. P.M.R. Carneiro, P.O. Box 65451, Dar-es-Salaam, Tanzania

TOPICAL PHENYTOIN VERSUS EUSOL IN THE TREATMENT OF NON-MALIGNANT CHRONIC LEG ULCERS

P.M.R. CARNEIRO and E.T.M. NYAWAWA

ABSTRACT

Objective: **To compare topical diphenylhydantoin (phenytoin) with Edinburgh University solution of lime (EUSOL) in terms of rate of ulcer healing, analgesic and antibacterial properties in non-malignant chronic leg ulcers.**

***Design*: A prospective randomized controlled study.**

***Setting*: Muhimbili National Hospital surgical wards from August 2000 to September 2001.**

***Patients*: one hundred and two patients with non-malignant chronic leg ulcers of various aetiologies, 50 in the study (phenytoin)group and 52 in the control(EUSOL) group.**

***Interventions*: Study group studied by sprinkling phenytoin powder and the control group with EUSOL, in both groups the ulcers were addressed daily and followed up for 28 days or until they epithelialised or were ready for skin grafting. The data collected included demographic characteristics of patients, aetiology of the ulcers, pus discharge, severity of pain due to the ulcers, bacterial cultures from ulcer swabs, rate of reduction in mean ulcer surface area and outcome of treatment.**

***Results*: The study enrolled 67 male and 35 female patients over a 14 month period (August to September 2001). Fifty patients formed the study group and 52 formed the controls. The age range was 12-56 years; the majority being in the 27-31 year age group. Major causes of chronic leg ulcers were those infected following trauma (27.5%), chronic non-specific inflammations (21.6%) and infected burn wounds (15.7%). At enrolment, the duration of ulcers ranged from 3-156 weeks and 3-128 weeks in the phenytoin and control groups respectively. Overall, there was significant reduction in pain($p<0.05$) on day seven in the phenytoin group. Furthermore in patients who presented with severe pain, there was a significant reduction in pain in the phenytoin group on the fourteenth day ($p<0.01$). Clearance of ulcer discharge was also significant in the phenytoin group on the seventh and fourteenth day of treatment($p<0.05$). The commonest bacteria isolated were *pseudomonas aeruginosa*(54.9%) and *staphylococcus aureus*(10.8%). However, bacterial colonization clearance was not statistically significant when the two groups were compared. The rate of formation of healthy granulation tissue was highly significant in the phenytoin group by the fourteenth and twenty first days of treatment ($p<0.001$).The phenytoin group showed significant reduction in the mean ulcer surface area on days 7,14,21 and 28 ($p<0.05$). Chronic ulcers due to animal bites healed fastest followed by those due to trauma.**

***Conclusion*: Phenytoin powder is cheap and easily applied topically on ulcers, effectively relieves pain, clears discharge and enhances formation of granulation tissue thereby promoting healing; reducing morbidity and financial burden enabling its use in resource-poor environments.**

INTRODUCTION

Non-malignant chronic leg ulcers of various aetiologies have been a major health problem worldwide including Tanzania, accounting for major patient morbidity and financial burden. Aetiologies of chronic ulceration of the leg include infected traumatic wounds such as animal bites, post operative wounds and burn injury, tropical ulcers ; arterial and venous insufficiencies stemming from vericose vein disease, arteriosclerosis, diabetes and prolonged pressure; trophic changes as a result of neurologic disorders and leprosy; as well as changes accompanying systemic diseases such as sickle cell disease, myxoedema and chronic infection.

Therapy of chronic leg ulceration has been varied and non-specific since no regime has been completely

effective. Treatment has been aimed at providing for the optimal condition required for the natural healing process to advance. This consists of halting or reversing the underlying conditions that caused the ulcer, controlling infection, rest and elevation. Systemic and topical antibiotic therapy has been used to control infection, while other topical therapies have included debridement (both mechanical and enzymatic), local antisepsis with numerous chemicals (iodine, peroxide, ultraviolet radiation, hypochlorites(1), sugars(honey)(2), specialized protective dressing, etc. All of these therapeutic approaches have been of limited success due to many factors including poor nutritional status, vascular insufficiency and the many difficulties of prolonged therapy.

Phenytoin (diphenylhydantoin), a hydantoin derivative first used in 1938 to control convulsive disorders(3), has been found to have a distinct and beneficial role in the biology of wound repair(4). Its ability to reduce pain and promote healing (5-7) suggests that it should be useful in treating chronic leg ulcers.

Given the strong laboratory(8-9) and clinical(3,10) evidence of phenytoin's effectiveness, a clinical trial was carried out to compare topical phenytoin with Edinburgh University Solution of Lime(EUSOL), a commonly used calcium hypochlorite solution for dressing chronic leg ulcers in our enviroment.

MATERIALS AND METHODS

This was randomized, controlled, prospective study. The study group consisted of 50 patients with non-malignant chronic leg ulcers treated with phenytoin powder and the control group consisted of 52 similar patients treated with EUSOL. The study was carried out in all surgical wards in Muhimbili National Hospital where patients with chronic leg ulcers are admitted. Patients taking oral phenytoin or hypersensitive to it and those on immunosuppressive or steroid therapy were excluded. Also not included were pregnant women and subjects with any other condition or therapy that might pose a risk.

The ulcers were cleaned with normal saline and debrided daily as required until a clean tissue base and healthy bleeding were observed. A uniform, thin layer of phenytoin powder was then applied on the ulcer surface in the study group and sterile gauze soaked in EUSOL in the control group. All ulcers were then dressed with sterile dry gauze. The dressings were changed every day for 28 days unless complete healing occurred or uniform granulation tissue appeared earlier. The latter then skin-grafted.

Swabs for culture and sensitivity from the ulcers were taken on admission, days 7,14,21 and 28. Patients were interviewed and the ulcers were inspected weekly by one investigator to assess presence of discharge (pus), severity of wound pain using the analog scale, appearance of healthy granulation tissue and rate of ulcer healing. The latter was assessed by tracing the ulcer area on a transparent plastic sheet and it's reduction in size measured by counting the size of the area by the number of squares covered on a millimeter paper. Determination of ulcer surface area was done on admission (baseline), days 7,14,21 and 28.

Ethical clearance and patient consent was obtained after fully explaining on details of the study. The results were then analyzed and subjected to statistical tests (Chi-square test for categorical variables and student's t-test for means).

RESULTS

One hundred and two patients with non-malignant chronic leg ulcers were enrolled over a 14 month period (August 2000-September 2001), 50 patients in the study group and 52 in the control group. Sixty seven were male and 35 were female patients, there was no significant difference in the sex distribution between the two groups. The mean age in the phenytoin group was 32.50±14.87 years and in the EUSOL group was 34.20± 14.72 years. A higher proportion of patients (19.6%) were in the age group 27-31 years but there was no significant difference in the age distribution. Major causes of ulcers (Table 1) were due to chronic infection following trauma (27.5%), chronic non-specific inflammations (21.6%), and infected burn wounds (15.7%). The mean duration of the ulcers at enrollment in the phenytoin group was 20.52±30.78 weeks and in the EUSOL group was 21.90±27.99 weeks, there was no statistical difference between the two groups. All patients presented with either bearable or severe pain and there was no significant difference between the two groups on admission. On day seven, (Table 2) a higher proportion of patients in the phenytoin group presenting with severe pain converted to experiencing bearable pain compared to the EUSOL group and this difference was statistically significant ($p<0.05$). Significant reduction in pain was further seen in the phenytoin group on day 14 ($p<0.01$) in patients who initially presented with severe pain (Table 3). A higher proportion of ulcers in the phenytoin group showed clearance of discharge (Table 4) by the seventh and fourteenth day and this difference was statistically significant ($p<0.05$). In both groups, all ulcers except one revealed a positive bacterial growth before starting treatment and the commonest bacteria isolated were *pseudomonas aeruginosa* (54.9%) and *staphylococcus aureus*(10.8%). However, absence of bacterial colonization on days 7,14,21 and 28 was not statistically different when the two groups were compared. None of the patients had a healthy granulation tissue on admission (Table 5) and the rate of its formation was highly significant in the phenytoin group by the fourteenth and twentyfirst days of treatment ($p<0.001$). The ulcer surface areas ranged from 14-300cm^2 and 12-300cm^2 and their means were 119.79±89.55cm^2 and 79.59±71.72 cm^2 in the study and control groups respectively. There was a significant reduction($p<0.05$ and $p<0.01$) in the mean ulcer surface areas in the phenytoin group on all days measured(7,14,21,28) (Table 6). Figure 1 compares the mean percentage reduction in surface area of the ulcers during treatment in the two groups revealing a faster rate of healing in the phenytoin group. Chronic ulcers due to animal bites healed faster followed by trauma (Figure 2).

Table 1

Distribution according to aetiology of ulcers

Aetiology	Phenytoin No.	EUSOL No.	Total No.	(%)
Trauma	16	12	28	27.5
CNSI*	10	12	22	21.6
Burn	7	9	16	15.7
Diabetic	5	8	13	12.7
Tropical	7	6	13	12.7
Animal Bite	3	2	5	4.9
Venous	2	3	5	4.9
Total	50	52	102	100.0

*Chronic non-specific inflammation

Table 2

Distribution according to severity of pain

Assessment Day	Treatment Group	Severity of Pain			P-value
		Severe	Bearable	No Pain	
Admission Day	Phenytoin	27	23	0	p<0.05
	EUSOL	24	28	0	
Day 7	Phenytoin	4	45	1	p<0.05
	EUSOL	24	27	1	
Day 14	Phenytoin	7	28	15	p<0.05
	EUSOL	7	34	11	
Day 21	Phenytoin	5	10	35	p<0.05
	EUSOL	7	25	20	
Day 28	Phenytoin	0	8	39	p<0.05
	EUSOL	2	12	32	

Table 3

Progress of patients presenting with severe pain

Assessment Day	Presence of Pain	Phenytoin	EUSOL	P-value
Admission Day	Yes	27	24	p>0.05
	No	0	0	
Day 7	Yes	23	24	p<0.05
	No	4	0	
Day 14	Yes	7	17	p<0.01
	No	20	7	
Day 21	Yes	5	7	p>0.05
	No	22	17	
Day 28	Yes	0	2	p>0.05
	No	27	22	

Table 4

Clearance of ulcer discharge

Assessment Day	Treatment	Nature of discharge			P-value
		Purulent/ foul-smell No.	Serous/ clear No.	Absent No.	
Admission Day	Phenytoin	49	1	0	P>0.05
	EUSOL	51	1	0	
Day 7	Phenytoin	37	13	0	P<0.05
	EUSOL	48	4	0	
Day 14	Phenytoin	12	35	3	P<0.05
	EUSOL	23	29	0	
Day 21	Phenytoin	3	28	19	P>0.05
	EUSOL	5	32	15	
Day 28*	Phenytoin	2	8	37	P>0.05
	EUSOL	3	16	32	

*By 28th day, three patients in the pheytoin group and one in the EUSOL group had been discharged.

Table 5

Healthy granulation tissue formation rate

Assessment Day	Presence of Healthy Granulation Tissue	Phenytoin	EUSOL	P-value
Admission Day	Yes	0	0	p>0.05
	No	50	50	
Day 7	Yes	3	0	p>0.05
	No	47	52	
Day 14	Yes	31	5	p<0.01
	No	19	47	
Day 21	Yes	44	25	p>0.01
	No	6	27	
Day 28	Yes	45	43	p>0.05
	No	2	8	

Table 6

Decrease in ulcer mean surface area (cm^2).

Assessment Day	Phenytoin	EUSOL	P-value
Day 7	20.92±13.45	14.90±17.39	p<0.05
Day 14	40.26±21.24	29.21±17.42	p<0.01
Day 21	54.55±22.31	43.13±17.27	p<0.01
Day 28	66.50±22.01	58.70±18.06	p<0.05

Figure 1

Mean percentage reduction in surface area of ulcer during treatment in the two groups

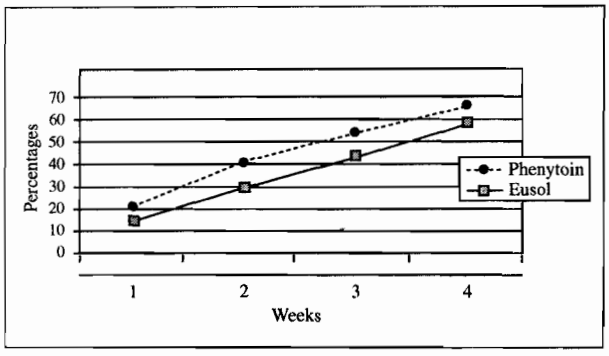
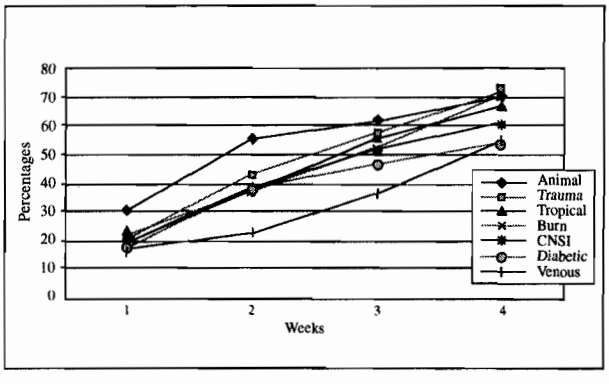


Figure 2

Mean percentage reduction in surface area phenytoin treated ulcers



DISCUSSION

Contrary to what is seen in the developed world, in our enviroment the lower limb is often vulnerable to trauma and the lack of appropriate management including resting the limb leads to chronic ulcer. Infection and poor circulation contribute to the chronicity of the ulcers(11).

This prospectively controlled trial demonstrates that topical application of phenytoin on ulcers of various aetiology is an effective and safe method to promote healing as was also shown in other studies(10-14). In the phenytoin treated group, ulcer discharge dissapeared faster; healthy granulation tissues appeared earlier and formed more rapidly and there was significant alleviation of pain minimising the use of analgesics. The local analgesic property of topical phenytoin is due to its selective depression of repetitive neuronal activity and synaptic transmission(4). The sodium-free phenytoin powder has been reported to avoid the initial burning sensation in patients(7). Phenytoin accelerates wound healing and improves the quality and vascularity of granulation tissue by increasing fibroblast proliferation(15-16) increasing collagen content and maturation(8-16) and decreasing collagenase activity(16-17).

Pendse and Sodan(10) found in their phenytoin-treated ulcers significant reductions in both surface area and bacterial colonization, however, the latter was not evident in this study. El Zayat(18) reported reduction of wound contamination with phenytoin and postulated that it is not a direct anti-bacterial effect, but rather the result of a change in wound pH and improvement in local circulation probably explaining the early clearance of ulcer discharge in our study.

The absence of local or systemic side effects of topical phenytoin in this study and others indicates its safety(14,18). Previous studies have excluded the occurrence of transwound absorption in large wounds(5,19). Further clinical trials are recommended to evaluate the optimal topical dose(amount and frequency); the use of a delivery vehicle or ointment base; combination with other agents or modes of therapy; amount of systemic absorption (if any); and mechanisms by which phenytoin acts. Modaghegh *et al*(7) postulates that phenytoin may increase the number or sensitivity of epidermal growth factor (EGF) receptors or affect EGF release.

Considering the effectiveness of phenytoin in accelerating ulcer healing by enhancing granulation tissue formation, minimising pain, reducing ulcer discharge and surface area, the authors strongly recommend its use as a safe, effective, easy-to-use, and inexpensive medicament in the treatment of ulcers of various aetiologies in resource-scarce countries.

ACKNOWLEDGEMENTS

The authors are grateful to the Dreyfus Health Foundation based in New York for supporting this research work and to Mr. C. Makwaya and Mrs. C. Mpembeni from the Department of Biostatistics and Epidemiology, Muhimbili University College of Health Sciences for assisting in the statistical analysis.

REFERENCES

1. Dakin, H.D. The use of certain antiseptic substances in the treatment of infetced wounds. *Brit. Med. J.* 1915; **2**:318-320
2. Oluwatosin, O.M., Olabanji, J.K., Oluwatosin, O.A., Tijani, L.A., Onyechi, H.U. A comparison of topical honey and phenytoin in the treatment of chronic leg ulcers. *Afr. J. Med. Sci.* 2000; **29**:31-34.
3. Rall, T.W. and Schleifer, L.S. Drugs effective in the therapy of the Epilepsies. In: Goodman and Gilman's. The pharmacological Basis of Therapeutics, Gilman A.G., Goodman L.S. and Gilman A. *Macmillan Publishing Co.,inc. New York., 6th Ed.* 1980: 448.

4. Smith, B.H., Bogock, S. and Dreyfus J. The Broad Range of Clinical Use of Phenytoin. Dreyfus Health Foundation. *New York.* 1988; 89-120.
5. Mendiola-Gonzalez, J.F., Espejo-Plascencia, I., Chapa-Alvarez, J.R. and Rodriquez-Noriega, E. Sodium diphenylhydantoin in burns: effects on pain and healing. *Invest. Med. Int.*, 1983; **10:**449-451.
6. Shapiro, M. Acceleration of gingival wound healing in non-epileptic patients receiving diphenylhydantoin sodium. *Exp. Med. Surg.* 1958; **16:**41-53.
7. Modaghegh, S., Salehian B., Tavassoli M., Djamshidi A., and Rezai A.S. Use of Phenytoin in healing of War and non-War wounds.A pilot study of 25 cases. *Int. J. Dermatol.* 1989; **28:**347-350.
8. Bazin, S. and Delaunay, A. Effect of phenytoin in the maturation of collagen in normal skin and granulomatous tissue. *CR Acad Sci.*, 1972; **275:**509-511.
9. Sklans, S, Taylor R.G. and Shaklar, G. Effect of diphenylhydantoin sodium on healing of experimentally produced fractures in rabbit madibles. *J. Oral Surg.* 1967; **25:**310-319.
10. Pendse, A.K. and Sodan, A. Topical phenytoin in wound healing. *Int. J. Dermatol.* 1993; **32:**214-216.
11. Rodriquez-Noriega, E., Esparza-Ahumada, S, Andrade-Perez, J.S., Espejo-Plascencia I., and Chapa-Alvarez J.R. Treatment of soft tisue ulcerations with topical diphenylhydantoinate. *Invest. Med. Int.* 1983; **10:**184-186.
12. Bansal, N.K. and Mukul, A.A comparison of topical phenytoin with normal saline in treatment of chronic tropical ulcer in leprosy. *Int. J. Dermatol.*, 1993; **32:**210-213.
13. Simpson, G.M, Kunz E. and Slafta J. Use of sodium diphenylhydantoin in treatment of leg ulcers. *N.Y. State J. Med.* 1965; **65:**886-888.
14. Muthukumarasamy, M.G., Sivakumar, G. and Manoharan, G. Topical phenytoin in diabetic foot ulcers. *Diabetic care.* 1991; **14:**909-911.
15. Matsuo, A. and Yajima, T. Cell proliferation and collagen fibrogenesis of cultured fibroblasts. *Jpn. J Oral Biol.*, 1985; **27:**53-63.
16. Moy, L.S, Tan, E.M., Holness, R. and Uitto, J. Effects of phenytoin on collagen metabolism and growth of skin fibroblasts in culture. *Clin. Res.* 1983; **31:**22A.
17. Bergenholtz, A. and Hanstrom L. The effect of diphenylhydantoin upon the biosynthesis and degradation of collagen in cat palatal mucosa in organ culture. *Biochem. Pharmacol.* 1979; **28:**2653-2659.
18. El-Zayat, S. Preliminary experience with topical phenytoin in wound healing in a war zone. *Milit. Med.* 1989; **154:** 178-180.
19. Bajaj, S.P. Presented at the First International Conference on the uses of phenytoin in wound Dermatology. *Int. J. Dermatol.* 1988; **27:**528-530.