Two percent topical phenytoin sodium solution in treating pyoderma gangrenosum: a cohort study

Hewa Fonsekage Sanjeewani Fonseka, Sandeepa Madhujith Bandara Ekanayake, Manel Dissanayake

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ABSTRACT

Oral phenytoin is an extensively used medicine for the treatment of convulsive disorders. Topical phenytoin has also been used for various types of ulcers. To determine the effectiveness of 2% topical phenytoin sodium solution in treating recalcitrant pyoderma gangrenosum. Six patients with treatment-resistant pyoderma gangrenosum who attended to Dermatology Unit/Ward were taken to the study and applied topical 2% phenytoin sodium solution to the wounds alone with other systemic therapy. Response to the treatment was assessed weekly. Three patients had idiopathic PG and other three had secondary diseases. At the end of the 4th week four patients showed complete resolution of the ulcers whereas other two patients showed the partial resolution. No adverse effects were noted. Phenytoin sodium 2% solution is beneficial for pyoderma gangrenosum (PG) with various etiologies. It enhanced the healing of the ulcer especially when the patient has treatment resistant disease.

Key words: pyoderma • Venous ulcers • Wound dressing

INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon, chronic, painful, ulcerative skin disease. In PG, the initial lesion appears as a red papule or pustule changing into a larger ulcerative lesion with undermined edges (1). The prognosis of PG is generally good, however, recurrences may occur and residual scarring is common. The diagnosis is made by excluding other causes of similar-appearing cutaneous ulcerations, including infection, malignancy, vasculitis, collagen vascular diseases, diabetes and trauma (2).

The mainstay of therapy for PG has been high-dose corticosteroids but not all patients have a favourable outcome. Other systemic agents have also been used such as cyclosporine (3), azathioprine (4), cyclophosphamide (5) and tacrolimus. However, all these systemic therapies can be complicated by serious side effects. Topical treatments that have been shown some effects are those with steroids, cyclosporine and tacrolimus (6). Topical phenytoin has proven useful for a wide variety of soft tissue wounds such as trophic ulcers, decubitus ulcers, diabetic foot ulcers, burns, traumatic wounds, war-related missile wounds, venous stasis ulcers and abscesses (7,8).

Authors: HFS Fonseka, (MBBS, MD), Department of Dermatology, Teaching Hospital, Kandy, Sri Lanka; SMB Ekanayake, (MBBS, MD), Department of Dermatology, Teaching Hospital, Kandy, Sri Lanka; M Dissanayake, (MBBS, MD), Department of Dermatology, Teaching Hospital, Kandy, Sri Lanka
Address for correspondence: HFS Fonseka, Senior Registrar in Dermatology, Department of Dermatology, Teaching Hospital, Kandy, Sri Lanka, 14/2, Sisila Mawaththa, Paraththa, Keselwaththa, Sri Lanka
E-mail: sanjeewani.fonseka@yahoo.com

Key Points

- pyoderma gangrenosum (PG) is an uncommon, chronic, painful, ulcerative skin disease
- topical phenytoin has proven useful for a wide variety of soft tissue wounds such as trophic ulcers, decubitus ulcers, diabetic foot ulcers, burns, traumatic wounds, war-related missile wounds, venous stasis ulcers and abscesses

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Key Points

- as topical phenytoin has been proven to be effective on various types of wounds, we started topical 2% phenytoin sodium suspension for patients with treatment-resistant PG and patients with slow response
- in this paper, we report a group of six patients with PG treated successfully with topical 2% phenytoin sodium solution

Systemic absorption of topical phenytoin is not significant except one case report which showed significant levels of serum phenytoin after topical phenytoin to a large wound (9).

The best method of delivery of topical phenytoin is not known. Phenytoin powder has been applied directly to wounds in a thin, uniform layer, and then covered with gauze. However, the powder from the capsules is reported to cause a white eschar-like coating. This can be prevented by mixing phenytoin with NaCl (0·9 %) and applying this with gauze (10). Injectable phenytoin has a high pH (about 12) and should not be used topically because it can damage skin (9). One suggested formula is the use of phenytoin powder (90% to 100%) with Polyox™. Polyox™ is a polymer that can bind with water and help the powder maintain contact with the skin (11). There were researches which were performed with 2% and 4% phynytoin sodium suspention (12). As researches are mostly performed with 2–4% phenytoin sodium, we decided to use phenytoin sodium suspension. In our country, topical tacrolimus is used very rarely because of its high cost and topical cyclosporine is not available at all, which are standard topical treatment for PG. Topical corticosteroids are the only topical drug that is freely available for PG in our country and when there is poor response to it there is no other cheap alternative. As topical phenytoin has been proven to be effective on various types of wounds (13–15), we started topical 2% phenytoin sodium suspension for patients with treatment-resistant PG and patients with slow response.

In this paper, we report a group of six patients with PG treated successfully with topical 2% phenytoin sodium solution.

MATERIALS AND METHODS

Patients

The study population included six patients with PG (idiopathic or secondary). Diagnosis was carried out with typical clinical findings, investigations and exclusion of other possible causes (Table 1). The subject had the willingness and the ability to understand and provide informed consent. (study design: a cohort study; study setting: Dermatology Clinic/Ward of Teaching Hospital Kandy Sri Lanka.)

Primary outcome measures

Wound improvement was measured using photographic documentation, measuring the size using oil papers and asking patients' view about treatment efficacy. Wounds were observed for the presence of healthy granulation tissue, reduction in surface dimensions and time to heal. Adverse events were also noted.

Intervention

Phenytoin sodium solution (2%) was applied directly (in wet gauze) to wounds daily. The solution was made using normal saline. Other interventions such as treating bacterial infection etc. were carried out accordingly (wound swabs were taken for bacterial culture and antibiotic sensitivity test (ABST) when indicated by clinical features).

Table 1 Clinical features and investigations for diagnosis of PG

Patient No	Biopsy*	Antibody positive	Antibody negative	Duplex (arterial and venous)	Protein electrophoresis	Specific clinical features
1	Not done		ANA, RF	Normal	Normal	
2	4	RF (weakly), U1RNP	ANA, dsDNA, SCL 70	Normal	Not done	Scleroderma, RA features†
3	1, 2		ANA, RF	Normal	Not done	Positive pathergy, orogenital ulcers
4	Not done	RF (weakly) U1RNP	ANA, SCL 70	Normal	Not done	Scleroderma†
5	3		ANA, RF	Normal	Normal	
6	Not done		ANA, RF	Normal	Normal	

*Biopsy findings: 1 – neutrophilic vascular reaction, 2 – leukocytockasia, 3 – tissue necrosis with mononuclear cell infiltrate, 4 – fibrosing inflammation.

†Not fulfilling criteria for diagnosis.

Table 2 Demographic data and treatment details of patients

Patient No	Age	sex	Duration of PG	Cause	Systemic therapy	Duration (month)	Duration of topical Betamethasone
1	55 years	Male	10 years	Idiopathic	Prednisolone, cyclophosphamide,	12	3 months
2	50 years	Female	10 years	MCTD	M. prednisolone pulse, azathioprine	20	6 months
3	25 years	Male	1 years	Behcet's	M. prednisolone pulse, azathioprine	6	6 weeks
4	40 years	Female	2 years	MCTD	Prednisolone, cyclophosphamide,	6	6 weeks
5	44 years	Female	8 years	Idiopathic	None		6 months
6	57 years	Female	10 years	Idiopathic	Prednisolone,azathioprine	8	2 months

MCTD, mixed connective tissue disorder.

Table 3 Details of ulcers and percentage improvement

Patient No	Site	Size (cm) before treatment		Percentage improvement at end of treatment			
		Length	Width	1st week	2nd week	3rd week	4th week
1	Lower calf	11	3·5	10	25	40	60
2	Medial maleolus	1	1	15	40	60	80
		1·2	1·5	20	40	75	100
3	Lateral calf	2	2	25	60	85	100
4	Medial calf	2	2	30	70	100	100
5	Foot-dorsum	3	2	30	50	80	100
6	Medial maleolus	5	4·5	5	10	15	20

Evaluation

Patients were followed up weekly at Dermatology Clinic and those who admitted were evaluated weekly at the ward.

RESULTS

Patients' demographic data and their treatments are shown in Table 2.

All six patients had been treated with betamethasone as the only topical therapy immediately prior to starting topical phenytoin sodium and the duration is mentioned in Table 2. Except patient 5 other patients were on systemic treatments which were continued, and topical betamethasone was discontinued after starting phenytoin sodium dressings. Systemic treatment was discontinued on patient 5 as a result of adverse effects and poor response 7 months prior to starting topical phenytoin sodium. Other topical treatments tried in the past were hypertonic saline dressings, povidone iodine dressings and topical antibiotics.

All six patients showed very mild improvement of wound size while being treated with systemic agents and topical betamethasone.

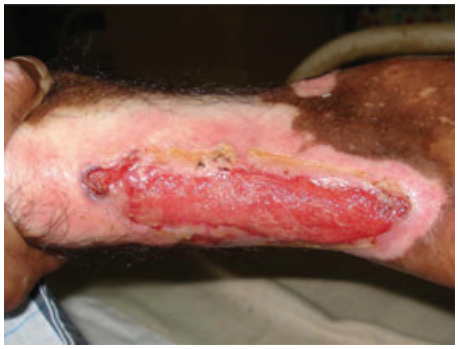

Figure 1. Patient 1 – before treatment.

The addition of topical 2% topical phenytion sodium solution was associated with fast healing of those ulcers and four out of six were completely healed at the end of 4th week (Table 3), whereas other two ulcers also showed a marked improvement (Figure 1–6). The improvement was associated with healthy granulation tissues, reduction of surface diameter, and we did not experience any increase in wound infections (patient 3 had pseudomonas infection before starting topical phenytoin which was treated with systemic ceftazidime

Key Points

- all six patients showed very mild improvement of wound size while being treated with systemic agents and topical betamethasone
- the addition of topical 2% topical phenytion sodium solution was associated with fast healing of those ulcers and four out of six were completely healed at the end of 4th week, whereas other two ulcers also showed a marked improvement
- the improvement was associated with healthy granulation tissues, reduction of surface diameter, and there was no increase in wound infections

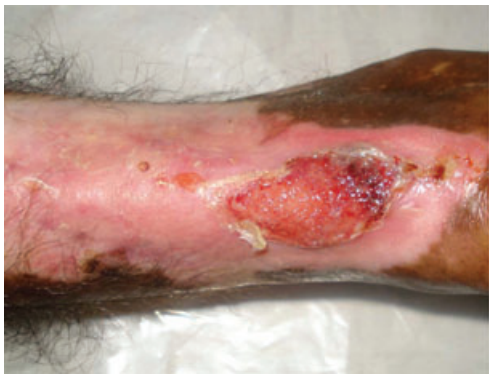

Figure 2. Patient 1 – after 4 weeks.

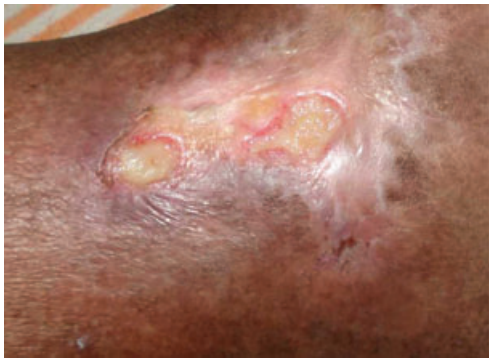

Figure 3. Patient 2 – after 1 week.

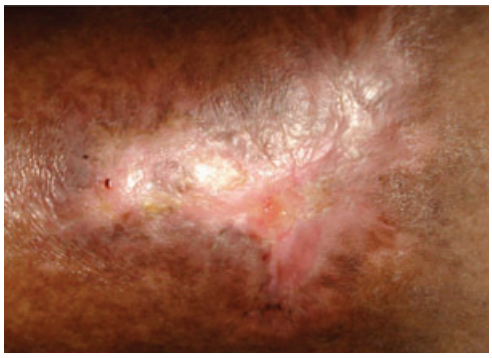

Figure 4. Patient 2 – after 4-week treatment.

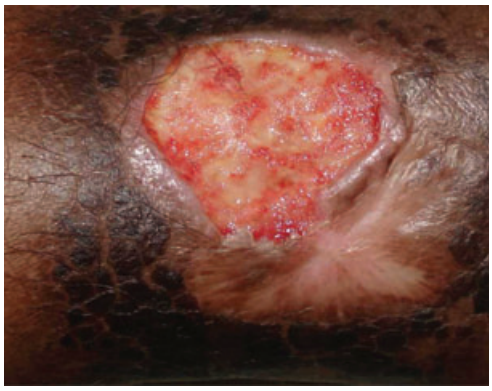

Figure 5. Patient 6 – before treatment.

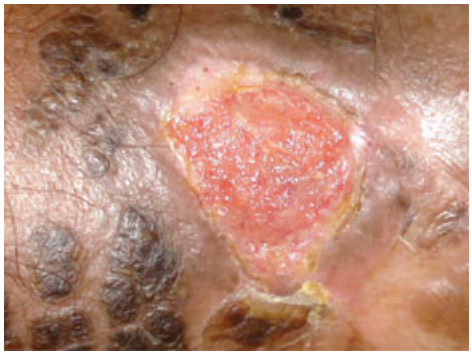

Figure 6. Patient 6 after 4-week treatment. There is evidence of surface reduction and healthy granulation tissue which was not achieved while using topical betamethasone.

Key Points

- as PG is an inflammatory disease it can be argued that systemic drugs may have halted the disease process and phenytoin may have simply helped in the healing process via its multiple mechanisms
- on the other hand, it can be argued that phenytoin sodium carries its own intrinsic anti inflammatory activity, because these patients responded to topical phenytoin therapy when there was poor response to combined systemic drugs with topical corticosteroids
- there is no current literature at present on topical phenytoin for PG and how it enhances the healing of PG
- it is unknown if phenytoin has intrinsic antibacterial activity, or if the effect of phenytoin on the bacterial load of wounds is mediated indirectly by effects on inflammatory cells and neovascularisation

for 7 days after culture ABST). Except mild transient burning sensation in two patients, none of the patients developed any side effects.

DISCUSSION

These results suggest that topical 2% phenytoin sodium solution is effective in treating patients with PG of various etiologies. The improvement was dramatic. Topical phenytoin may be highly effective when other systemic or topical treatments have been unsuccessful. As PG is an inflammatory disease it can be argued that systemic drugs may have halted the disease process and phenytoin may have simply helped in the healing process via its multiple mechanisms. On the other hand, it can be argued that phenytoin sodium carries its own intrinsic anti-inflammatory activity, because these patients responded to topical phenytoin therapy when there was poor response to combined systemic drugs with topical corticosteroids. However, there is no current literature at present on topical phenytoin for PG and how it enhances the healing of PG.

Topical phenytoin causes fibroblast proliferation, enhancing the formation of granulation tissue, decreasing collagenase activity (by reducing its production or secretion or both), promoting deposition of collagen and other connective tissue components, decreasing bacterial contamination, and decreasing wound exudate (9,16,17).

A number of clinical studies show that phenytoin decreases the bacterial load of wounds (18–21). Topical phenytoin was reported to eliminate *Staphylococcus aureus*,

Escherichia coli, *Klebsiella* spp. and *Pseudomonas* spp. from wounds within 7–9 days (18). It is unknown if phenytoin has intrinsic antibacterial activity, or if the effect of phenytoin on the bacterial load of wounds is mediated indirectly by effects on inflammatory cells and neovascularisation (18). In our cohort of patients, we noted that secondary bacterial infections were less and wound surface looked healthy.

Phenytoin sodium is freely available, cheap and easy to prepare. If this cheap treatment modality is effective it will be a great advantage for doctors and patients. The apparent stimulatory effect of phenytoin on connective tissue suggests an exciting possibility for its use in wound healing which need to be further researched. For countries with limited resources topical phenytoin may be an alternative drug for PG. Although randomised control trials are needed to assess its efficacy with stranded drugs, the low incidence of PG makes it difficult task.

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Key Points

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- the apparent stimulatory effect of phenytoin on connective tissue suggests an exciting possibility for its use in wound healing which need to be further researched
- for countries with limited resources topical phenytoin may be an alternative drug for PG
- although randomised control trials are needed to assess its efficacy with stranded drugs, the low incidence of PG makes it a difficult task