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# Original Articles

# THE EFFECT OF PHENYTOIN ON HEALING OF WAR AND NON-WAR INTRACTABLE WOUNDS

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**ABSTRACT**

Phenytoin (PHT), a drug in clinical use for over fifty years as an anticonvulsant, has been reported to promote the healing of skin and soft tissue wounds, ulcers and second degree burns.

We treated 19 patients with war-related missile wounds and 6 with chronic, non-healing (previously treated at least for 5 months with antibiotics and betadine or acetic acid dressing) civilian ulcers with topical phenytoin sodium powder daily without antibiotic therapy for up to 4 weeks. Missile wounds had a mean healing time of 2 weeks and civilian intractable ulcers, a maximum healing time of 4 weeks, compared to historical controls requiring 6-8 weeks for missile wounds and at least 5 months of non-effective previous treatment for intractable wounds.

Twenty two patients showed complete healing within four weeks. Three required skin grafts for final closure. PHT provided rapid pain relief. Although seventeen wounds had positive bacterial cultures prior to treatment, none were positive after one week of PHT treatment. No antibiotics were required. We believe wider use of this safe, inexpensive, readily available, and easy-to-use wound healing agent is indicated.

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## INTRODUCTION

Phenytoin (PHT), used topically or orally, has been reported to enhance the healing of various types of cutaneous ulcers, including venous stasis, decubitus, diabetic and trophic ulcers in leprosy, as well as second-degree burns.

Bodkin, in 1945, reported that phenytoin promoted healing in pruritus ani.[1] In 1958, Shapiro studied the effects of oral phenytoin pretreatment on the healing of surgically-created gingival wounds in patients with periodontal disease. Wounds in the phenytoin-treated patients not only showed accelerated healing, but also were less painful. Histological examination revealed accelerated clot organization and neovascularization, decreased inflammatory infiltrate, increased numbers of young fibroblasts, increased numbers of collagen fibrils, and prominent epithelial proliferation.[2]

Subsequent work substantiated Shapiro's findings and extended the use of phenytoin to topical applicatoin in periodontal disease.[3-6] Much of this work was done in East Germany and France in the 1970's. A topical preparation of phenytoin for use in periodontal disease is currently marketed in France.

The benefits of topical PHT in the treatment of chronic skin ulcers and second-degree burns were

reported by Rodriguez-Noriega, Gonzalez, et al[8] in 1983. Currently there are topical phenytoin clinical trials being conducted for ulcers and/or burns in the Dominican Republic, Ghana, India, Mexico, and Srilanka, among other countries.[9-12] Some work has also been done in the United States, and further trials are being organized there.

Because of these encouraging results, and because of our need for easily applicable, efficacious, inexpensive and readily available topical agents for the treatment of wounds, we have conducted a clinical trial of topical phenytoin in war and other wounds at the Shahid Rahnamun Hospital in Tehran. It was our hope that the use of topical phenytoin would alleviate the suffering of patients afflicted with such wounds.

## PATIENTS AND METHODS

Twenty-five patients were treated with topical sodium phenytoin in an open trial. Nineteen of these patients had war-related missile injuries. The other six had the following wounds: decubitus ulcers (3), diabetic ulcer (1), iatrogenic (1) and industrial (machine) injury (1) (see Table I). All the patients were male, and age ranged from 18 to 65.

Most of the war-injured patients were treated with topical phenytoin within ten days of the injury. The six patients with non-war wounds had previously been treated for at least five months with various other therapies including antibiotic therapy and betadine and/or acetic acid dressing. Their lesions had not only failed to improve, but they actually worsened.

At the onset of phenytoin treatment, all antibiotics and antiseptic dressings were discontinued. Wound swabs were taken for bacterial cultures initially and repeated weekly during phenytoin treatment. Wound area was measured by planimetry in some patients when possible, and initial wound size ranged from 12-700 $cm^2$.

All wounds were debrided as necessary. Necrotic tissue was removed until a clean tissue base and healthy bleeding were observed. At this point, the wound was cleansed with normal saline, dried, and covered with a uniform, thin layer of phenytoin sodium powder. Dressing change and phenytoin application was performed daily during the course of treatment, which ranged from 2 to 4 weeks, depending on the wound.

## RESULTS

With phenytoin treatment, 22 of the 25 patients had complete wound healing within 2-4 weeks. The remaining 3 patients had a satisfactory granulation response to topical phenytoin, but did require skin grafting for final wound closure. In the missile wounds, where treatment was usually begun within ten days of injury, mean healing time was 2 weeks compared to historical controls requiring 6-8 weeks. The non-war lesions that had been unresponsive to various treatments over a five-month period, required longer treatment periods, and maximum healing time was 4 weeks.

**Table I. Types of wounds.**

| Type of wounds | No. of Patients |
|---|---|
| War wounds | 19 |
| Bed sores | 3 |
| Diabetic neuropathy | 1 |
| Iatrogenic | 1 |
| Machine injury | 1 |
| **Total** | **25** |

The patient requiring the longest treatment (4 weeks) was a 65 year old man with diabetic neuropathy. He had a deep wound in the third interphalangeal space of his left foot with an *E.coli*-positive culture. His wound had progressively worsened despite six months of antibiotic therapy and betadine dressing twice daily. He had been referred to us for amputation. With phenytoin treatment and without antibiotic therapy, his lesion was completely healed after four weeks and the culture became negative after one week. Amputation was not required.

In all wounds, healthy granulation tissue formed and wound exudate ceased by the end of the first week of PHT treatment. With regard to wound bacteriology, all 17 initially positive wound cultures (see Table II) were negative after one week of phenytoin treatment. As noted above, no antibiotics were used.

Another important benefit of the topical application of phenytoin powder was the relief of pain. Although the use of phenytoin sodium powder can produce an initial burning sensation, this resolves within 5 minutes. Non-sodium containing phenytoin apparently does not produce burning, but was not avaliable to us for these patients.

Two case reports serve to illustrate the effectiveness of the phenytoin powder:

### Case 1

A 25-year old man with muscle herniation secondary to a war injury had undergone surgical closure of the fascia of the anterior compartment of his left lower

**Table II. Wound culture results.**

| Type of Bacteria | No. of Cultures |
|---|---|
| *E.coli* | 6 |
| Staph coagulase-positive | 5 |
| *Klebsiella* | 3 |
| *Pseudomonas* | 3 |

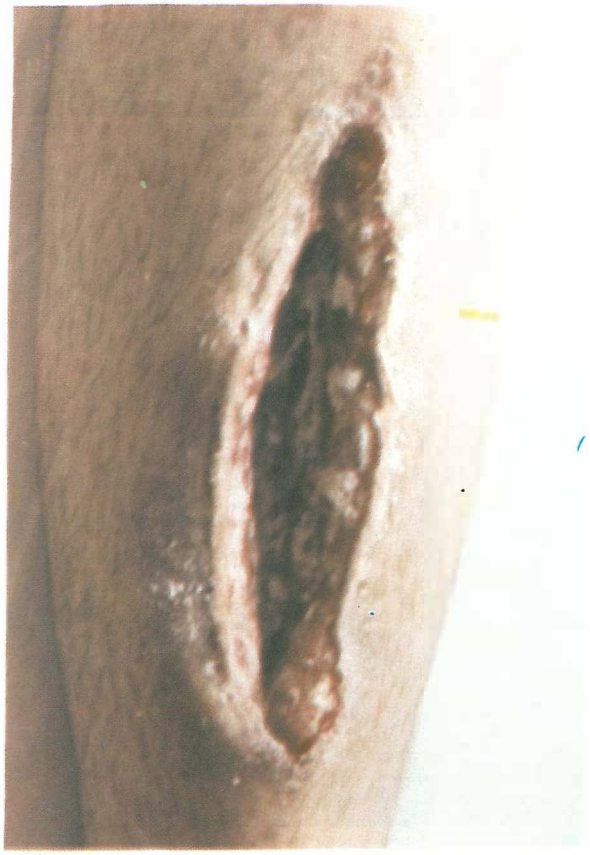

**Fig. 1,A.** Contaminated wound before treatment with PHT.

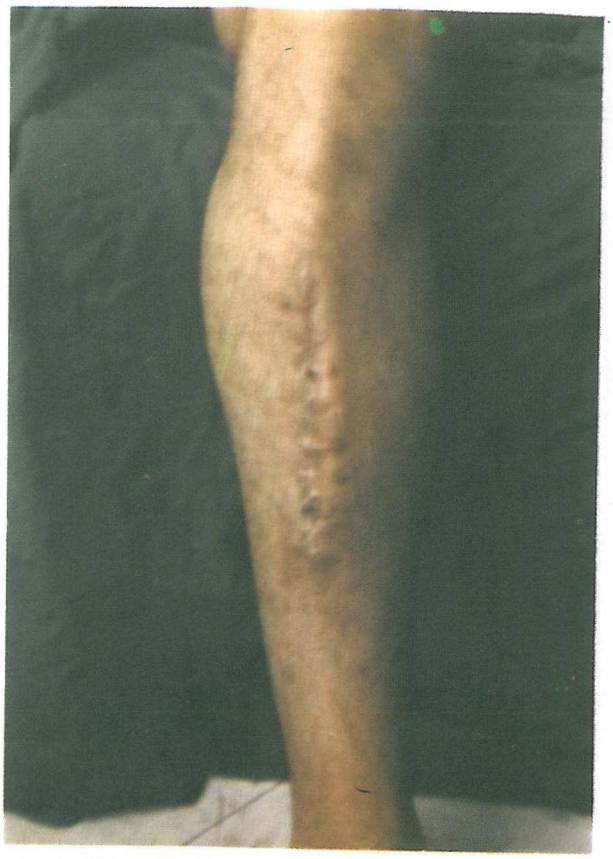

**Fig. 1,B.** One week after treatment with topical phenytoin. Clean wound with granulation tissue.

leg. Subsequently he developed an anterior compartment syndrome requiring fasciotomy. Postoperatively, the wound became infected and did not heal. He underwent eight surgical debridements and treatment with various antibiotics including gentamicin and cephalosporins over a five-month period with no improvement.

Because of his failure to improve, he was referred to our department. On admission, he had a 60 $cm^2$ grossly contaminated wound of the left anterior lower leg (Fig. 1,A). Tibia was exposed. The patient had a left peroneal nerve palsy and could not extend the left great toe and foot. He was in severe pain, and had hyperesthesia in the wound area.

After debridement, phenytoin powder was applied. No antibiotics were used. Following a week of PHT treatment, the wound culture was negative, exudate disappeared, and healthy granulation tissue appeared in the floor and edges of the wound (Fig.1, B). The patient was free of pain.

After three weeks of PHT treatment, granulation tissue filled the wound and it could be closed with sutures (Fig.1,C). Subsequently, there was functional recovery of the left peroneal nerve, which had previously shown no signs of regeneration. The patient was now able to extend his left great toe and foot **(Fig. 1,C).**

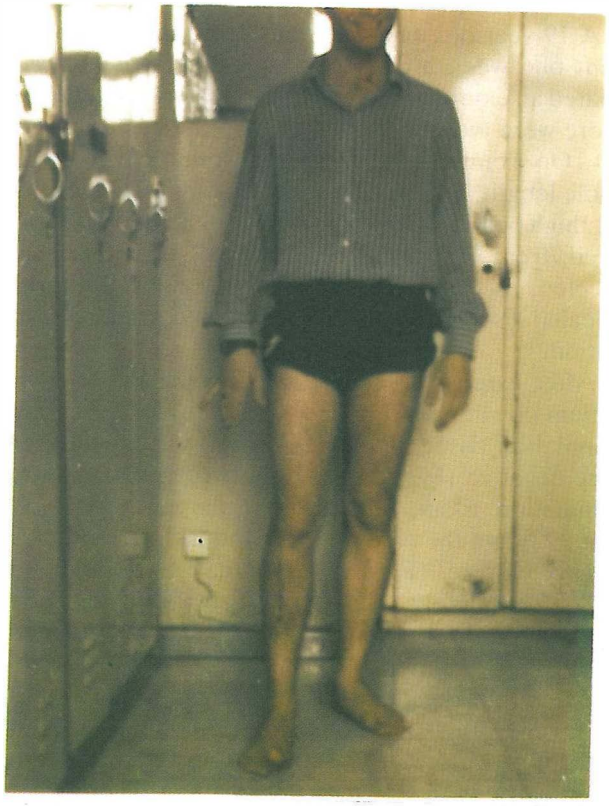

**Fig. 1,C.** After closure and complete healing.

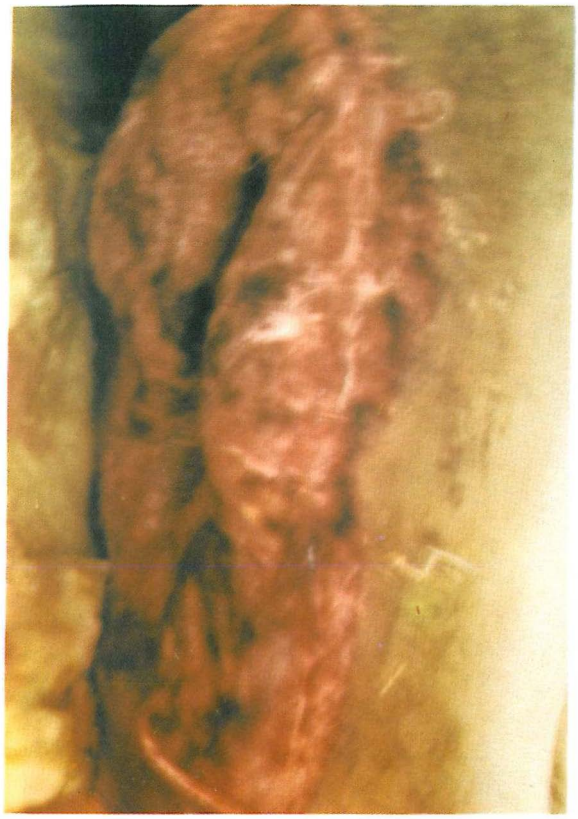

**Fig. 2,A.** Contaminated wound before treatment with PHT.

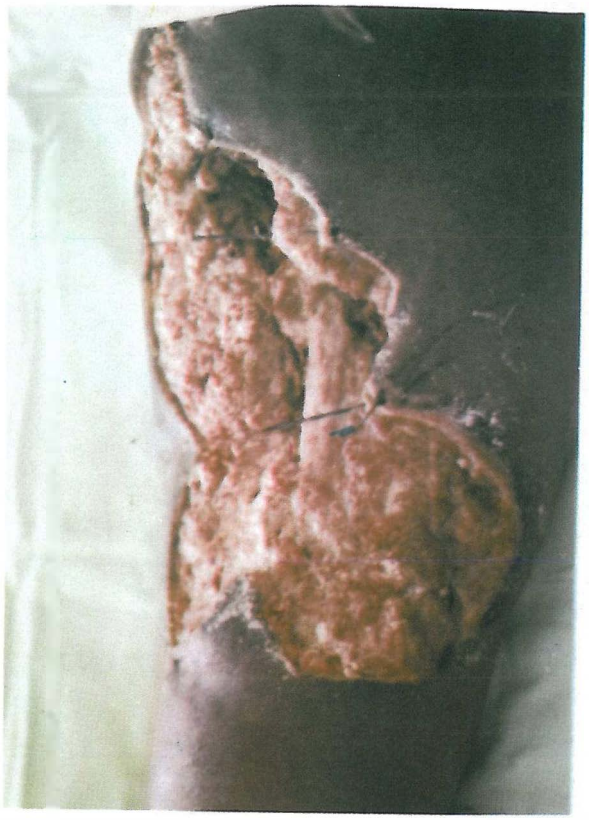

**Fig. 2,B.** Clean wound with granulation tissue,

**Case 2**

A 19-year old man was transferred to our department one week after several missile fragments had created an extensive wound of the posterior left thigh. There were two smaller wounds on the posterior left calf. On examination the major wound covered the whole length and two thirds the circumference of the left thigh posteriorly (Fig.2,A). By planimetry it measured 70 $cm.^2$ It was full of necrotic tissue and grossly infected, as were the two smaller wounds. Cultures revealed *Pseudomonas*. There was no sciatic nerve fuction.

After extensive surgical debridement, phenytoin sodium powder was applied. One week later healthy granulation tissue had appeared and wound cultures were negative (Fig.2,B). Within two weeks, healthy granulation tissue had covered the entire wound (Fig.2,C) and the patient underwent skin grafting for wound closure (Fig.2,D). Thereafter the wound healed completely (Fig.2,E). When the patient was ambulated, it was noted that there had been return of sciatic nerve function.

Other than the initial burning sensation, there were no adverse effects with the exception of one generalized skin rash after the first application of the powder to extensive bed sores in a paraplegic patient. The powder application was discontinued and the rash resolved.

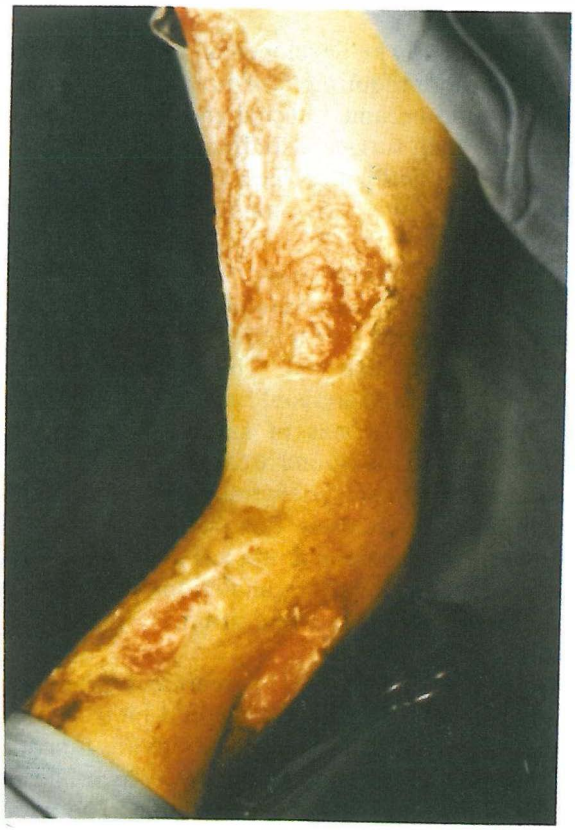

**Fig. 2,C.** Two weeks after phenyoin treatment-healthy granulation tissue of thigh and leg.

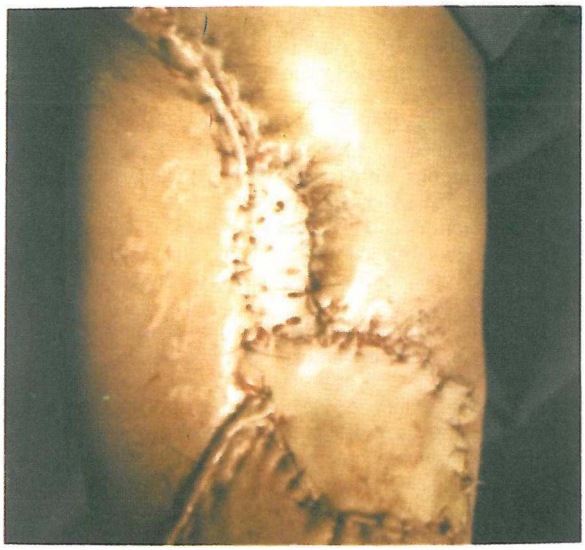

**Fig. 2,D.** The same wound following closure and skin grafting.

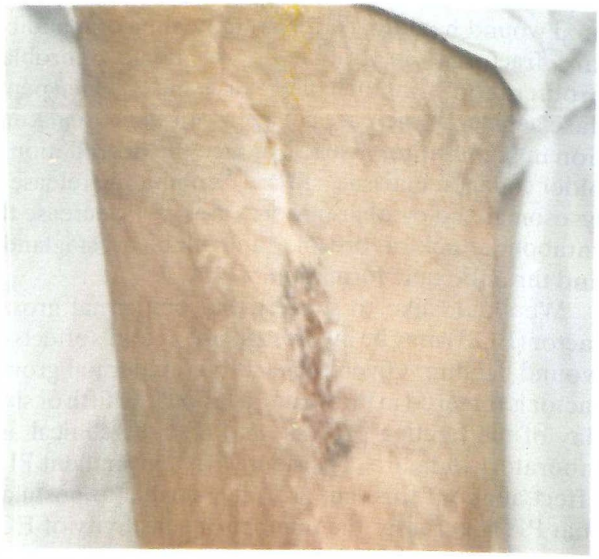

**Fig. 2,E.** Site of the healed wound on the posterior aspect of the right thigh.

## DISCUSSION

Phenytoin has a dramatic effect on the healing of wounds. Applied topically, it stimulates the formation of granulation tissue; provides local pain relief, reducing the need for pain medications; decreases wound exudation and results in elimination of bacterial contamination and infection; and leads to complete healing or provides a healthy granulation tissue base for skin grafting and surgical wound closure. Our findings are consistent with reports of other trials in various types of wounds and ulcers and emphasizes the particular usefulness of topical phenytoin powder in war wounds, under conditions of treatment that are especially difficult.

An optimal wound healing treatment regimen is one that is effective, inexpensive, safe, readily available, and easy to apply. Based on our experience, topical-phenytoin meets these criteria and is more effective than other therapeutic measures currently available to us. Because of the rapid healing it induces, hospital stays are shortened. The need for antibiotics and analgesics is reduced, thereby yielding further cost savings and minimizing the possibility of toxicity or dependence resulting from use of these agents. With the exception of one case of skin rash, which appeared on the first application of the powder and resolved with ceasation of therapy, the method has proved very safe in our hands. The cost of phenytoin itself is minimal and it is both readily available and easy to use, even under the most difficult war-time conditions.

Because of the difficult conditions under which we had to work, there were many measurements we were not able to make and many questions we were not able to answer. Even consistent planimetry and photography were met with difficulty. More quantitative bacteriology studies and wound biopsies would have been valuable. However, our clinical observations were very clear: phenytoin is a very effective wound healing agent.

In future clinical trials and applications, important questions to be answered include optimal topical dose (amount and frequency); the possible use of a delivery vehicle or ointment base; combination with other agents or modes of therapy; amount, if any, of systemic absorption; and mechanisms by which phenytoin acts. Definition of the latter may provide improved or new approaches to its use.

For example, as part of our own studies of optimal delivery modes for topical phenytoin, we have evaluated the effects of topical phenytoin on the healing of standardized full-thickness skin wounds in 24 rats. (Although this data is to be the subject of a separate report, a summary is relevant here). The rats were divided into six groups: four treated with different formulations of phenytoin (gel, cream, phenytoin sodium powder, and sodium-free phenyton powder), one with a topical excipient only, and the sixth, a no-treatment control.

Until the fifth or sixth day of treatment, there was no clear difference between the groups. From this point on however, granulation tissue formation and healing was clearly much faster in the four PHT groups, with the sodium-free phenytoin providing the best overall results.

Phenytoin has been reported to have various effects on the wound healing process. Clinical studies indicate several major features: decreased inflammatory response, increased fibroblast proliferation, increased collagen content, and increased new blood vessel formation.[2,7,8] In the laboratory, PHT has been shown to increase tensile wound strength,[13,14] promote cor-

neal wound healing,[15] accelerate healing of mandibular fractures in rabbits,[16] stimulate fibroblast proliferation,[17] inhibit collagenase and collagen peptidase activity,[18] increase collagen content and maturation in granulation tissue,[19] reduce the degradation of older collagen in tissue culture,[20] inhibit the release of lysosomal and cytoplasmic enzymes,[21-23] decrease the catabolic effects of cortisol,[24] and inhibit prostaglandin and thromboxane formation.[25]

We would like to suggest that epidermal growth factor (EGF) may be involved in phenytoin's effects on wound healing. Given the fact that epidermal growth factor is released in the wound at about the fifth or sixth day of the healing process, and that the clinical and laboratory data are consistent with a prominent PHT effect at about this time, it is reasonable to postulate that PHT increases the number or sensitivity of EGF receptors.

The mechanisms by which phenytoin reduces wound bacterial contamination are not known. Rather than a direct antibacterial effect, improvements in wound pH and local circulation consistent with the enhanced formation of granulation tissue seems likely to be responsible.

The local analgesic property of topical pheyntoin is consistent with its membrane stabilizing actions, including modulation of ion flux and selective inhibition of repetitive neuronal activity and synaptic transmission.

We were surprised by the rapidity of recovery of nerve function in three of our cases. Although it is difficult to determine what was precisely responsible for this phenomenon, its unusual character suggested the possibility that phenytoin may have enhanced this recovery directly. Further studies on this point are necessary.

In conclusion, data from the present trial and those of others are consistent in indicating that topical phenytoin is an easy-to-use, effective, safe, readily available, and inexpensive wound healing agent.

We hope that this report will serve to stimulate others to use topical phenytoin and report on their experience.

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