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Effect of Local Application of Phenytoin on Wound Healing in Surgical Wounds: A Scientific Review

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Abstract

Surgical wound healing is a dynamic biological process influenced by local tissue response, vascularity, infection control, and systemic patient factors. Delayed wound healing contributes significantly to postoperative morbidity and healthcare costs. Phenytoin, a hydantoin derivative traditionally used as an antiepileptic agent, has demonstrated unexpected wound-healing properties when applied topically. This review critically evaluates experimental and clinical evidence regarding the role of locally applied phenytoin in enhancing wound healing in surgical wounds. Available data suggests that topical phenytoin accelerates granulation tissue formation, promotes fibroblast proliferation, enhances collagen deposition, and improves wound tensile strength. Clinical studies in surgical and procedure-related wounds report faster epithelialization and reduced healing time with minimal adverse effects. However, heterogeneity in study design, formulation, and outcome assessment limits definitive conclusions. This review highlights current evidence, mechanistic insights, clinical applicability, and areas requiring further high-quality research.

Keywords: Collagen deposition, epithelialization, fibroblast proliferation, granulation tissue, surgical wound healing, topical phenytoin, wound tensile strength

INTRODUCTION

Optimal wound healing following surgery is essential for favorable outcomes and prevention of complications, such as surgical site infection, wound dehiscence, and incisional hernia. The healing process progresses through overlapping phases of hemostasis, inflammation, proliferation, and remodeling. Any disruption in these phases can result in delayed healing [1–5].

It is one of those classic "happy accidents" in medical history. When phenytoin first hit the scene in 1938 as a revolutionary way to control seizures, no one expected it to have anything to do with skin. But doctors soon noticed a strange pattern: patients on long-term therapy were developing gingival hyperplasia – basically, their gum tissue was growing at an accelerated rate.

While this was a headache for dentists, it was a lightbulb moment for wound care researchers. They realized that if phenytoin could trigger tissue growth in the mouth, it might be the key to "restarting" the healing process in stubborn skin wounds [6–10].

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HOW IT ACTUALLY WORKS

Rather than just sitting on the surface, phenytoin gets to work on a cellular level. It essentially acts as a project manager for the body's repair crew by:

- *Boosting Fibroblasts:* It nudges the cells responsible for connective tissue to work faster.
- *Building Scaffolding:* It promotes collagen deposition, which is the "glue" that holds a healing wound together.

- *Cleaning Up:* It helps reduce bacterial activity and calms excessive inflammation that often stalls healing.

From Chronic Ulcers to the Operating Room

For years, this treatment was mostly reserved for "problem" cases, like diabetic foot ulcers or pressure sores that refused to close. However, the focus has recently shifted toward surgical recovery. The logic is simple: if we can use phenytoin to optimize the environment of a fresh surgical incision, we might be able to prevent scars from widening, stop wounds from reopening (dehiscence), and get patients back on their feet much sooner.

This review takes a close look at the latest evidence to see if this old-school epilepsy drug is ready for a second career as a staple in modern surgical aftercare [11–16].

MECHANISM OF ACTION

The wound-healing effects of topical phenytoin are mediated through multiple biological pathways:

Fibroblast Proliferation

Phenytoin has been shown to stimulate both migration and proliferation of fibroblasts at the wound site, thereby enhancing the synthesis of extracellular matrix components. Fibroblasts are essential cells in the proliferative phase of wound healing, as they produce collagen, proteoglycans, and other structural proteins required for granulation tissue formation. Increased fibroblast activity promotes rapid deposition and organization of collagen fibers, which helps in filling the wound defect and strengthening the newly formed tissue. In addition, improved matrix formation supports epithelial cell migration and wound contraction, ultimately contributing to faster healing and improved quality of the repaired tissue.

Collagen Synthesis and Tensile Strength

Experimental models have demonstrated that wounds treated with phenytoin show a significant rise in hydroxyproline content, which is a key biochemical marker of collagen synthesis and deposition. Enhanced fibroblast proliferation and stimulation of extracellular matrix production lead to improved collagen maturation and better organization of collagen fibers within the granulation tissue. As a result, the newly formed tissue exhibits greater tensile strength and resistance to mechanical stress. In addition, phenytoin promotes angiogenesis and stabilizes the wound environment, thereby accelerating tissue remodeling and restoring structural integrity more effectively compared to untreated wounds.

ANGIOGENESIS

Topical phenytoin therapy has been associated with a marked increase in capillary density within the developing granulation tissue of healing wounds. The drug stimulates endothelial cell proliferation and promotes neovascularization, resulting in improved angiogenesis at the wound site. Enhanced formation of microvasculature ensures better delivery of oxygen, nutrients, and essential growth factors to regenerating tissues. This improved perfusion supports fibroblast activity, collagen deposition, and epithelial cell migration. Consequently, the wound environment becomes more favorable for cellular proliferation and tissue remodeling, leading to accelerated healing, reduced necrotic debris, and more efficient restoration of normal tissue architecture.

Modulation of Inflammation

Phenytoin appears to attenuate excessive inflammatory responses by reducing leukocyte infiltration, thereby preventing prolonged inflammation that may delay healing.

Antimicrobial Effect

Although not a primary antimicrobial agent, phenytoin has been reported to reduce bacterial colonization, possibly by improving local tissue resistance and vascularity.

EXPERIMENTAL EVIDENCE

Animal studies form the foundation of phenytoin's wound-healing rationale. Rodent models have consistently demonstrated accelerated wound contraction, increased fibroblast density, enhanced collagen deposition, and superior tensile strength in phenytoin-treated wounds compared to controls. These findings provide biological plausibility for clinical application in surgical wounds.

Clinical Evidence in Surgical Wounds

Clinical evaluation of topical phenytoin has been carried out through a variety of research designs, including randomized controlled trials, comparative clinical studies, and observational case series. These investigations have assessed its effectiveness in different types of wounds, such as chronic ulcers, burn injuries, and postoperative wounds. Most studies report faster development of healthy granulation tissue, reduction in wound size, and shorter healing duration when compared with conventional dressings. Researchers have also evaluated pain relief, infection control, and frequency of changes in dressing, noting improved patient comfort and reduced treatment costs. Overall, the accumulated clinical evidence suggests that topical phenytoin is a useful adjunct in promoting wound healing.

Surgical and Procedure-Related Wounds

Several controlled studies involving surgical wounds – such as post-fistulotomy wounds, episiotomy incisions, and minor operative wounds – have reported improved healing parameters with topical phenytoin. Outcomes include:

- Faster granulation tissue formation.
- Reduced time to complete epithelialization.
- Improved wound healing scores.
- Reduced postoperative pain in some studies.

An illustrative comparison of mean healing time between control and phenytoin-treated wounds is shown in Figure 1.

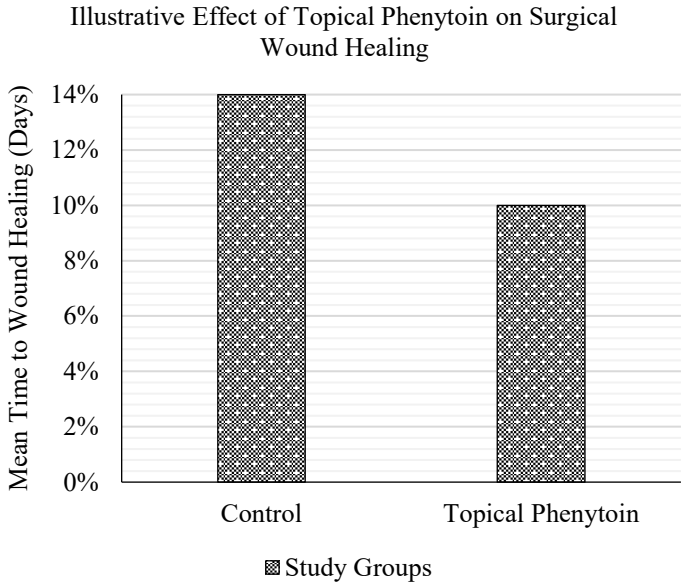

Figure 1. Illustrative effect of topical phenytoin on mean wound-healing time.
Note: Graph represents trend observed across published studies and is for conceptual demonstration.

Serial photographic documentation showed progressive granulation tissue development, decreased slough, and gradual epithelialization of the burst abdomen wound following topical phenytoin therapy (Figure 2).

- Progressive granulation tissue formation and wound contraction were observed after topical phenytoin application (Figure 2).
- Serial clinical photographs illustrate gradual healing of the postoperative burst abdomen wound (Figure 2).
- Marked epithelialization and reduction in wound size occurred over time following treatment, as shown in Figure 2.
- The wound demonstrated healthy granulation and progressive closure during follow-up (Figure 2).
- Sequential images document the stages of wound healing after local phenytoin therapy (Figure 2).

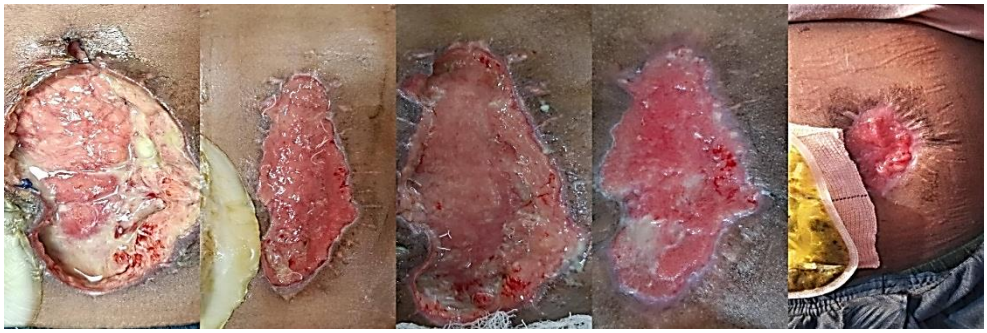

Figure 2. Serial clinical photographs demonstrate progressive healing of a postoperative burst abdomen wound following local application of topical phenytoin.
Note: All clinical images were obtained after informed patient consent, and patient identity has been adequately concealed.

CHRONIC WOUND LITERATURE (SUPPORTIVE EVIDENCE)

Although not surgical wounds per se, studies on diabetic foot ulcers and venous ulcers consistently demonstrate enhanced granulation and reduced healing time with topical phenytoin, indirectly supporting its reparative potential.

Safety and Tolerability

Topical phenytoin is generally well tolerated in most patients and has a favorable safety profile when applied to cutaneous wounds. Reported adverse effects are uncommon and typically mild, consisting mainly of transient local irritation, burning sensation, or mild erythema at the application site. Because the drug is used locally, systemic absorption is minimal, and clinical studies have not demonstrated significant systemic toxicity or serious drug-related complications. However, careful use is recommended when it is applied over very large open wounds or highly vascular areas, as increased absorption may theoretically occur. Proper monitoring and judicious dosing help ensure safety while maintaining its therapeutic benefits in wound healing.

Limitations of Existing Evidence

Despite promising findings, several limitations persist:

- Small sample sizes in most studies.
- Lack of standardized phenytoin formulation and dosage.
- Inconsistent outcome measures.
- Limited long-term follow-up.
- Few high-quality trials focused exclusively on clean surgical incisions.

These limitations underscore the need for well-designed, adequately powered randomized trials.

FUTURE DIRECTIONS

Future research should focus on:

- Standardization of topical phenytoin concentration and formulation.
- Multicenter randomized controlled trials in defined surgical wound populations.
- Objective outcome measures including tensile strength, infection rates, and scar quality.
- Cost-effectiveness analysis.

CONCLUSION

Topical application of phenytoin demonstrates significant potential as an adjunctive agent in enhancing surgical wound healing. Its multifactorial mechanism – including fibroblast stimulation, collagen synthesis, angiogenesis, and inflammation modulation – supports its biological plausibility. Current clinical evidence suggests improved healing outcomes with minimal adverse effects. However, heterogeneity in existing studies precludes routine recommendation. High-quality randomized controlled trials are essential before widespread clinical adoption.

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