Section: Orthopedics

Original Research Article

THE ROLE OF TOPICAL PHENYTOIN IN ENHANCING WOUND HEALING OUTCOMES IN TRAUMATIC WOUNDS

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Abstract

Background: Effective management of traumatic wounds is critical for proper healing. Phenytoin, primarily used to treat seizures, has demonstrated wound-healing properties, including collagen production, angiogenesis, anti-inflammatory effects, and antimicrobial action. These benefits make it promising for accelerating the healing of traumatic wounds and chronic ulcers. The aim is to evaluate the effect of topical phenytoin on traumatic wound healing, focusing on granulation tissue formation, pain reduction, and healing time. **Materials and Methods:** This prospective case-control study was conducted at the Department of Orthopedic Surgery, Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu, India.Patients with traumatic wounds were randomly divided into two comparable groups: a study group treated with phenytoin dressings and a control group treated with saline dressings. Wounds were evaluated on days 2, 4, 6, 8, 10, 12, and 14 for healing parameters. **Result:** By day 14, the study group showed significantly better outcomes than the control group, with wound surface area (38.4 ± 29.05 cm² vs. 50.28 ± 24.33 cm²), granulation tissue percentage (84.12 ± 9.71% vs. 61.72 ± 9.01%), and VAS scores (4.75 ± 1.08 vs. 5.52 ± 1.24). By day 21, complete healing time was significantly shorter in the phenytoin group (19.76 ± 4.28 days) compared to controls (33.64 ± 7.31 days). Phenytoin also demonstrated superior microbial control, with 92% of wounds showing negative cultures by day 18. **Conclusion:** Topical phenytoin significantly enhances granulation tissue formation, reduces pain, and accelerates wound healing, making it a safe, cost-effective solution for managing traumatic wounds and reducing patient morbidity.

INTRODUCTION

Traumatic wounds are a common health problem and are a frequent challenge for orthopedic surgeons. The management of traumatic wounds is crucial, especially when associated with a fracture, as the condition of the soft tissue has a significant bearing on the fracture union. A definitive bony fixation can be done only when the surrounding soft tissue condition is favorable. A healthy wound with good granulation tissue and absence of infection are favorable prognostic indicators.[1] Traumatic wounds are associated with an increased cost of medical care, prolonged morbidity, and, if extensive, can lead to mortality.[2]

In 1937, Tn. Wigton Ha and Shapiro,[3] observed that patient who are taking oral phenytoin tablet for seizure have increase in gum tissue growth. Patients during chronic treatment with topical phenytoin due to increased production of inflammatory fibroblasts, cytokines, growth factors and genetic susceptibility, these stimulatory effect of phenytoin on connective tissue has propounded the possibility of using it in wound healing.

In 1939, Kimball observed that nearly half the patients who used oral phenytoin developed gingival hyperplasia as a side effect.[2-5]

In 1958, Shapiro studied the effects of oral phenytoin pre-treatment on the healing of surgically created gingival wounds in patients with periodontal disease. This apparent stimulatory effect on connective tissue has prompted its use in wound healing in traumatic wounds.[3,6-8]

It is thought to promote wound healing through multiple mechanisms.[9-13] Its efficacy has also been found to extend to pain alleviation via its membrane-stabilizing action and anti-bacterial action via direct and indirect mechanisms.[4,10]

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Modaghegh S et al. conducted a pilot study on the effects of topical phenytoin where 19 cases of war wounds were included.[9] Similarly, Pendse et al. included 7 patients of traumatic wounds in their study on heterogeneous wounds [10]. However, there is minimal number of studies on the effect of topical phenytoin in traumatic wounds.

Background and rationale:

Phenytoin was synthesized in 1908 as potent anti epileptic agent, as on observation unwanted side effects of gingival hyperplasia noted, which quotes basis for wound healing. Phenytoin sodium dressing has been used for healing of, diabetic ulcers,[4,5] decubitus ulcer,[6] venous ulcer,[7] leprosy tropic ulcers[8] ,traumatic wounds etc.[9,10] many existing clinical studies have reported enhancement of wound healing with insignificant adverse effects.

Phenytoin may promote wound healing by a number of mechanisms, including stimulation of fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism, and antibacterial activity. Hydroxyproline is an Amino acid, a major component of collagen by forming hydrogen bonds. Its level was more in tissues treated with phenytoin and increases collagen synthesis and facilitate rapid wound healing. Overdose may lead to toxicity and systemic complications.

Aims and objectives: Our aim was to compare the efficacy of topical phenytoin with conventional saline wound dressings in the healing of traumatic wounds in terms of rate of reduction of wound size, percentage of granulation tissue formation, number of days required for wound healing and, pain alleviation.

MATERIALS AND METHODS

A prospective case-control study was conducted at the Department of Orthopedic Surgery, Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu, India. The study aimed to investigate the efficacy of phenytoin sodium in treating traumatic wounds.

The study included 100 participants, divided into two groups:

- Group 1: 70 participants with traumatic wounds treated with phenytoin sodium
- Group 2: 30 participants with traumatic wounds treated with regular treatment

The sample size was calculated using the World Health Organization (WHO) calculator, with a significance level of 5% and a test power of 90%. The study was conducted over one year.

Ethical clearance was obtained from the Institutional Ethics Committee (IEC) of Government Mohan Kumaramangalam Medical College, Salem ((link unavailable) GMKMC&H/114/ICE//2023), and the study conforms to the standards of the Declaration of Helsinki.

The inclusion criteria for the study consisted of individuals with trauma wounds, aged above 5 years, with full-thickness traumatic wounds involving skin and subcutaneous tissues. The exclusion criteria included patients with superficial abraded wounds, Grade III B wounds (Gustilo-Anderson classification) with deep wounds exposing bone, patients allergic to phenytoin, immune-compromised patients, and patients with vascular impairment.

Informed written consent was obtained from all patients who met the inclusion and exclusion criteria. The patients were then randomized into two equal and comparable groups. The cases and controls were comparable with respect to age, smoking history, and diabetic history

Wound cultures were taken from all patients, and antibiotics were administered to both groups. Wound debridement was performed as and when necessary. Wound measurements using tissue paper tracing and pain assessment using the Visual Analogue Scale (VAS) were conducted on day 0.

Dressings were done daily, followed by alternate days, depending on wound soakage in both groups. The dressings were continued until the wound healed or was healthy enough to carry out closure using secondary suturing/split skin graft/flap cover.

In the control group, the wounds were cleaned with normal saline, and dry dressings were applied. In the study group, phenytoin powder was used instead. The amount of phenytoin needed was determined based on the surface area of the wound, with doses ranging from 100 mg to 300 mg.

Wound size was measured by tracing the outline on butter paper, transferring it to graph paper, and taking the maximum diameter in two different areas perpendicular to each other. The dosage of phenytoin was determined based on the wound size, with the following dosages: 0-25 mm^2 (100 mg), 25-50 mm^2 (150 mg), 50-75 mm^2 (200 mg), and >75 mm^2 (300 mg).

Phenytoin powder was uniformly applied over the surface of the wound. Healing was assessed at the end of every week, evaluating the percentage of granulation tissue formation, pain alleviation as measured by VAS, and the percentage reduction of wound size by serial measurements. The number of days required for complete wound healing or wound bed readiness for grafting/secondary closure was also recorded.

The patients in both groups were assessed for culture sensitivity on days 0, 7, and 14 to determine the antibacterial effect of phenytoin.

RESULTS

On day 14, the wound surface area, percentage of granulation tissue, VAS score amongst cases was 38.4 ± 29.05 cm2, 84.12 ± 9.71%, 4.75 ± 1.08, and that of controls was 50.28 ± 24.33 cm2, 61.72 ± 9.01%, 5.52 ± 1.24, respectively As shown in [Figure 1].

On day 21, the wound surface area, percentage of granulation tissue, VAS score amongst cases were

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27.4 ± 20.88 cm2, 93 ± 4.46%, 2.6 ± 0.94, and that of controls were 39.92 ± 23.24 cm2, 79.56 ± 8.19%, and 4.68± 1.17, respectively. As shown in [Figure 2]. The time taken for wound healing was 19.76 ± 4.28 days amongst cases and 33.64 ± 7.31 days amongst controls As Shown in [Figure 3].

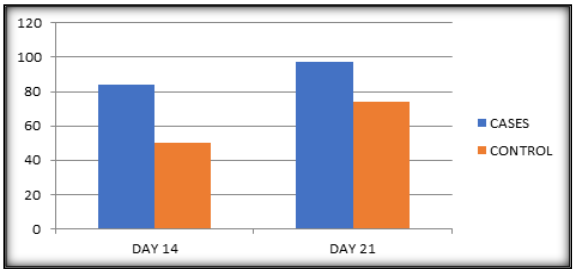


Figure 1: percentage of granulation tissue formation in cases and control

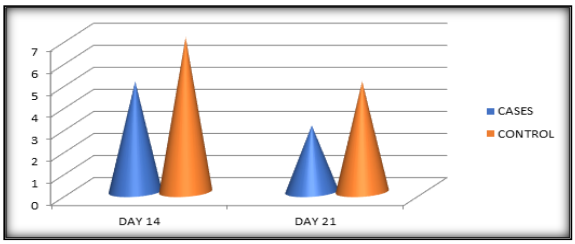


Figure 2: visual analogue score in cases and control

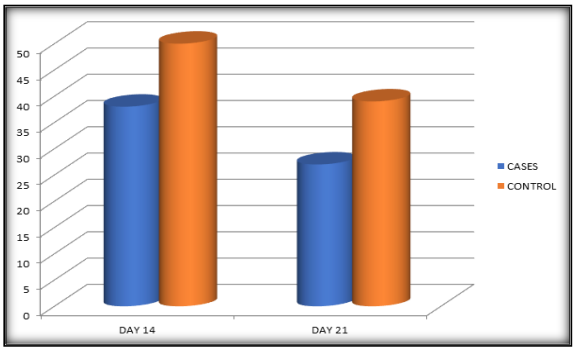
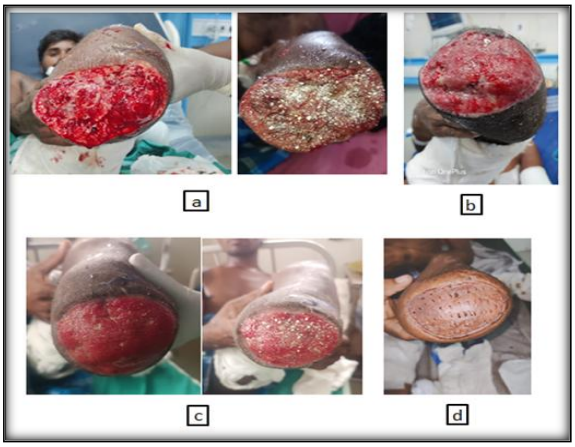


Figure 3: percentage of reduction in wound surface area in cases and control

CASE 1:

Serial photographs of wound healing with phenytoin dressings:

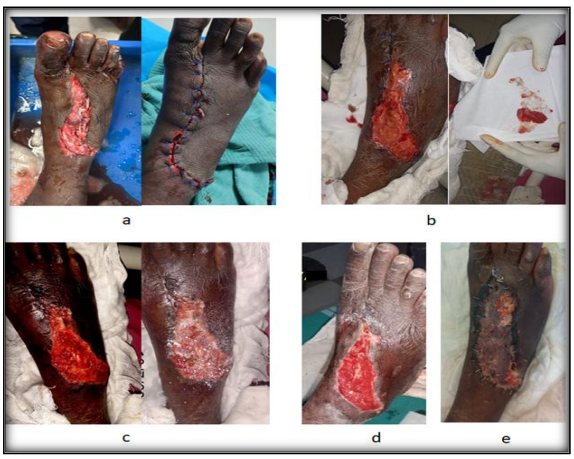
a) Wound on day 0
b) Wound on day 14
c) Wound on day 19
d) Post SSG Wound on day 26



CASE 2:

Serial photographs of wound healing with phenytoin dressings:

a) Wound on day 0
b) Wound on day 7(wound dehiscence occurs on day 4 and phenytoin dressing started on Day 4)
c) Wound on day 14
d) Wound on day 21
e) Post SSG Wound on Day 28



DISCUSSION

Wound dressings have progressed from providing mechanical protection and controlling local infection to the level of providing an environment that promotes wound healing. Over the years, wound dressings have evolved from simple dressings that only provide physical protection and prevent infections to more advanced agents such as hydrocolloids, honey, papaya, negative pressure wound therapy, betadine and aloevera. The search for an efficient, affordable, and practical wound dressing is still ongoing as researchers strive to discover new and effective methods of treating wounds.[12]

Phenytoin has been investigated in the management of wounds. Phenytoin is a drug from the group of hydantoins that is used as an anticonvulsant drug. Because of the chemical effect on sodium and calcium channels in the nerve tissue of the brain, it inhibits them and prevents the generation of action

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potentials. One of the side effects of phenytoin that was observed after its long-term use was hyperplasia of patients' gums which became the basis for further studies on the effect of phenytoin on wound healing. Phenytoin has been discovered to have a positive impact on wound healing by encouraging several key processes involved in tissue repair. It can help promote the growth of fibroblasts, which are crucial for tissue repair and can also boost collagen production, a significant component of the extracellular matrix that provides support and structure to tissues. Additionally, phenytoin has the potential to decrease the activity of collagenase, an enzyme that can break down collagen and slow down the healing process.[12]

Phenytoin also has anti-inflammatory properties and can reduce the production of cytokines such as interleukin 1, which can contribute to inflammation and delay wound healing.[12-15] Furthermore, it can also promotes neovascularisation,[11] by increasing the production of growth factors such as VEGF and TGF-beta, which can enhance blood flow to the wound area and support tissue repair. Furthermore, phenytoin has antibacterial properties and can reduce the bacterial load of common wound pathogens such as Staphylococcus aureus, Klebsiella, and Pseudomonas.[16-18] This can help prevent infection and promote proper wound healing.[19,20] In addition, phenytoin can ease local pain by stabilizing cell membranes and has been shown to promote nerve regeneration, which can lead to the development of new granulation tissue and a faster healing time.[11]

In summary, phenytoin has multiple mechanisms of action that contribute to the promotion of wound healing, including the stimulation of fibroblast proliferation and collagen production, reduction of inflammation, promotion of neovascularization, antibacterial activity, and the ability to ease pain and promote nerve regeneration.[14-16]

Most effective approach for administering topical phenytoin remains uncertain, our study incorporated a dry powdered phenytoin to potentially prevent the formation of a white eschar coating. Several investigations have compared the wound-healing impacts of topical phenytoin to other treatments, such as silver sulfadiazine (Carneiro et al.),[21] collagen dressing with antibiotics (Rhodes et al.),[6] and EUSOL dressings (Lodha et al.).[22,23] These studies have demonstrated that topical phenytoin can heighten the number of negative wound cultures,diminish pain, rapid healing, encourage healthier granulation tissue, and lower bacterial contamination.[24]

In our study, we found that topical phenytoin was more effective than normal saline dressings in improving wound healing. Our results were consistent with previous studies conducted by Tauro et al.25and Muthukumarasamy et al,[19] which reported a significant increase in granulation tissue formation and a faster reduction in wound surface area in the phenytoin group. The antibacterial action of phenytoin was also demonstrated in a study by Pendse et al.[10] Furthermore, histopathological studies have shown that phenytoin-treated wounds have increased neovascularization and lymphocyte infiltration, contributing to its antibacterial action.[22] Phenytoin is well tolerated with minimal side effects, and systemic absorption of phenytoin is negligible.[26,27] No hypersensitivity reactions to phenytoin have been reported.[28]

CONCLUSION

Our study demonstrates the efficacy of topical phenytoin in enhancing wound healing outcomes in patients with traumatic wounds. The results show a statistically significant improvement in granulation tissue formation, pain relief, and wound surface area reduction in the phenytoin-treated group compared to the control group. Furthermore, the reduced healing time observed in the phenytoin group has significant implications for cost savings and improved patient outcomes. Given its safety profile, availability, and affordability, topical phenytoin emerges as a promising adjunctive treatment for traumatic wounds, warranting further research and clinical consideration.

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