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Original Article

FROM SEIZURES TO WOUNDS: THE POTENTIAL OF PHENYTOIN IN TRAUMATIC WOUND MANAGEMENT

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ABSTRACT

Objective: Phenytoin is a medication primarily used to treat seizures, but it has been discovered to have the potential for wound healing due to its ability to increase collagen production, promote new blood vessel growth, reduce inflammation, fight infections, and encourage new skin growth. These effects are particularly useful for healing chronic wounds like pressure ulcers, diabetic ulcers, traumatic wounds, and venous ulcers.

Methods: This is a two-year prospective study conducted between January 2020 and December 2022 at the Government General Hospital in Kurnool. A study was conducted on 60 patients with traumatic wounds, dividing them into two groups. One group received topical phenytoin dressing, while the other received normal saline dressing. The study compared wound surface area, granulation tissue percentage, pain ratings on the visual analog scale, and healing time between the groups on day 14 and day 21.

Results: On day 0, cases and controls had similar wound surface areas (62.17±25.74 cm2 and 62.14±21.57 cm2, respectively) and VAS scores (8.81±1.22 and 8.88±1.52). By day 14, cases had significantly smaller wound surface areas (41±32.32 cm2), a higher percentage of granulation tissue (75.56±7.30%), and lower VAS scores (4.57±1.78) compared to controls (53.28±25.33 cm2, 58.45±7.01%, and 6.32±1.02, respectively). By day 21, cases had even smaller wound surface areas (28.3±31.75 cm2), a higher percentage of granulation tissue (93±3.46%), and lower VAS scores (2.78±0.42) compared to controls (40.34±34.23 cm2, 72.56±5.05%, and 4.82±1.27, respectively). The time for wound healing was significantly shorter for cases (22.76±7.28 d) compared to controls (32.64±9.31 d). On day 21, negative cultures were found in 80% of wounds in the study group and 50% of wounds in the control group, with a statistically significant difference (P-value<0.05).

Conclusion: Topical phenytoin dressing had positive effects on wound healing by increasing the rate of granulation tissue formation, providing better pain relief, and shortening the healing time. It was found to be a safe, effective, and cost-effective option for wound healing due to its various mechanisms. The study highlights the significance of phenytoin in treating traumatic wounds, particularly in patients with limited access to expensive wound-healing medications.

Keywords: Phenytoin, Wound healing, Traumatic wound, Granulation tissue, Saline dressing

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INTRODUCTION

Phenytoin, which is a type of medication that helps to control seizures, can lead to an increase in gum tissue growth in patients who take it orally observed by, Tn. Wigton Ha [1] and Shapiro [2]. However because it appears to have a positive effect on connective tissue, scientists have looked into whether it could be used for wound healing. Topical phenytoin has been tested on a range of wounds, including those caused by diabetes [3, 4], pressure [5], and leprosy [6], as well as traumatic wounds [7, 8]. DaCosta and colleagues observed that promoting angiogenesis at an early stage led to increased collagen deposition [8]. Kato and co-workers found impaired degradation of collagen in human gingival fibroblasts [9]. Shakeri *et al.* studied the role of membrane stabilization in wound healing [10]. Hasamnis and team investigated the effect of a substance on the epithelialization of wounds [11]. Swamy and colleagues investigated early transcriptional responses in human dermal fibroblasts [12]. Although some studies have looked into the impact of topical phenytoin on wounds caused by War [7] and Trauma [8], more research is required in this area. Our objective was to compare how effective topical phenytoin is compared to standard saline wound dressings in terms of reducing the size of traumatic wounds, promoting the formation of granulation tissue, reducing the number of days required for wound healing, and alleviating pain.

MATERIALS AND METHODS

A two-year prospective case-control study was conducted at Government General Hospital Kurnool, involving 60 participants. The study was approved by the institutional ethical review committee (IEC-KMC-GGH/27/1/2020), and written informed consent was obtained from all participants.

The study focused on adult patients between 20 and 60 y of age, who had full-thickness traumatic wounds affecting the skin and subcutaneous tissue, and who were willing to participate. Patients with comorbid conditions that could affect wound healing, such as liver and kidney disease, uncontrolled diabetes, vascular issues, those on steroids, immunocompromised patients, those with a history of oral phenytoin use, and those who were allergic to phenytoin, were excluded from the study.

After screening patients based on the inclusion and exclusion criteria, 60 individuals were selected for the study and randomly assigned to two equal groups using a lottery method. Both groups received a 1-gram intravenous ceftriaxone infusion twice daily for five days, and wound debridement was performed as required. On day 0, wound measurements were taken using tissue paper tracing, and the pain was evaluated using the Visual Analogue Scale (VAS).

The amount of phenytoin used in the study group(n=30) was determined based on the wound size [3], with 100 mg applied up to 5 cm, 150 mg for wounds between 5 and 10 cm, 200 mg for wounds between 11 and 15 cm, and 300 mg for wounds greater than 15 cm. The phenytoin tablets were crushed and mixed with 5 ml of normal saline for every 100 mg of the drug, and the resulting suspension was applied uniformly over the wound surface. The control group, on the other hand, received normal saline and moist dressings. Healing progress was evaluated on days 14 and 21 in terms of the

percentage of granulation tissue formation, pain alleviation measured by VAS, percentage reduction of wound size based on serial measurements, and the duration of time required for complete wound healing. Both groups were also evaluated for culture sensitivity on days 14 and 21 to assess the antibacterial effect.

RESULTS

This study involved 60 patients who had traumatic wounds, and they were equally distributed into two groups–cases (n=30) and controls (n=30). Of the total patients, 44 (74%) were male, while 16 (26%) were female. The patients had an average age of 34 y, with ages ranging from 20 to 60 y. The patients were classified into three age groups, including 15 patients (25.0%) aged between 20 and 35 y, 25 patients (42%) aged between 35 and 45 y, and 20 patients (33%) aged between 45 and 60 y.

The study assessed the percentage of granulation tissue present on the wound surface area on days 14 and day 21. The results showed that on day 14, the mean percentage of granulation tissue in the cases (n=30) was 75.56% with a standard deviation of 7.30, while in the controls (n=30), it was 58.45% with a standard deviation of 7.01. This difference between the two groups was statistically significant, with a P-value of 0.01. Similarly, on day 21, the mean percentage of granulation tissue in the cases was 93% with a standard deviation of 3.46, whereas, in the controls, it was 72.56% with a standard deviation of 5.05. The difference between the two groups was statistically significant, with a P-value of 0.001.

Table 1: Percentage of granulation tissue present on the wound surface area

Days	Cases (n=30)	Control (n=30)
14 d	75.56±7.30	58.45±7.01
21 d	93±3.46	72.56±5.05

Data are given as mean±SD.

The study measured pain alleviation using the Visual Analogue Scale on day 0, day 14, and day 21. On day 0, the Visual Analogue Score was 8.81±1.22 among cases (n=30) and 8.88±1.52 among controls (n=30). On day 14, the Visual Analogue Score for cases was 4.57±1.78, while that for controls was 6.32±1.02. On day 21, it was 2.78±0.42 for cases and 4.82±1.27 for controls. The difference between the groups was statistically significant, with a P-value of 0.02.

Table 2: Pain alleviation using the Visual Analogue Scale

Days	Cases (n=30)	Control (n=30)
Day 0	8.81±1.22	8.88±1.52
Day 14	4.57±1.78	6.32±1.02
Day 21	2.78±0.42	4.82±1.27

Data are given as mean±SD.

To determine the reduction in wound size, the surface area of the wound was measured at regular intervals. On day 0, the surface area of the wounds in both the cases (n=30) and control groups (n=30) was similar, with an average of 62.17±25.74 cm2 and 62.14±21.57 cm2, respectively. On day 14, the surface area of the wounds among cases decreased to 41±32.32 cm2, while it decreased to 53.28±25.33 cm2 among controls. On day 21, the surface area further reduced to 28.3±31.75 cm2 among cases and 40.34±34.23 cm^2 among controls. Consequently, the percentage reduction in wound surface area on day 21 was found to be higher in cases (54.45%) compared to controls (35.08%).

Table 3: The surface area of the wound

Days	Cases (n=30)	Control (n=30)
Day 0	62.17±25.74 cm^2	62.14±21.57 cm^2
Day 14	41±32.32 cm^2	53.28±25.33 cm^2
Day 21	28.3±31.75 cm^2	40.34±34.23 cm^2

Data are given as mean±SD.

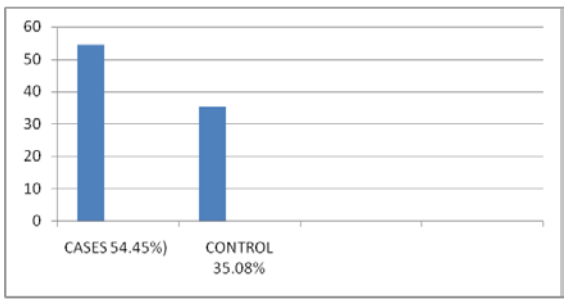

Fig. 1: The percentage reduction in wound surface area on day 21

On day 21, both groups of patients were examined to check for the antibacterial effect by testing the cultures of their wounds. In the study group (n=30), 24 out of 30 wounds (80%) had no detectable bacterial growth, whereas in the control group (n=30), only 15 out of 30 wounds (50%) showed no bacterial growth.

The study measured the time it took for the wound to heal or for the wound to be prepared for further medical treatment. Results showed that the average duration for the study group (n=30) was 22.76±7.28 d, while the average duration for the control group (n=30) was 32.64±9.31 d. The difference between the two groups was statistically significant, with a P-value of 0.01, indicating that the treatment had an impact on the healing time of wounds.

DISCUSSION

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, betadine, and aloe vera. Researchers now not only evaluate the effectiveness of these agents in wound healing but also their cost, accessibility, and practicality. 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.

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 [10]. Additionally, phenytoin has the potential to decrease the activity of collagenase, an enzyme that can break down collagen and slow down the healing process [10].

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 [10]. Furthermore, it can encourage neovascularisation [9] 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 [9]. Furthermore, phenytoin has antibacterial properties and can reduce the bacterial load of common wound pathogens such as Staphylococcus aureus, Klebsiella, and Pseudomonas [15, 16]. This can help prevent infection and promote proper wound healing [17, 18]. 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 [9].

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 [3, 8-14].

Although the most effective approach for administering topical phenytoin remains uncertain, our study incorporated a suspension to potentially prevent the formation of a white eschar coating [5]. Several investigations have compared the wound-healing impacts of topical phenytoin to other treatments, such as silver sulfadiazine (Carneiro *et al.* [19]), collagen dressing with antibiotics (Rhodes *et al.* [5]), and EUSOL dressings (Lodha *et al.* [20]). Meena K *et al.* [21] investigated rats. These studies have demonstrated that topical phenytoin can heighten the number of negative wound cultures, diminish pain, expedite healing, encourage healthier granulation tissue, and lower bacterial contamination [22]. However, few studies have specifically explored the effects of phenytoin on traumatic wounds [7, 8].

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.* [23] and Muthukumarasamy *et al.* [17] 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.* [18]. Furthermore, histopathological studies have shown that phenytoin-treated wounds have increased neovascularization and lymphocyte infiltration, contributing to its antibacterial action [21]. Phenytoin is well tolerated with minimal side effects, and systemic absorption of phenytoin is negligible [24, 25]. No hypersensitivity reactions to phenytoin have been reported [26].

CONCLUSION

Our research found that patients with traumatic wounds who received topical phenytoin treatment showed better wound healing compared to those treated with normal saline. We observed a significant difference in the rate of granulation tissue formation, pain relief as indicated by the visual analogue scale, and the percentage of wound surface area reduction between the two groups. Additionally, the time required for wound healing was reduced, leading to lower costs. Overall, topical phenytoin is a practical, cost-effective, and safe agent for treating traumatic wounds that are readily available and applicable.

LIMITATIONS

The scope of our study is constrained due to a limited duration of observation and a small number of participants; the study only focused on a specific type of wound or injury. This could limit the applicability of the findings to other types of injuries or wounds.

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AUTHORS CONTRIBUTIONS

All authors participated in every aspect of the study, including conceptualization, design, data collection, data analysis, interpretation, manuscript preparation, critical review, and approval of the final version to be published.

CONFLICTS OF INTERESTS

The authors confirm that they have no conflicts of interest related to this research, authorship, and publication of this article

REFERENCES

1. Wigton HA. Dilantin in the treatment of epilepsy. Nebr State Med J. 1947 Jul;32(7):272. PMID 20246690.
2. Shapiro M. Acceleration of gingival wound healing in non-epileptic patients receiving diphenylhydantoin sodium (Dilantin, epanutin). Exp Med Surg. 1958;16(1):41-53. PMID 13537920.
3. Jayalal JA, Kumar SJ, Dhinesh TD, Kadar JM. The efficiency of topical phenytoin on healing in diabetic foot ulcer: a randomized controlled trial. Int J Sci Stud. 2015 Jun;3(3):84-9.
4. Ahmed A, Ahmed MI. A comparison of the efficacy of topical use of phenytoin and Vaseline gauze dressing with Vaseline gauze dressing alone in the healing of diabetic foot ulcers. J Postgrad Med Inst. 2014;28(3):297-302.
5. Rhodes RS, Heyneman CA, Culbertson VL, Wilson SE, Phatak HM. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. Ann Pharmacother. 2001 Jun;35(6):675-81. doi: 10.1345/aph.10267, PMID 11408983.
6. Bhatia A, Nanda S, Gupta U, Gupta S, Reddy BS. Topical phenytoin suspension and normal saline in the treatment of leprosy trophic ulcers: a randomized, double-blind, comparative study. J Dermatolog Treat. 2004 Sep;15(5):321-7. doi: 10.1080/09546630410018085, PMID 15370401.
7. Modaghegh S, Salehian B, Tavassoli M, Djamshidi A, Rezai AS. Use of phenytoin in healing of war and non-war wounds. A pilot study of 25 cases. Int J Dermatol. 1989;28(5):347-50. doi: 10.1111/j.1365-4362.1989.tb01363.x, PMID 2666326.
8. Pendse AK, Sharma A, Sodani A, Hada S. Topical phenytoin in wound healing. Int J Dermatol. 1993 Mar;32(3):214-7. doi: 10.1111/j.1365-4362.1993.tb02799.x. PMID 8444538.
9. DaCosta ML, Regan MC, Al Sader M, Leader M, Bouchier Hayes D. Diphenylhydantoin sodium promotes early and marked angiogenesis and results in increased collagen deposition and tensile strength in healing wounds. Surgery. 1998 Mar;123(3):287-93. doi: 10.1016/S0039-6060(98)70181-3, PMID 9526520.
10. Kato T, Okahashi N, Kawai S, Kato T, Inaba H, Morisaki I. Impaired degradation of matrix collagen in human gingival fibroblasts by the antiepileptic drug phenytoin. J Periodontol. 2005 Jun;76(6):941-50. doi: 10.1902/jop.2005.76.6.941, PMID 15948689.
11. Shakeri F, Tebyanian H, Karami A, Babavalian H, Tahmasbi MH. Effect of topical phenytoin on wound healing. Trauma Mon. 2017 Sep;e35488. doi: 10.5812/traumamon.35488, PMID 29114460, PMCID PMC5661412.
12. Hasamnis A, Mohanty B, Muralikrishna, Patil S. Evaluation of wound healing effect of topical phenytoin on excisional wound in albino rats. J Young Pharm. 2010;2(1):59-62. doi: 10.4103/0975-1483.62215. PMID 21331193.
13. Swamy SM, Tan P, Zhu YZ, Lu J, Achuth HN, Moochhala S. Role of phenytoin in wound healing: microarray analysis of early transcriptional responses in human dermal fibroblasts. Biochem Biophys Res Commun. 2004 Feb 13;314(3):661-6. doi: 10.1016/j.bbrc.2003.12.146. PMID 14741686.

14. Hollisaz MT, Khedmat H, Yari F. A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings for the treatment of pressure ulcers [ISRCTN33429693]. BMC Dermatol. 2004 Dec 15;4(1):18. doi: 10.1186/1471-5945-4-18, PMID 15601464, PMCID PMC545970.
15. Hasamnis A, Mohanty B, Muralikrishna, Patil S. Evaluation of wound healing effect of topical phenytoin on excisional wound in albino rats. J Young Pharm. 2010;2(1):59-62. doi: 10.4103/0975-1483.62215. PMID 21331193.
16. El Zayat SG. Preliminary experience with topical phenytoin in wound healing in a war zone. Mil Med. 1989 Apr;154(4):178-80. doi: 10.1093/milmed/154.4.178, PMID 2499825.
17. Muthukumarasamy MG, Sivakumar G, Manoharan G. Topical phenytoin in diabetic foot ulcers. Diabetes Care. 1991 Oct;14(10):909-11. doi: 10.2337/diacare.14.10.909, PMID 1773690.
18. Pendsey SP. Understanding diabetic foot. Int J Diabetes Dev Ctries. 2010 Apr;30(2):75-9. doi: 10.4103/0973-3930.62596, PMID 20535310, PMCID PMC2878694.
19. Carneiro PM, Nyawawa ET. Topical phenytoin versus EUSOL in the treatment of non-malignant chronic leg ulcers. East Afr Med J. 2003 Mar;80(3):124-9. doi: 10.4314/eamj.v80i3.8680. PMID 12762426.
20. Lodha SC, Lohiya ML, Vyas MC, Bhandari S, Goyal RR, Harsh MK. Role of phenytoin in healing of large abscess cavities. Br J Surg. 1991 Jan;78(1):105-8. doi: 10.1002/bjs.1800780132, PMID 1998849.
21. Meena K, Mohan AV, Sharath B, Somayaji SN, Bairy KL. Effect of topical phenytoin on burn wound healing in rats. Indian J Exp Biol. 2011 Jan;49(1):56-9. PMID 21365997.
22. Carneiro PM, Rwanyuma LR, Mkony CA. A comparison of topical phenytoin with silverex in the treatment of superficial dermal burn wounds. Cent Afr J Med. 2002 Sep-Oct;48(9-10):105-8. PMID 14562531.
23. Tauro LF, Shetty P, Dsouza NT, Mohammd S, Sucharitha S. A comparative study of the efficacy of topical phenytoin vs conventional wound care in diabetic ulcers. Int J Med Med Sci. 2013;3:8-16.
24. Kodela SR, Kumar TJP, Vivek D. Outcome of topical phenytoin in the management of diabetic ulcers. IOSR JDMS. 2016 Jul;15(7):39-54. doi: 10.9790/0853-1507123954.
25. Anstead GM, Hart LM, Sunahara JF, Liter ME. Phenytoin in wound healing. Ann Pharmacother. 1996 Jul-Aug;30(7-8):768-75. doi: 10.1177/106002809603000712, PMID 8826558.
26. Bhatia A, Prakash S. Topical phenytoin for wound healing. Dermatol Online J. 2004 Jul 15;10(1):5. doi: 10.5070/D30Z3612W1, PMID 15347487.