Section: General Surgery

Original Research Article

PHENYTOIN IN WOUND HEALING: EXPLORING ITS EFFICACY IN SPECIFIC WOUND TYPES

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ABSTRACT

Background: The prevalence of chronic leg ulcers is on the rise, driven by factors such as an aging population, occupations involving prolonged standing, and increased incidence of risk factors like smoking, obesity, and diabetes. The aim is to evaluate the efficacy of topical phenytoin in various wound types, including diabetic, venous and traumatic ulcer. Assess the antimicrobial efficacy of topical phenytoin in the context of wound healing. **Materials and Methods:** The present study is a prospective comparative study conducted at the Department of General Surgery for a period of one year. The study consisted of a total of 40 patients older than 20 with particular forms of lesions, such as venous leg ulcers, traumatic ulcer, or diabetic foot ulcers, presence of the wound for a certain duration to ensure chronicity and resistance to standard wound care treatments who have not received prior treatment with phenytoin for wound healing were included in study. Out of the 40 patients enrolled in the study, they were divided into two groups. Twenty-three patients received topical phenytoin dressings and were classified as the study group, while 17 patients underwent conventional saline dressing and were classified as the control group. **Result:** There were 17 males and 6 females in the study group, 7 males and 10 females in the control group. The mean age in the study group was 53.82yrs, and the mean age in the control group was 52.35yrs. The most common type of ulcer found in our study was venous ulcer (45%), followed by diabetic ulcer (32.5%), and traumatic ulcer (22.5%). Diabetic ulcer is more common in the 51-60 age group. Assess dressing effectiveness by calculating the percentage of ulcer area covered by healthy granulation tissue after 14 days. The mean area of granulation tissue formation in the control group is 8.0412 cm2 ± 2.46058(SD) and in the study group is 9.6443 cm2 ± 2.16809(SD) of the total ulcer surface area. The granulation tissue formation as % of ulcer surface in the control group is 74.51% of total ulcer surface area and in the study group is 95.35% of total ulcer surface area. Potential difference in Swab Test scores between the groups exposed to Phenytoin and Saline revealed a significant difference in variances between the Phenytoin and Saline groups ($F = 7.139$, $p = 0.011$). **Conclusion:** Potential therapeutic efficacy of Phenytoin in the treatment of diabetic, venous, and traumatic ulcers is promising.

INTRODUCTION

Wound healing is a process involves a complex interaction between epidermal and dermal cells, the extracellular matrix, controlled angiogenesis and plasma derived proteins. All of these orchestrated by a slew cytokines and growth factors. Extracellular matrices (ECM), red and white blood cells, platelets, growth factors, cytokines, and other components all play a role in the complicated process of wound healing. Even if the regular process of skin restoration makes certain wounds appear to heal naturally, it is difficult to get ideal tissue regeneration and cell reorganization, especially in severe wounds like diabetic ulcers. It takes a complicated interaction between a variety of cell types, cytokines, mediators, and the vascular system for a wound to heal. The initial cascade of blood vessel constriction and platelet aggregation is intended to stop bleeding. A variety of inflammatory cells begin to swarm in after that, commencing with neutrophils. Angiogenesis, thrombosis, and re epithelialization are all aided by

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the mediators and cytokines released by these inflammatory cells. In turn, the fibroblasts lay down extracellular elements that will act as support.[1]

Phenytoin, chemically known as 5,5-diphenylhydantoin, was first introduced in the 1930s as a breakthrough in the treatment of epilepsy.[2] Its discovery marked a significant milestone in the medical field, as it was one of the first antiepileptic drugs that effectively controlled seizures without causing excessive sedation. Phenytoin belongs to the class of drugs known as hydantoins and is recognized for its ability to stabilize voltage-gated sodium channels in neurons, preventing the abnormal, excessive electrical activity that underlies epileptic seizures.[3,4]

Diabetic ulcers are a significant and increasingly prevalent complication of diabetes mellitus, with profound implications for the health and quality of life of affected individuals. It often exhibit slow wound healing and a higher risk of infections. A serious and growingly common consequence of diabetes mellitus, diabetic ulcers have a substantial negative impact on a person's health and quality of life. The non-healing nature of these chronic wounds can result in serious problems such as tissue necrosis, infection, and in the worst situations, amputation. Studies have demonstrated that Phenytoin has a beneficial effect on wound closure, decreased inflammation, and increased collagen deposition in diabetic wounds.[5]

Venous ulcers, caused by venous insufficiency, frequently occur on the lower extremities as chronic wounds. Venous ulcers, often referred to as venous stasis ulcers, are a prevalent and debilitating condition that affects a significant portion of the population, particularly among the elderly. The slow healing and recurrent nature of these chronic wounds not only place a heavy load on the healthcare system but also significantly lower the quality of life for individuals who live with them. Phenytoin has shown potential in improving granulation tissue formation and accelerating wound healing in venous ulcers.[6]

Traumatic ulcers, also known as recurrent aphthous stomatitis (RAS) or canker sores, are a common and often painful oral mucosal condition experienced by individuals of all ages. These small, superficial ulcers can be very uncomfortable and make it difficult to carry out daily tasks like eating and speaking. It also resulting from external injuries or tissue damage, vary in severity. Existing research on Phenytoin's role in traumatic ulcer healing has suggested positive effects on wound contraction and epithelialization.[7] Nonetheless, the scarcity of studies in this area underscores the necessity for more comprehensive investigations to determine its true potential as a therapeutic option for traumatic ulcers. Despite the recognized wound-healing properties of Phenytoin, there is limited research on its specific application in diabetic, venous, and traumatic ulcers.[8] Therefore, further studies are crucial to fill these information gaps and enhance scientific understanding of Phenytoin's role in wound healing across diverse ulcer types.

In conclusion, Phenytoin holds promise as a potential therapeutic drug for the treatment of diabetic, venous, and traumatic ulcers. Existing studies provide valuable insights into its effects, but additional rigorous research, including randomized controlled trials, is necessary to confirm its efficacy and safety for each type of ulcer.[9] By addressing these research gaps, we can advance evidence-based wound care methods and develop tailored treatment approaches for patients with chronic ulcers, ultimately improving patient outcomes and reducing the burden on healthcare systems.

MATERIALS AND METHODS

The present study is a prospective comparative study conducted at the Department of General Surgery in NRI Institute of Medical Sciences, Vishakhapatnam, Andhra Pradesh, spanning from September 2023 to November 2023. The study consisted of a total of 40 patients, and the research was approved by the Institutional Ethical Committee. Initially, 53 patients underwent phenytoin dressing, but only 40 patients provided consent to be included in the study. Therefore, a convenient sampling method was employed to select the 40 participants who have different types of chronic ulcers (diabetic, venous, or traumatic ulcers) for the study. This study design allows for a comprehensive evaluation of the chosen medical procedures and their outcomes.

Inclusion Criteria

Adults older than 20 with particular forms of lesions, such as venous leg ulcers, traumatic ulcer, or diabetic foot ulcers, presence of the wound for a certain duration (e.g., a minimum of two weeks) to ensure chronicity and resistance to standard wound care treatments. 3. Patients who have not received prior treatment with phenytoin for wound healing.

Exclusive Criteria

Wounds showing signs of severe infection, as they may require immediate specialized care, with a known hypersensitivity or allergy to phenytoin or any of its components.

This study is designed as a randomized controlled trial (RCT) to investigate the efficacy of topical phenytoin in various wound types, including diabetic, venous, and traumatic ulcers, while also determining the optimal dosage to achieve maximum efficacy and minimize adverse effects. The RCT design ensures the random allocation of participants into either the study group (receiving topical phenytoin) or the control group (receiving a placebo or standard wound care). Blinding measures may be employed to reduce bias.

Patient recruitment will involve selecting individuals with different wound types and obtaining informed consent. Demographic information and wound details, such as size, location, and duration, will be documented at baseline.

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The study population was split into two groups based on willingness for topical phenytoin therapy. The non-willing group received conventional saline dressings (control). Patient selection used purposive sampling. All underwent physical and clinical examinations, peripheral vascular and neuropathic assessments, and routine investigations. Wounds were debrided as needed, and surface areas measured twice, with the identical result recorded or the average if different.

The treatment group will receive topical phenytoin with dosages calculated based on wound size. The control group will receive a placebo or standard wound care. Wound healing progress and patient-reported outcomes will be assessed regularly. Tissue samples may be collected for histological analysis (granulation tissue formation), and laboratory tests may monitor blood levels of phenytoin.

Data analysis will involve comparing outcomes of treatment between the study and control groups using appropriate statistical methods. The study's findings will be interpreted, and a scientific report summarizing the results and conclusions will be prepared. The RCT design ensures that any observed differences can be attributed to the treatment (phenytoin) rather than other factors, making the study robust and reliable. The descriptive statistics provide a snapshot of the central tendency (mean), variability (standard deviation), and precision of the mean estimate (standard error) for each group. Data visualization is a powerful tool that transforms complex datasets into accessible and meaningful representations, enhancing the comprehension and interpretation of information. Through the use of graphical elements such as charts, graphs, and maps, data visualization brings clarity to patterns, trends, and relationships within the data.

Preparations: The investigation of the optimal delivery method for topical phenytoin in wound healing continues. While direct use of phenytoin powder with gauze is effective, it may result in a white coating issue, which can be mitigated by incorporating NaCl. Injectable phenytoin, due to its high pH, poses a risk to the skin. Notably, in a rat model, phenytoin powder outperformed alternative formulations. Research-grade powder and phenytoin gel hold promise as options, with the latter offering practicality and water-binding properties. The choice of delivery method significantly influences the assessment of phenytoin's effectiveness in wound healing, emphasizing the importance of this ongoing investigation.[9]

Dressings were done daily, followed by on alternate days depending upon the wound soakage in both the 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. The wound was cleaned with normal saline, and moist dressings were done in the control group. In the study group, phenytoin suspension was used instead. The amount of phenytoin needed was determined on the surface area of the wound as follows.4 Up to 5 cm.sq:100 mg, 5–9 cm.sq: 150 mg, 10–15 cm.sq: 200 mg, >15 cm.sq: 300 mg.

The phenytoin tablets were crushed and mixed with 5 ml of normal saline for every 100 mg of the drug. The suspension so prepared was uniformly applied over the surface of the wound. Throughout a 14-day period, both the study and control groups underwent daily monitoring. Wound cultures were meticulously obtained at the commencement of treatment and on the 14th day. Following this two-week period, a comprehensive assessment of the wounds was conducted in the study groups, encompassing a thorough comparison of surface area, granulation tissue formation rate, and a detailed evaluation of the antibiotic effect of phenytoin.

RESULTS

Out of the 40 patients enrolled in the study, they were divided into two groups. Twenty-three patients received topical phenytoin dressings and were classified as the study group, while 17 patients underwent conventional saline dressing and were classified as the control group. All patients belonged to middle and low socio-economic groups. There were 17 males and 6 females in the study group, 7 males and 10 females in the control group.

Table 1: Gender Vs specific ulcer

Gender	Diabetic Ulcer	Traumatic Ulcer	Venous Ulcer
F	8(62%)	7(78%)	12(67%)
M	5(38%)	2(22%)	6(33%)

Traumatic ulcers are more common in females. In male's diabetic and venous ulcers are more common.

Table 2: Age -wise distribution of patients.

Age Group	Phenytoin	Saline
31-40	1	2
41-50	6	7
51-60	12	5
61-70	4	3

The mean age in the study group was 53.82yrs, and the mean age in the control group was 52.35yrs. The most common type of ulcer found in our study was venous ulcer (45%), followed by diabetic ulcer (32.5%), and traumatic ulcer (22.5%).

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Table 3: Age group Vs Specific ulcer

Age group	Diabetic Ulcer	Traumatic Ulcer	Venous Ulcer
31-40	0	0	3(17%)
41-50	4(31%)	2(22%)	7(39%)
51-60	6(46%)	4(44%)	7(39%)
61-70	3(23%)	3(33%)	1(6%)
Total	13(32.5%)	9(22.5%)	18(45%)

The graph shows that venous ulcer is more common in all age groups. Most common age group is observed in 51-60. Diabetic ulcer is more common in the 51-60 age group.

Table 4: Ulcer surface area

Group	N	Mean	SD	Median	T Value	P value
Saline	17	12.02	2.23	11.08	−2.13	0.0399
Phenytoin	23	10.43	2.06	11.165		siginificant
Total	40	10.31	2.17	11.08		

The mean ulcer surface area in the control group(saline) is 12.02 cm2 and in the study group(phenytoin) is 10.43 cm2.

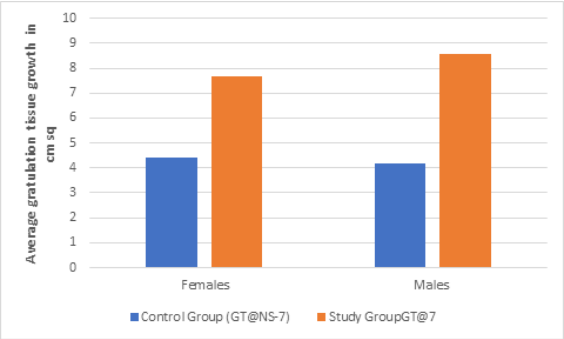

Figure 1: Average gratulation tissue growth after 7 days in both female and male.

The study reveals a significant increase in granulation tissue growth in the study group (GT@7) compared to the control group (GT@NS-7) among females. On average, the study group exhibited a substantial improvement, suggesting the potential efficacy of the intervention in enhancing wound healing. Among males, the study group (GT@7) demonstrated a noteworthy increase in granulation tissue growth compared to the control group (GT@NS-7). The average granulation growth tissue is less when normal saline is used instead of Phenytoin. Both males and females having almost same on 7th day of treatment. Slightly tissue growth is more for males on 14th day.

Table 5: Area of granulation tissue formation at 14 days.

Group		N	Mean	MEDIAN	Std. Deviation	Std. Error Mean	T Value	P- Value
GT@D- 14	PHENYTOIN	23	9.6443	9.9200	2.16809	0.45208	2.183	0.035
	SALINE	17	8.0412	7.5000	2.46058	0.59678		

Assess dressing effectiveness by calculating the percentage of ulcer area covered by healthy granulation tissue after 14 days, revealing its impact on wound healing. The mean area of granulation tissue formation in the control group is 8.0412 cm2 ± 2.46058(SD) and in the study group is 9.6443 cm2 ± 2.16809 (SD) of the total ulcer surface area.

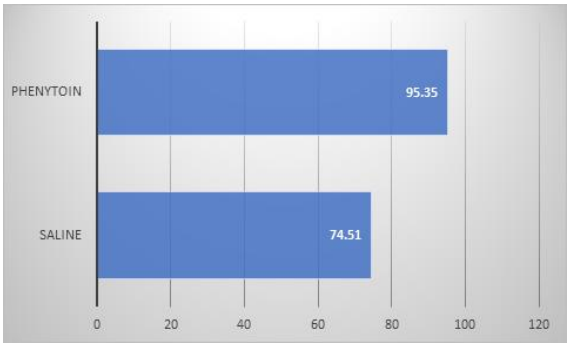

Figure 2: Granulation tissue formation as % of ulcer surface area

The granulation tissue formation as % of ulcer surface in the control group is 74.51% of total ulcer surface area and in the study group is 95.35% of total ulcer surface area.

An independent samples t-test was conducted to examine the potential difference in Swab Test scores between the groups exposed to Phenytoin and Saline. Levene's test for equality of variances was first employed to assess the assumption of equal variances. Levene's test revealed a significant difference in variances between the Phenytoin and Saline groups ($F = 7.139$, $p = 0.011$). As a result of this violation of the assumption of equal variances, the t-test was conducted with adjusted degrees of freedom.

The independent samples t-test, assuming unequal variances, indicated a statistically significant difference in Swab Test scores between the Phenytoin ($M = 0.09$, $SD = 0.288$) and Saline ($M = 0.76$, $SD = 0.437$) groups ($t = -5.910$, $df = 38$, $p = 0.000$). The mean difference was -0.678 ($SE = 0.115$). The 95% confidence interval for the difference ranged from -0.910 to -0.446. These findings suggest

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a substantial difference in Swab Test scores between the two groups, with the Saline group exhibiting significantly higher scores compared to the Phenytoin group.

DISCUSSION

The evolution of wound dressings reflects a transformative progression from the basic provision of physical protection, exudate absorption, and local infection control through topical medications to a sophisticated stage aimed at fostering an optimal environment for enhanced wound healing. Modern wound dressing agents play a pivotal role in promoting granulation tissue formation, signifying a paradigm shift toward therapies that actively contribute to the wound healing process.

This study was conducted to assess the efficacy of Phenytoin dressings in the treatment of various types of chronic ulcers. Our focus on chronic lower limb ulcers is driven by their inherent difficulty in achieving healing, a challenge confronted by researchers worldwide. Phenytoin stands out as a promising therapeutic agent, necessitating thorough exploration for its potential application across a diverse spectrum of ulcer etiologies. This research aims to contribute valuable insights into the effectiveness of Phenytoin in addressing the complex landscape of chronic ulcers. In this section, we discuss our study's observational aspects, comparing them with similar national and international research for contextual insights.

In the present study, the age ranged from 30-70 years with a mean age in the study group being 53.82yrs and in the control group being 52.35 years. 42.50% of the study population belonged to the range of 51-60yrs. 40% of the population was older than 50yrs and remaining belongs to 61-70yrs. The results were similar to a study by KS Sandhu et al,[10] in which the mean age was 53.50±7.52 (SD) yr in study group, while 53.35±7.29 (SD) yr in the control group. Maximum number of cases were present in 51-60 years with 57.5 per cent of the total number of cases. In the study by Carneiro et al,[11] the mean in the Phenytoin group was 32.5±14.87years and in the EUSOL group was 34.2±14.72years. According to Bharadva et al,[12] the age of the patients varied from 25 to 75 years. The maximum number of cases (52%) belong to the age group of 45 to 65 years. The mean age in the study group was 51.35±12.50 years and in the control group was 53.17±12.60 years.

Table 6: Comparison of Mean Age among various studies

Studies	Mean Age (in years)	
	Study Group	Control Group
Present Study	53.82	52.35
KS Sandhu et al (2018) (10)	53.50±7.52 (SD)	53.35±7.29 (SD)
Carneiro et al (2003) (11)	32.5±14.87	34.2±14.72
Bharadva et al (2017) (12)	51.35±12.50	53.17±12.60

In our study, males predominated, constituting 74% of the sample, while females comprised only 26%. Our findings highlight that chronic leg ulcers are more prevalent among individuals with lower educational and socioeconomic status. This may be attributed to limited understanding, financial constraints, and delayed access to treatment. Our results align with, albeit slightly surpass, trends observed in comparable national and international studies. The chronicity observed in elderly male patients is likely influenced by factors such as poor financial condition, low literacy, socioeconomic disparities, and associated comorbidities. In a study by Tauro L.F et al,[13] 66% of the study population were male patients, whereas only 34% were female patients.

In a study by Carneiro et al,[11] sixty-seven (65.7%) were male, and 35(34.3%) were female patients. Females were more commonly affected (62%) than males (38%), in a study conducted by Hokkam E et al.[14] In a study by Bharadva PB et al,[12] 47(83.9%) were male, and 9(16.1%) were female patients. A study by KS Sandhu et al,[10] showed that 67.5% were male, while 32.5% were female. Female preponderance was seen in a study by Korber A et al.[15] In their study, 60% of the subjects were female, while only 40% were male.

Table 7: Comparison of gender distribution among various studies

Studies	Males (in %)	Females (in %)
Present Study	.74	26
KS Sandhu et al. (2018) (10)	67.5	32.5
Bharadva PB et al (2017)(12)	83.9	16.1
Hokkam E et al. (2011) (14)	38	62
Korber A et al. (2010) (15)	40	60
Tauro L.F et al.(2009) (13)	.66	34
Carneiro et al (2003) (11)	.65.7	34.3

In Western societies, vascular diseases are the primary contributors to chronic lower limb ulcers. Conversely, in developing countries, chronic ulcers often result from trauma, infections, malignancies, and inadequately managed diabetes The most common type of ulcer found in our study was venous

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ulcer (45%), followed by diabetic ulcer (32.5%), and traumatic ulcer (22.5%). Venous ulcer more common in all groups. Most common age group is observed in 51-60. Diabetic ulcer is more in 51-60 yr. Carneiro et al,[11] in their study, reported that the major causes of chronic leg ulcers were those infected, following trauma (27.5%), chronic non-specific inflammations (21.6%) and infected burn wounds (15.7%). Dubhashi SP et al,[16] reported that the different cases included in the study were wound infections (21.3%), trophic ulcers (22%), diabetic foot ulcers (34%), venous ulcers (14.7%) and pressure sores (8%). According to a study by Gokhale Y et al,[17] 25% had venous ulcers, 40% had ulcers due to vasculitis, 10% had arterial ulcer, 10% due to Pyoderma gangrenosum, 5% Tuberculosis, 2.5% malignancy and for 7.5% patients cause could not be found out. Venous insufficiency was responsible for 45 to 60% of leg ulcers, while 10 to 20% were due to arterial insufficiency, 15 to 2% diabetic and 10 to 15% were due to combinations of these factors, in a study by Mekkes JR et al. (2003).[18] In a study by Korber A et al. (2010),[15] most frequent relevant aetiologies were the chronically venous insufficiency within 70 leg ulcers, an underlying vasculitis within 16, mixed arterio-venous ulcers within six, a Graft-versus-Host Disease within four patients

Table 8: Comparison of ulcer distribution among various studies

Studies	Predominant Ulcer Type
PRESENT STUDY	venous(45%) > diabetic > Traumatic
Carneiro et al. (2003)(11)	Traumatic (27.5%)
Dubhashi SP et al. (2015) (16)	Diabetic (34%)
Gokhale Y et al. (2017) (17)	Vasculitis (40%)
Mekkes JR et al. (2003) (18)	Venous (45-60%)
Korber A et al. (2010) (15)	Venous (70%)

Current our study says topical phenytoin is generally safe, with rare side effects such as slight transient burning sensation and occasional rash in one patient during this 14 days of duration.

In both groups, no side effects occurred during the application of dressings, which is comparable to a study by Bharadva PB et al.[12] Hokkam A et al,[14] reported a transient burning sensation in 7.4% of their study group. A generalised rash that resolved when treatment was stopped has been reported by Rhodes. Hypertrophic granulation tissue was noted in 10~36 per cent of patients in two studies by Muthukumaraswamy et al,[19] and Pendse et al.[20] This is reversed by stopping treatment, and it is suggested that stopping treatment when the wound area is covered with a granulation base can prevent this effect. Systemic absorption of topical phenytoin is not significant.

The prevalence of chronic leg ulcers is on the rise, driven by factors such as an aging population, occupations involving prolonged standing, and increased incidence of risk factors like smoking, obesity, and diabetes. The persistence of these ulcers in elderly male patients is believed to be associated with poor financial conditions, low literacy, unfavourable socioeconomic status, and related comorbidities. Phenytoin emerges as an economical and superior alternative for ulcer care. Its healing properties involve accelerating granulation tissue formation and reducing bacterial load. The use of topical phenytoin dressing is associated with shorter hospital stays, alleviating the financial burden on patients. Notably, it boasts advantages such as absence of side effects, ease of use, and ready availability. Despite its cost-effectiveness compared to conventional moist dressings, the absence of a commercially available phenytoin dressing is a current limitation.

Limitations

The study has significant limitations, including a small sample size and a non-blinded design, which may introduce bias and affect generalizability. The restricted participant pool challenges the statistical robustness of the findings, urging caution in applying results broadly. The brief duration of the study may overlook sustained effects, highlighting the need for extended observation. Additionally, the absence of a cost analysis neglects broader economic implications for patients. To address these limitations, a more extensive, randomized controlled study with a larger participant pool and longer duration is essential for stronger evidence and a comprehensive understanding of the intervention's impact, including economic aspects.

CONCLUSION

In conclusion, the potential therapeutic efficacy of Phenytoin in the treatment of diabetic, venous, and traumatic ulcers is promising. While existing studies have provided valuable insights into its effects, a critical need for additional rigorous research, particularly in the form of randomized controlled trials, is evident to conclusively establish its efficacy and safety across diverse ulcer types. Bridging these research gaps is essential to advancing evidence-based wound care methodologies and developing tailored treatment approaches for patients grappling with chronic ulcers. This comprehensive approach aims to substantially improve patient outcomes and concurrently alleviate the burden on healthcare systems by ensuring the implementation of effective and targeted interventions.

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