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The Impact of Topical Vitamin D on Wound Healing in Second-Degree Burn Injuries

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ABSTRACT

The effects of vitamin D may accelerate wound healing and have anti-inflammatory and antioxidant effects. The present study aimed to determine the effect of topical vitamin D on the healing of second-degree burn wounds in Wistar rats. This experimental in vitro study involved a sample of 32 male Wistar rats. Superficial second-degree burns were induced in the hairless back of the animals. They were randomly divided into four equal groups. In the burnt area, no topical treatment was applied in the control group. In the Vaseline group, a petroleum-based ointment was applied twice daily for 14 days. In the vitamin D group, topical vitamin D ointment, specifically 50 micrograms per gram, was applied twice daily, and in the Silver sulfadiazine cream group, silver sulfadiazine cream was applied twice daily for 14 days. To evaluate the efficacy of treatment, four rats in each group were anesthetized on days 0, 7, and 14, and their skin was processed for histological examination. At the end of the study, the area of the wound in the Vaseline group decreased more than other groups (75.02 ± 21.77 cm^2) (p = 0.03). The mean wound healing percentage was 38.23 ± 6.53 cm^2 in the Vaseline group, 45.61 ± 6.53 cm^2 in the vitamin D group, 43.59 ± 3.33 cm^2 in the silver group, and 63.58 ± 5.51 cm^2 in the control group; the Vaseline group had a significant difference with all three other groups ($p < 0.05$). In conclusion, vitamin D ointment improved histological changes of tissue components in the process of healing; therefore, the maximal rate of healing was seen in the Vaseline group. These findings suggest that they can be used as topical treatment agents for burn wounds.

Introduction

Traumatic thermal injuries, commonly referred to as burns, represent a prevalent and potentially life-threatening condition, often resulting in significant disability and diminished quality of life.[1] Statistical analyses indicate that burns constitute the fourth most common form of injury worldwide, surpassing traffic accidents, falls, and physical violence.[2] Notably, approximately 6.6 million individuals endure burn injuries globally, annually succumbing to over 265,000 cases.[3,4] These statistics underscore the substantial burden of burn injuries on global health, with mortality rates approaching 1% of all deaths.[5] A cornerstone of burn care is the prevention and management of wound infection, a critical determinant of patient outcomes.

Burn injuries are classified into three degrees based on their severity, ranging from mild to severe.[6] First-degree burns involve the outermost layer of skin (epidermis) and manifest as redness, tenderness, and localized pain without blistering (image of first-degree burn), which typically heal within a week without scarring.[7] In second-degree burns, the epidermis and dermis, the two outermost layers of skin, are affected, leading to the formation of blisters and in third-degree

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burns, the damage extends further, penetrating all skin layers and potentially reaching deeper tissues, including muscle and bone.[1] Due to the destruction of sensory nerves in third-degree burns, these injuries may not elicit pain, but they carry a significantly elevated risk of infection and mortality.[8]

The timely and effective healing of burn wounds remains a significant challenge in medical science.[9] Burn injuries disrupt the skin's barrier function, leading to a cascade of inflammatory and immune responses that impair the regeneration process of epithelial cells.[10] Vitamin D has been demonstrated to influence several aspects of wound healing, including the inflammatory and immune response.[11] It modulates the activity of immune cells, promoting an anti-inflammatory environment and enhancing the production of antimicrobial peptides.[11] Additionally, vitamin D stimulates the proliferation and differentiation of both fibroblasts and keratinocytes, the essential cell types involved in wound repair.[12] The favorable effects of vitamin D supplementations on wound healing, insulin resistance, biomarkers of inflammation and oxidative stress may be mediated by its impact on stimulating the phagocytosis and killing the bacteria by macrophages, suppressing interferon-g-mediated macrophage activation[13], activating insulin receptor expression, and the downregulation of cytokine generation.[14]

As there is evidence that vitamin D intake may accelerate wound healing and has anti-inflammatory and antioxidant effects, we hypothesized that vitamin D might help wound repair faster. While research on the healing effects of vitamin D has yielded mixed results, the absence of studies evaluating the impact of topical vitamin D on second-degree burn wounds, a notoriously protracted healing process, highlights the need for novel treatment strategies that can accelerate wound healing and minimize patient-associated side effects.[15] Therefore, the present study aimed to determine the effect of topical vitamin D on the healing of second- degree burn wounds in Wistar rats.

Materials and Methods

This experimental *in vitro* study was approved by Ethics committee of Urmia University of Medical Sciences (Ethical code: IR.UMSU.AEC.1401.024). This research was conducted in compliance with the research ethics standards.

This study involved a sample of 32 male Wistar rats, weighing between 220 and 250 grams and aged between 6 and 8 weeks. The rats were obtained from the laboratory animal reproduction and maintenance facility at Urmia University of Medical Sciences, where they were housed under standardized conditions, including a 12-hour light-dark cycle and a humidity level of approximately 50 to 55 percent (image of standard laboratory animal housing).

Animals

A total of 32 male Wistar rats, aged 6 weeks and weighing 220-250 g, were obtained from the laboratory animal reproduction and maintenance facility at Urmia University of Medical Sciences. The rats were housed in individually ventilated cages under standard conditions: temperature of 23 ± 2 °C, humidity of 50-55%, and a 12-hour light-dark cycle. The rats were fed with standard rat chow and water ad libitum (image of standard laboratory animal housing).

Sample Sizing Method

In animal studies, it is recommended to use the resource equation approach to determine the sample size.[16] Based on this approach, the acceptable degree of freedom (DF) in a one-way analysis of variance is between 10 and 20. With this description, the minimum and maximum number of animals in each group can be calculated based on the following formulas. In the present study, the number of groups (K) is equal to 4, and by placing in the following formulas, the minimum and maximum number of animals in each group is calculated as 2 and 4 mice, respectively.

$$\text{Minimum } n = 10/k + 1$$

$$\text{Maximum } n = 20/k + 1$$

Burn Wound Induction

The rats' back fur was shaved using an electric shaver and the shaved area was disinfected with betadine (povidone-iodine) 5% solution. The animals were then anesthetized by an intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg) to induce a deep sedation state. To create a second-degree burn, a round metal device made of aluminum with a diameter of approximately 1.5 cm was heated to 100 °C in boiling water. The heated device was promptly placed on the shaved area behind the rat for 10 seconds, causing a controlled second-degree burn. Afterward, all animals received lactate Ringer's solution (2 ml/100 g body weight/IP) for immediate resuscitation. Each rat was then placed in a separate cage and maintained under the previously described conditions. Tissue samples were collected from the burn site on days 4, 9, and 14. Tissue removal was performed by injecting 2% lidocaine around the burn area, followed by excision using a No. 15 scalpel, scissors, and forceps.[8]

Experimental Groups and Treatments

The study involved 32 rats, evenly divided into four groups (n = 8) to assess the efficacy of topical vitamin D

ointment in the treatment of second-degree burn wounds. Each group received a different treatment: Control group: No topical treatment was applied. Vaseline group: A petroleum-based ointment (Vaseline) was applied twice daily for 14 days. Topical vitamin D ointment group: Topical vitamin D ointment, specifically 50 micrograms per gram, was applied twice daily for 14 days, based on previous studies that demonstrated its potential benefits.[17] Silver sulfadiazine cream group: Silver sulfadiazine cream, an antimicrobial agent commonly used to treat burn wounds, was applied twice daily for 14 days.

Assessment of Wound Healing

To assess wound healing progress, the wound area was measured every 48 hours until complete healing. Digital photographs of the wounds were taken using a Sony Cybershot DSC-P72 camera. These images were then analyzed using image processing software (Digimizer 5.2.2.0) to determine the wound area. Additionally, the wound length was measured three times and the average value was used to minimize measurement error.

To calculate the percentage of wound healing, the wound area was measured using calipers with millimeter accuracy on the designated test days (days 0, 7, and 14). The percentage of healing was then calculated using the following formula:[18]

% healing = (current wound area / initial wound area) × 100

Sample Collection

On days 0, 7, and 14, four rats from each group were anesthetized using a combination of ketamine and xylazine to minimize pain and discomfort. A skin sample was collected from the burn site of each anesthetized rat.

Histopathological Examination

For histological analysis, the formalin-fixed skin samples were subjected to standard processing procedures, including dehydration with a series of ethanol solutions, embedding in paraffin, and sectioning into 5-µm thick slices. These sections were then stained with hematoxylin and eosin (H&E) method to microscopic evaluation by an Olympus light microscope.[17]

Statistical Analysis

Data were reported as mean ± standard deviation (SD). Multiple comparisons between different groups were performed using one-way ANOVA followed by Tukey's post-hoc test. A *p*-value of less than 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 22.

Results

The effect of burn injury on losing weight of rats is shown in Table 1. No significant differences were observed between groups in the loss of weight after burn injury.

Table 2 displays the comparison of wound size in different time periods which shows a continuous reduction in wound size over time between the groups ($p < 0.05$). The wound area of vitamin D group did not show significant changes on all measured days except on the eleventh and thirteenth days, which decreased significantly ($p < 0.001$). In the Vaseline group, the mean wound areas on the first and third days were similar, but it had the significant decrease on the fifth, seventh, ninth, eleventh, and thirteenth days ($p < 0.001$). In the silver group, until the seventh day, the mean wound area changes were similar, and only on the ninth, eleventh, and thirteenth days, the wound area had a significant decrease compared to other days. There was no significant change in the wound area of the negative control group on all measured days except thirteen day ($p < 0.001$) (Figure 1, Table 2).

According to between group comparison, the mean wound areas between the four groups were not statistically significant until the seventh day ($p < 0.05$), but from the ninth day, the mean wound area in the Vaseline group was lower than other groups (124.18 ± 16.28 cm^2). Therefore, the mean wound area of the Vaseline group (111.11 ± 21.40 cm^2) was significantly less than the vitamin D group (123.05 ± 35.28 cm^2), silver group (138.36 ± 20.04 cm^2) and negative control group (149.56 ± 31.71 cm^2) on the eleventh day ($p = 0.04$). On the 13th day, mean area of the wound in the vitamin D group (94.04 ± 30.04 cm^2), was less than Vaseline group (75.02 ± 21.77 cm^2), Silver group (95.02 ± 9.99 cm^2), and negative control group (138.66 ± 35.29 cm^2), which was statistically significant ($p = 0.03$).

The percent of wound contraction was shown in Table 3. The intra-group comparison of the mean wound percentage in the four groups showed that wound percentage was significantly reduced in all four groups at each time period ($p < 0.001$). The mean percentage of wound changes of the vitamin D group showed no significant difference until eleventh days, but there was a significant decrease on the thirteenth day (45.61 ± 3.47)

Table 1. Mean ±SD weights of the rats after burn injury in different groups

Variable	Group 1 (Negative control) (n = 5)	Group 2 (Vaseline) (n = 6)	Group 3 (Vitamin D) (n = 6)	Group 4 (Silver sulfadiazine) (n = 6)	*p*-value
Weight (g)	207.00 ± 8.36	205.83 ± 7.78	204.00 ± 4.14	209.83 ± 7.78	0.47

Table 2. Mean wound size (cm²) of the animals groups treated with various topical ointments in post burn injury.

Variables	Group 1 (Negative control) (n = 5)	Group 2 (Vaseline) (n = 6)	Group 3 (Vitamin D) (n = 6)	Group 4 (Silver sulfadiazine) (n = 6)	*p*-value
1st day	192.98 ± 42.49	214.97 ± 75.33	177.10 ± 60.01	216.68 ± 56.32	0.63
3rd day	176.67 ± 38.43	207.83 ± 73.16	164.20 ± 54.41	206.01 ± 53.77	0.48
5th day	165.79 ± 41.66	189.68 ± 62.18	150.05 ± 50.39	189.48 ± 45.72	0.48
7th day	148.79 ± 47.55	156.68 ± 42.59	151.68 ± 42.59	175.55 ± 39.66	0.79
9th day	168.63 ± 36.35	124.18 ± 16.28	142.4 ± 55.06	162.81 ± 38.48	0.52
11th day	149.56 ± 31.71	111.11 ± 21.40	123.05 ± 35.28	138.36 ± 20.04	0.04
13th day	138.66 ± 35.29	75.02 ± 21.77	94.04 ± 30.04	95.02 ± 9.99	0.03
***p*-value**	< 0.001	< 0.001	< 0.001	< 0.001	

Table 3. Comparison of the percentage of wound contraction among four groups in different time periods.

Variables	Group 1 (Negative control) (n = 5)	Group 2 (Vaseline) (n = 6)	Group 3 (Vitamin D) (n = 6)	Group 4 (Silver sulfadiazine) (n = 6)	*p* -value
3rd day	91.85 ± 6.70	96.79 ± 2.30	92.82 ± 3.55	95.15 ± 3.31	0.21
5th day	85.68 ± 5.60	89.34 ± 6.84	84.85 ± 4.18	88.37 ± 8.96	0.62
7th day	76.28 ± 7.49	75.03 ± 9.42	85.37 ± 8.49	82.16 ± 9.32	0.68
9th day	77.88 ± 4.58	64.31 ± 6.03	67.88 ± 4.14	72.04 ± 4.21	0.29
11th day	68.99 ± 2.07	56.96 ± 1.49	60.01 ± 5.24	26.11 ± 4.08	0.33
13th day	63.58 ± 5.51	38.23 ± 6.53	45.61 ± 3.47	43.59 ± 3.33	0.02
***p* -value**	< 0.004	< 0.001	< 0.001	< 0.001	

($p < 0.001$). In Vaseline group, there was an outstanding decrease in wound percent only on thirteen day (38.23 ± 6.53). In the silver group, until the ninth day, the changes in the wound percentage were similar, and only on the eleventh and thirteenth days, there was a significant decrease in the wound percentage ($p < 0.001$). There was no significant change in the mean wound percentage of the negative control group until the eleventh day. Only on the 13th day, its changes were significant (63.58 ± 5.51) ($p > 0.05$).

In the comparison between the groups, the mean wound percentage of four groups was similar on all measured days except on the 13th day that the mean wound percent of silver group was significantly less than other groups (43.59 ± 3.33)($p = 0.02$) (Figure 2, Table 3).

Histopathological Findings

Histopathological examination with light microscopy revealed that the healing process in the Vaseline group was more rapid compared to the silver and vitamin D ointment groups, with a significant reduction in wound depth. Epithelialization was complete in all three groups, with moderate fibrosis observed in the Vaseline group and severe fibrosis in the negative control group. Inflammation was moderate in the Vaseline, vitamin D, and silver groups, with a decrease to mild levels at the end

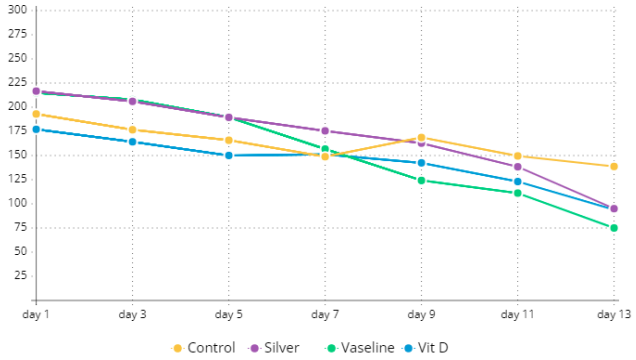

Figure 1. The mean size of wound area (cm²) in different groups in different time periods.

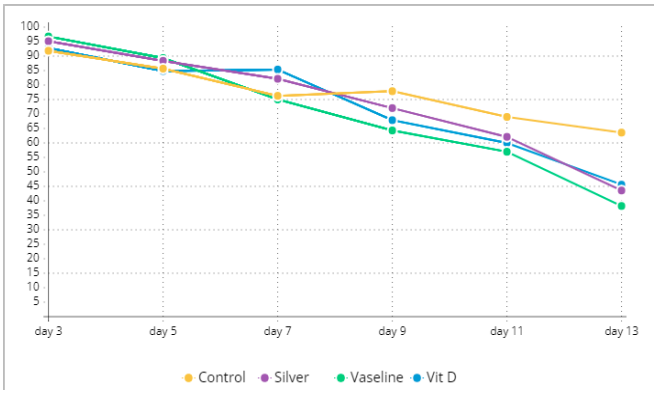

Figure 2. Comparison of the percentage of wound contraction among four groups in different time periods.

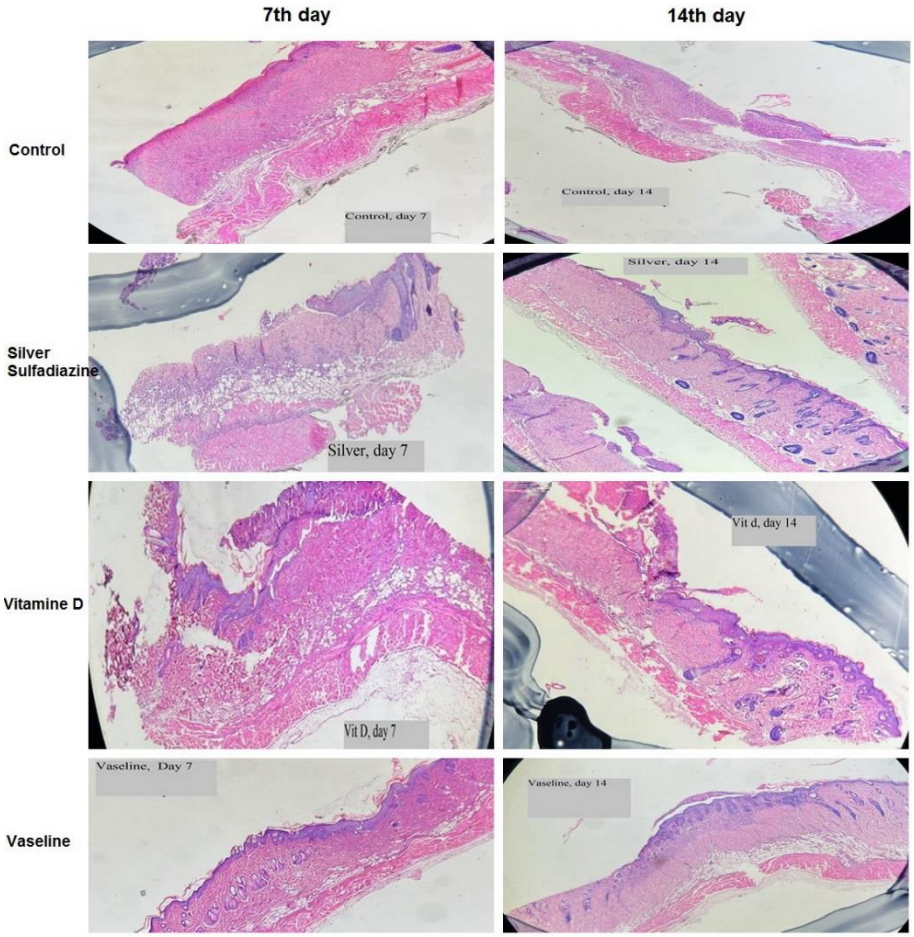

Figure 3. Histopathologic observations of skin tissue between four studied groups on 7th and 14th day.

of the study, particularly in the Vaseline group. Hair follicle formation was observed in all samples from the Vaseline group, while no follicles were observed in the silver, vitamin D, or dressing groups. These findings demonstrate the potential of topical Vaseline application in promoting wound healing, reducing inflammation, and preventing fibrosis, while also supporting hair follicle regeneration (Figure 3).

Discussion

Burns and their associated injuries are a significant public health concern, causing significant mortality, disability, and socioeconomic burdens worldwide.[19] Effective burn management prioritizes wound healing and expediting the epithelialization process.[20] Wound healing is a complex and orchestrated process encompassing three distinct phases: inflammation, cell proliferation, and tissue maturation.[21] The ability of a therapeutic agent to modulate tissue blood circulation, either through biochemical or pharmacological mechanisms, holds the potential to prevent the progression of burn depth (stasis area) and promote successful wound healing.[22] In light of these observations, this study sought to investigate the potential effects of topical vitamin D application on the repair of superficial skin burns in a rat model.

The average wound area is widely utilized as a benchmark for assessing the progress of burn wound healing.[23] This study's evaluation of wound size demonstrated that by the 11th and 13th days after the intervention, the Vaseline-treated groups exhibited significantly accelerated wound healing and reduced wound size compared to the other groups, indicating the efficacy of topical Vaseline application in promoting wound repair. Additionally, both the vitamin D and silver groups exhibited significant differences compared to the control group in terms of wound area, wound percentage, and wound healing percentage; however, no significant difference was observed between the vitamin D and silver groups themselves. These findings align with histopathological observations, which revealed enhanced collagen deposition, angiogenesis, and minimal inflammation in the Vaseline-treated group. The wound condition in the control group was notably inferior to that observed in the other three groups.

While the impact of vitamin D on wound healing has not been extensively studied,[24,25] established research suggests a connection between vitamin D deficiency and an increased risk of developing chronic wounds.[26] A study demonstrated that topical application of a low dose of vitamin D3 can expedite wound closure in individuals with epidermolysis bullosa dystrophy.[27] Another study

conducted by Razzaghi *et al*. revealed that daily oral administration of 50,000 units of vitamin D3 for 12 weeks led to a reduction in the length, width, and depth of diabetic foot ulcers.[21] Vitamin D's influence on wound healing is multifaceted, encompassing the inflammatory and immune response,[28] as well as the proliferation and differentiation of fibroblasts and keratinocytes.[29] Vitamin D's anti-inflammatory properties are thought to suppress monocytes and inflammation mediated by Langerhans cells, thereby promoting wound repair.[30] Additionally, vitamin D3 treatment diminishes the expression of pro-inflammatory cytokines IL-1α, IL-6, and IL-8 by keratinocytes.[31] Moreover, vitamin D weakens adaptive immunity while enhancing innate immune responses.

The findings of this study revealed no significant difference in the reduction of wound area and the percentage of wound healing between the vitamin D and silver groups at the conclusion of the study. Previous research has demonstrated silver's anti-inflammatory and antimicrobial properties. Studies by Wasef *et al*. and Siczek *et al*. described anti-inflammatory mechanisms following silver administration in burn wounds and in a mouse model of irritable bowel syndrome (IBS).[32,33] Silver sulfadiazine's ease of use, lack of pain upon administration, low toxicity, low sensitivity, and antibacterial effects have made it the gold standard among topical antimicrobial drugs for burn patients globally.[34] However, contradicting these findings, a recent systematic review reported that silver sulfadiazine exhibits inferior therapeutic outcomes and less evidence of efficacy in preventing wound infection compared to alternative dressings.[35]

Histopathologic examination in this study revealed that the Vaseline group exhibited superior healing outcomes compared to the other groups, demonstrating significant improvements in wound depth, fibrosis, epithelialization, inflammation, and even hair follicle formation. A pivotal randomized controlled trial comparing Vaseline to topical antibiotic ointment for postoperative wound care in ambulatory surgery patients demonstrated equivalent infection rates.[36] Consequently, 69.4% of Mohs surgeons recommend the use of Vaseline for wound care after routine procedures. However, a study cautioned against using Vaseline as an immediate first aid measure for burns, suggesting its application as a subsequent dressing for minor burns.[37]

According to our hypothesis that vitamin D might help wound repair better; therefore, Vaseline group showed better wound healing than Vitamin D group did. Based on reviewed literature, these results could point that Vaseline can be useful for healing superficial wounds[38]. Moreover, studies show that petroleum jelly (Vaseline) is just as effective as an antibiotic ointment for non-infected wounds[39]. Medical and scientific literature suggests that minor skin injuries typically heal optimally when undisturbed by deleterious influences.[40] Studies have demonstrated that Vaseline pure petroleum jelly promotes effective healing of minor wounds, allowing for healthy wound healing without infection, irritation, or dressing adherence, while maintaining skin hydration.[41] Similarly, Vaseline application to sunburn and minor burns has been shown to protect the damaged area while preserving the natural healing process.[37] As discussed before, the immunological function of vitamin D manifests anti-bacterial and anti-inflammatory activity, acting on the link between innate and acquired immunity.[42] Vitamin D is a regulator of the innate immunity of the oral cavity.[43]

One of the limitations of this study is that due to financial limitations and lack of financial support from the university, we were not able to purchase a kit for biochemical measurement, and as a result, this item was not measured in this study. Also, contrary to our hypothesis, it was shown that the vitamin D group has less wound healing than the Vaseline group in this study, so further human studies are needed to address this issue precisely.

Our study findings indicated that the beneficial effects of vitamin D on wound healing were less pronounced compared to Vaseline, but superior to both silver and the control group. The percentage of wound healing in the Vaseline group was significantly higher than the other three groups. Furthermore, histopathologic examination revealed more favorable changes in the Vaseline group compared to all three groups. These findings suggest that Vaseline's promotion of wound healing may be attributed to its antioxidant and anti-inflammatory properties, and its ability to stimulate collagen synthesis. This study demonstrates that Vaseline, and in its absence, vitamin D, can be effective in promoting wound healing.

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Conflict of Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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