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# The Effects of Topical Vitamin C Solution on Burn Wounds Granulation: A Randomized Clinical Trial

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## Abstract

**Background and Objectives:** Vitamin C or ascorbic acid is the most efficient water-soluble antioxidant. Studies show intravenous and oral vitamin C assist with burn healing. However, the effects of topical applications of vitamin C remain unstudied. This study aimed to evaluate the effects of topical vitamin C solution on the granulation tissue reduction of second-degree burn wounds.
**Methods:** This clinical trial was conducted on 30 patients with second-degree burns affecting two or more regions or extended limb areas who had been admitted to the Vasee Hospital burn unit in Sabzevar, Iran during Aug-Dec 2016. In light of the multiple factors influencing burn wound healing, each subject served as his or her own control. Additionally, the depth of burn wounds in each area between limbs of the same patient was similar. Patients routinely received sulfadiazine ointment on two contiguous or separate body parts. Vitamin C solution was applied to one randomly chosen part of the body or one randomly chosen limb. Burn wounds were examined on days one (a baseline measure) and three, seven, and 14 days after the initial assessment, using the Bates-Jensen Wound Assessment Tool. Written informed consent was obtained from the patients prior to the study. Data analysis was performed in SPSS version 20 using repeated measures ANOVA.
**Results:** In the experimental region, the mean granulation score was $5.00 \pm 0.00$ at baseline and reached $1.83 \pm 0.87$ on day 14. In the control group, mean granulation score was $5.00 \pm 0.00$ at baseline and increased to $2.67 \pm 0.88$ on day 14. On day 14, a significant difference was observed between the mean granulation scores for the experimental and control regions ($P = 0.004$).
**Conclusions:** Topical administration of a vitamin C solution could be effective in promoting the healing of second-degree burn wounds.

*Keywords:* Topical Vitamin C Solution, Granulation, Wound, Burn

## 1. Introduction

Skin burns are among the most important challenge in medicine and remain a major public health issue worldwide (1). Skin injuries occur due to chemicals, ultraviolet radiation, radioactivity, electricity, and boiled water (2, 3). Acute thermal injuries requiring medical treatment affect nearly half a million Americans each year, with approximately 40,000 hospitalizations and 3,400 deaths annually (4).

First-degree burn affects the epidermis. Superficial second-degree burns involve damage that penetrates into the papillary dermis. Deep second-degree burns involve damage extending beyond the reticular dermis. Burns that destroy all layers of the skin down to the subcutaneous fat are third-degree burns (5). First- and superficial second-degree burns heal almost without scars, while deep second-degree and third-degree burn lead to the formation of hypertrophic scars during the healing process, and patients often require reconstructive surgery (6).

Wound healing is divided into three phases: inflammation, re-epithelialization and granulation tissue formation, and matrix formation and remodeling. The phases of wound repair overlap considerably. Inflammation is divided into early and late phases, denoting neutrophil-rich and mononuclear cell-rich infiltrates, respectively. Wound contraction begins after the granulation tissue is well-established, and collagen accumulation begins shortly after the onset of granulation tissue formation (7).

Burn wound care includes the use of topical antimicrobial agents with basic dressing to absorb exudates from the wound and outer layers (8). Various dressings are used for burn wound healing (9) and typically, topical antibiotics are used to limit the growth of bacterial colony (10). Silver sulfadiazine is the standard topical antimicrobial for burn wounds (11).

Considering that many synthetic drugs used to treat burn wounds are expensive and cause problems such as allergies, researchers are seeking out alternative medicines

to advance recovery and reduce treatment costs. Vitamin C or ascorbic acid is a water-soluble antioxidant. Vitamin C protects the skin against UV rays, free radicals, and other damage. In addition to anti-inflammatory effects, it is an agent for skin depigmentation (12). Infusions of vitamin C have beneficial effects in burn patients and reduce the need for fluid resuscitation. Burn patients are usually given oral vitamin C (13-15). Some studies on pigs have shown that a topical 10% solution of vitamin C applied to the skin can increase vitamin C levels in the skin (12, 16). In previous studies, the effects of topical vitamin C solution were assessed for the treatment of bedsores (15). Other studies assessed the effect of vitamin C solutions on erythema after carbon dioxide laser treatments and chronic wound healing of the cornea. However, its effects on human burn wounds have not been assessed. The aim of this study is to determine the effects of topical vitamin C solutions on the granulation tissue of burn wounds. Because evidence supports the effects of intravenous and oral vitamin C on burn wound healing in humans (14, 17), we conducted this study to examine whether topical vitamin C may have similar effects on the granulation tissue of burn wounds.

## 2. Methods

In this study, 30 patients with second-degree burns in two or more body parts or a limb who had been admitted to the burn ward at Vasee hospital in Sabzevar, Iran were asked to participate in the study. Patients provided informed consent prior to participation.

Because multiple factors impact burn wound healing, each participant served as his or her own control to account for potential confounds based on individual differences in burn wound healing processes. The inclusion criteria were that participants had to have two contiguous or separate burns on their body. The depths of each area compared were also quite similar. The intervention region received vitamin C solution while the control regions did not receive vitamin C. Both parts of each patient's body received sulfadiazine ointments. All burn wounds were observed and scored by a specialist. After debridement and washing with water and normal saline solution, the section of the burn wound was dried with sterile gauze. Then silver sulfadiazine ointment 1% with a thickness of 1.5 mm was laid using a sterile glove on the surface of the wound. After the same washing and drying process, the other burned limb or part of the body that was considered in the study received the intervention treatment. A vitamin C 10% solution was applied on the surface of the wound using a sterile swab, up to a maximum area of 225 square centimeters. Then, silver sulfadiazine 1% ointment at a thickness of 1.5 mm was applied, and the burn wound was dressed.

In this study, the healing of granulation tissue was assessed on days 1, 3, 7, and 14 after burn injury. After opening the dressings for replacement, the wounds were evaluated by the main investigator using the Bates-Jensen checklist. To control for observer bias, digital photos were taken during treatment. At the first opportunity, a specialist in plastic surgery reviewed the photos and scores.

### 2.1. Vitamin C Solution

Vitamin C is an antioxidant drug that can be used topically in dermatology. The absorption of vitamin C in the gut is low, even in cases of high oral dosage. In addition, the bioavailability of vitamin C into the skin is inadequate when it is administered orally. The use of topical vitamin C is therefore favored in dermatology (12). We used 5 mL vials containing 500 mg of vitamin C, manufactured by the Daroo Pakhsh Company. Vitamin C solutions should be used in topical administrations at 1% - 25% concentrations. Vitamin C is unstable and, upon exposure to light, is oxidized to dehydroascorbic acid. The stability of vitamin C is maintained by a pH > 3.5 (18). We used a vitamin C 10% solution with a pH = 6, in accordance with the findings of Mester's study on the effects of vitamin C on bedsores (19).

### 2.2. Bates-Jensen Wound Assessment Tool

The Bates-Jensen wound assessment tool is a validated wound assessment tool (20). It is used in many healthcare settings as a means of standardized wound assessment and documentation of wound status. It is also used to measure treatment outcomes (20). It consists of 15 items, of which one item represents the granulation of the wound. Each item is rated on a five-point Likert scale, where "1" represents the best and "5" reflects the worst healing of granulation. The Bates-Jensen wound assessment tool has been validated in previous Iranian studies (21, 22).

### 2.3. Statistical Analysis

Data analysis was performed using SPSS 20. Krowith-Mokhly test was used to evaluate the homogeneity of variances. Repeated measures analysis of variance was used to investigate the effects of vitamin C on wound healing on days 1, 3, 7, and 14 after the initiation of treatment.

### 2.4. Ethics

The ethics committee of Sabzevar University of Medical Sciences approved the study protocol and proposal (approval number: IR.MEDSAB.REC.1394.60). Permission was obtained from Vasee hospital officials to engage in the study. The objectives of the study were explained to all

participants, and written informed consent was obtained from all participants prior to the study. Participants could quit the study at any time, and researchers ensured the study objectives were aligned with the values and beliefs of participants. The researchers were obligated to inform the officials and participants about the results of the study. The IRCT code of the current research is IRCT2015101224487N1.

## 3. Results

The sample included 30 patients referred to the burn unit at Vasee hospital. The mean age of the participants was 43.03 ± 11.9 years. Eighteen patients were male (60%) and 12 patients were female (40%). The average patients' body mass index (BMI) was 27.82 with a standard deviation of 4.080. The assumption test of Krowith-Mokhly was rejected with 99% confidence ($P < 0.001$). After correcting for the degrees of freedom, the epsilon test was checked. We used the Greenhouse-Geisser epsilon to assess the effects because this test is conservative for small-sized samples. The results indicated that the mean scores of granulation decreased from the first day to 14th day ($P < 0.001$) and there were significant differences between the two groups in terms of the rate of decrease for the mean granulation scores ($P < 0.001$). The mean scores of granulation at the four measurement points significantly differed between the two groups ($P = 0.004$). Figure 1 shows that the areas that received topical vitamin C showed faster granulation tissue growth compared to the areas without vitamin C, especially on days 7 and 14.

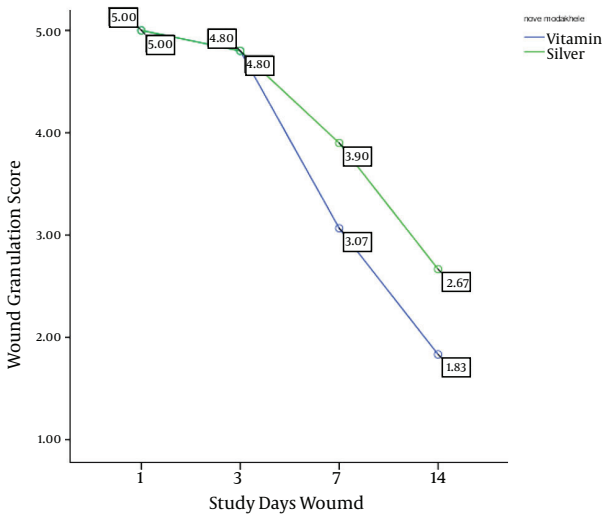


**Figure 1.** Comparison of the Mean Granulation Tissue Scores Between the Two Regions

Comparing the mean granulation scores across the different days showed that there was no significant difference between the two groups on the first and third days, but significant differences were observed on seventh and fourteen days. In the intervention region, the mean granulation scores on days 7 and 14 were 3.07 and 1.83, respectively. In the control region, the corresponding scores were 3.90 and 2.67, respectively, on days 7 and 14 (Table 1).

**Table 1.** Comparison of the Mean Wound Granulation Scores for Both Regions[a]

| Group<br>Statistical Indicators | | Intervention<br>Mean ± SD | Control<br>Mean ± SD |
|---|---|---|---|
| Granulation score | First day | 5.00 ± 0.0 | 5.00 ± 0.0 |
| | Third day | 4.80 ± 0.66 | 4.80 ± 0.66 |
| | Seventh day | 3.07 ± 1.01 | 3.90 ± 1.02 |
| | Fourteenth day | 1.83 ± 0.87 | 2.67 ± 0.88 |
| Effects of Time | df = 2.51 | F = 264.5 | P < 0.001 |
| Interactive Effect of dressing and time | df = 2.51 | F = 9.3 | P < 0.001 |
| Dressing effect | df = 1 | F = 9.11 | P = 0.004 |

[a]Test: Repeated measure ANOVA.

## 4. Discussion

This study aimed to investigate the effect of topical vitamin C solution on the granulation of burn wounds among 30 patients referred to the burn unit of Vasee hospital in Sabzevar, Iran. The results showed a significantly greater reduction in granulation tissue in vitamin C recipients than the controls. Vitamin C helps burn healing in two ways. It helps building collagen in skin tissue. Collagen synthesis is a process for healing burns. Vitamin C removes free radicals and causes further improvements at the site of the burn wound. Experts believe that when the body experiences stress, such as a burn, the recommended daily allowance of vitamin C is not enough (17).

Our results aligned with the limited studies in this area. Mester's study showed that topical vitamin C promoted the development of granulation tissue during healing from bedsores. This granulation tissue formed beginning on the seventh day of treatment with topical vitamin C. This study showed that vitamin C solution plays a vital role in collagen formation and that oral intake of the solution enhances its effect (19). Lima's study on mice showed less wound inflammation, fewer macrophages, more granulation tissue, more collagen fibers, and more new blood vessels in an intervention group that received vitamin C compared to the control group (23).

Due to the lack of an ointment containing only vitamin C, we used a vitamin C solution on wounds, making application difficult. We recommend that, in future studies, an ointment containing only vitamin C be used. The findings of this study can be used to inform more effective burn wound healing practices. Further studies are needed to compare the topical application of vitamin C ointments and mixed antioxidant ointments on burn wound healing.

### *4.1. Study Limitations and Strengths*

The primary limitations of this study were the lack of burn patients with bilateral burns or long burn wounds, which resulted in prolonged duration of sampling in this study. We recommend that future studies be conducted in large burn hospitals with more participants available. In addition, it was impossible for us to examine some wound healing indicators like the inflammation rate, number of collagen fibers, and number of blood vessels microscopically. The strengths of this study were that we controlled the confounding variables by designing a clinical trial where each patient was his or her own control to explore solely the effects of vitamin C on burn wounds.

### *4.2. Conclusions*

Findings confirmed the hypothesis of the study, and showed that a vitamin C solution reduced burn wound granulation tissue more than controls. The results of this study can be a basis for future studies on burn wound healing. Use of topical vitamin C can accelerate the healing of granulation tissue. Topical vitamin C usage may reduce the length of hospitalization, reduce infections, and morbidity in cases of burn wounds. In addition, the results of this research could be used in other fields, such as the pharmaceutical industry to manufacture topical medications for wound healing.

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## Footnote

**Authors' Contribution:** Hamid Rabat Sarpooshi was the main investigator who wrote the proposal, collected the data, and wrote the first draft. Forough Mortazavi contributed to the study design and revision of the final draft. Mojtaba Vaheb supervised burn wound healing assessment, Yasser Tabarayee contributed to the statistical analysis.

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