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Original Article

Impact of 3% Simvastatin Topical Cream on the Healing of Bedsores: A Double-Blinded Randomized Clinical Trial

Afarin Aghajari[a], Mahgol Moaref[a], Reza Ganji[a*]

[a]*Department of Clinical Pharmacy, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

Abstract

Since the prevalence of pressure ulcers has been increasing in recent years, they need a new and efficient treatment. The pleiotropic effects of statins can be used for this purpose. This study aimed to evaluate the appropriate formulation of 3% simvastatin (SIM) topical cream and its effect on the healing of bedsores. At first, the appropriate formulation of SIM topical cream was investigated. In a randomized, double-blind trial, 42 patients were divided into two groups: placebo and SIM cream, and used these creams for three weeks, once every 12 hours on a clean bedsore. Bedsore dimensions were measured at the beginning and end of the study. Seventy-seven percent of patients in the SIM group and 35% in the placebo group had more than 20% healing of bedsores. Age (P=0.03), gender (P=0.01), statin use (P=0.04), and diabetes (P=0.04) had statistically significant impacts on bedsore healing. Also, better wound healing in the non-diabetic patients was observed. It seems that the topical cream of SIM significantly affects the healing of bedsores and can also be used in bedsores of diabetic patients. In diabetic patients with bedsores, blood sugar control through nutritional counseling and consumption of regular diabetic medication seems to be very effective and efficient.

Keywords: Bedsore, Simvastatin, Statins, Topical drug, Ulcers, Wound healing.

1. Introduction

Bedsore refers to skin, muscle, and subcutaneous tissue damage caused by pressure, shear, or friction. It often occurs in bony prominences, as a common complication of long-term hospitalized patients, such as people with coma and paraplegia, as well as wheelchair users [1]. Today, these wounds are one of the five most common causes of patient injury in the world and a preventable problem in terms of patient safety [2], and they are divided into four degrees (from lesions with red areas without skin change, tissue destruction, and necrosis to muscle and bone damage) [3]. Protecting the integrity of the skin is the main way to prevent these ulcers [4].

Corresponding Author: Dr. Reza Ganji, Assistant Professor of Clinical Pharmacy, Department of Clinical Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Golestan Blv. Ahvaz, Iran. E-mails: rgpharm777@gmail.com

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Statins, which are reductase inhibitors, have been shown to affect wound healing [5]. It should be noted that wound healing is a natural physiological process that occurs in response to structural damage of tissues, including skin [3]. Additionally, statins have been shown to reduce scarring by reducing the expression of connective tissue growth factor [6]. Simvastatin (SMV), which is one of the most commonly prescribed statins, has been found to have wound-healing effects beyond cholesterol reduction [5] and have pleiotropic wound healing effects, including anti-inflammatory activity and improved endothelial function, which can improve the healing process [6]. Also, SIM can improve the epithelialization and revive the normal skin epidermal barrier by reducing iso-prenylation downstream targets of mevalonate and farnesyl pyrophosphate (FPP). This mechanism of action is believed to be responsible for the wound-healing effects of SIM [7].

Previous studies have demonstrated that the topical application of medicated formulations could prove their potential in healing diabetic wounds. Specifically, a slow-release topical formulation of SIM has been shown to improve wound healing [8-10], and it has limited side effects such as skin irritation [7] and xerosis [11]. A study has shown that the topical application of combined Phyllanthus emblica Linn. and SIM could enhance wound healing by upregulating angiogenesis and reducing neutrophil infiltration in mice with diabetic wounds [12]. Topical creams containing statins are a clinically convenient and cost-effective option for skin application [11]. They are popular due to their ease of use, attractive appearance, and lack of residue post-application [11]. Therefore, in this study, we formulated a cream of 3% SIM for topical use in wounding bedsores and compared its results with a placebo.

2. Materials and Methods

2.1. Stage 1: SIM topical cream formulation

Initially, SIM medicinal powder with 99% purity was produced, and then a suitable formulation was developed to create a topical cream containing 3% SIM. During this process, factors such as the formulation's stability and physicochemical properties, the product's expandability, release examination, water content and nature of the product, and wound characteristics such as pH and viscosity of wound fluids were taken into account. We examined four formulations to get better results, and finally, the fourth formulation was accepted. This study was performed according to the Declaration of Helsinki guidelines and approved by the Ahvaz Jondishapur University of Medical Sciences ethics committee by the code of IR.AJUMS.REC.1398.178 was registered in the Iranian Registry of Clinical Trials system with the registration number IRCT20200602047634N1 (URL: https://en.irct.ir/trial/). Written informed consent was obtained from all enrolled patients.

2.1.1. Preparation of topical formulation: containing drug

2.1.1.1. Preparation of oily phase

To create the oily phase of the topical formulation, stearic acid (8%), cetyl alcohol (4%), liquid paraffin (20%), and eucerin (4%) were weighed and poured into a 50 ml beaker.

After the complete dissolution of the contents, 1.5 grams of SIM powder was added to the mixture.

2.1.1.2. Preparation of the aqueous phase

In the other 50 ml beaker, glycerin (5%), propylparaben (0.24%), methylparaben, triethanolamine (0.24%), borax (2%), and purified water (51.5%) were mixed and placed on the bain-marie at the same time as the content of the oily phase. After 30 minutes, the temperature of the aqueous phase material reached close to that of the oily phase mixture. In this study, we examined four formulations, and finally, the fourth formulae were approved (**Table 1**).

Table 1: Final cream composition.

Aqueous phase	Gr (%)	Oily phase	Gr (%)
Glycerin	2.5 (5)	Simvastatin	1.5 (3)
Triethanolamine	1 (2)	Stearic acid	4 (8)
Methylparaben	0.12 (0.24)	Cetyl alcohol	2 (4)
Propylparaben	0.12 (0.24)	Liquid paraffin	10 (20)
Purified water	25.7 (51.5)	Eucerin	2 (4)
Burax	1 (2)	-	-

2.1.1.3. Combination of aqueous and oily phases

After the complete dissolution of each beaker, oil phase content was added to the aqueous phase content and stirred until the final beaker content changed from liquid to semi-solid.

2.1.1.4. Placebo formulation

The topical formulation of the placebo was similar to the topical formulation of the main drug, without SIM powder.

Physicochemical tests were evaluated in both SIM and placebo formulations, including appearance characteristics (color, smell), spreadability, ability to leave the cream from the tube, stability, viscosity, uniformity, thermal changes, melting and freezing cycles, and microbial protection. One of every ten creams produced was randomly selected as a sample and subjected to physicochemical tests.

2.2. Stage 2: Applying SIM topical cream on bedsores of diabetic patients

Initially, 48 patients with 2nd or 3rd-degree bedsores were selected to participate in this study. They were randomly divided into intervention and control groups (n=24 in each group). For randomization, 48 patients were divided into six blocks of 8, and the codes were placed in sealed envelopes. Without knowing the code on the sealed envelope and the tube, the clinical caregiver delivered the cream of placebo or SIM to the patient, and based on this, and the patients were divided into two therapeutic intervention groups. Finally, due to the loss of samples during the study, 23 patients in the intervention and 19 patients in the control group remained.

Demographic characteristics of patients, including age, gender, weight, diabetes, blood pressure (BP), bedsore degree, and history of medicines usage, such as the history of taking drugs of the statin groups or the history of statin allergy, were collected. Both groups received the standard antibiotic treatment, which included 1 g ceftriaxone once every 12 hours and 600 mg clindamycin once every 8 hours.

2.3. Intervention groups

The control group received a placebo, and the intervention group received 3% SIM cream. Both groups used their creams topically every 12 hours for three weeks. Three tubes were

delivered for each patient during treatment (1 per week). Before applying the cream and at the end of 3 weeks, the dimensions and degree of each patient's bedsores were measured by the below formula:

$$Healing\ ratio\ (\%) = \left[\frac{(Area0-Area4)}{Area0}\right] \times 100$$

(Area 0 and Area 4: bedsore dimension on the first and last day of treatment, respectively)

2.4. Diabetic patient's evaluation

Considering the importance of diabetes and its special effect on the condition of ulcers, we investigated and followed up on the ten diabetic patients in the SIM group separately and filled out a questionnaire for each of them.

2.5. Statistical analysis

Data were presented as frequency (percent), median (range), or mean (standard deviation (SD)). The comparison between the two studied groups was done using a Chi-score statistical test. All analyses were performed using SPSS version 26 (IBM Corporation, Armonk, NY). Also, the significance level is considered as $P<0.05$.

3. Results and Discussion

To reach the most suitable formulation, we tried four different formulations, whose characteristics are shown in **Table 2**; finally, the fourth formulation was selected for treatment. In the clinical evaluation, we found no significant differences in gender, weight, smoking, alcohol consumption, physical activity, oral statin use, or diabetes between the two groups, as shown in **Table 3** ($P>0.05$). In the SIM group, wound healing of patients was statistically significantly different than in the placebo group ($P<0.05$).

In evaluating bedsore's length, width, and depth improvement, there were no significant differences between these variables with gender, weight, age, BP, smoking, alcohol consumption, oral use of statins, and diabetes in the control group ($P>0.05$). Regarding physical activity, only the length improvement of bedsores had a statistically significant difference (P=0.03).

Table 2: Final cream composition. Base type of F1-3 were erasable with water but F4 was water absorbent.

Formulae	Contain SIM	Color	Smell	Spreadability	Stability	Monotony	Extrudability
F1	Yes	Yellowish white With a greasy appearance	Malodor	Very low	Unstable	Low	Very bad
	No	Yellowish white With a greasy appearance	Malodor	Very low	Unstable	Low	Very bad
F2	Yes	Yellowish white	Malodor	Very low	Unstable	Low	Very bad
	No	Yellowish white	Malodor	Very low	Unstable	Low	Very bad
F3	Yes	white	Appropriate	Low	Stable	Appropriate	Medium
	No	white	Appropriate	Low	Stable	Appropriate	Medium
F4	Yes	white	Appropriate	Appropriate	Stable	Appropriate	Very good
	No	white	Appropriate	Appropriate	Stable	Appropriate	Very good

Table 3: Comparison of characteristics and wound healing of patients in the two groups.

Variables		Group		*P*-value
		Control (n (%))	Intervention (n (%))	
Gender	Female	6 (31.6)	11 (47.8)	0.28
	Male	13 (68.4)	12 (52.2)	
Weight	>70	10 (50)	12 (54.5)	0.76
	<70	10 (50)	10 (45.5)	
Smoking	Yes	11 (57.9)	17 (73.9)	0.39
	No	8 (42.1)	6 (26.1)	
Alcohol consumption	Yes	18 (94.7)	22 (95.7)	0.89
	No	1 (5.3)	1 (4.3)	
Physical activity	Yes	11 (57.9)	13 (56.5)	0.92
	No	8 (42.1)	10 (43.5)	
Oral Statins use	Yes	11 (57.9)	13 (56.5)	0.92
	No	8 (42.1)	10 (43.5)	
Diabetes	Patient	8 (42.1)	10 (43.5)	0.92
	Healthy	11 (57.9)	13 (56.5)	
Wound healing	Yes	7 (35)	17 (77)	**<0.05**
	No	13 (65)	5 (23)	

In the SIM group, there were no significant differences between weight, BP, smoking, alcohol consumption, diabetes, and physical activity with wound dimensions ($P>0.05$). Also, age (P=0.03), gender (P=0.01), and statin use (P=0.04) had statistically significant differences with the wound's depth, and in terms of diabetes, the length of the wound was different (P=0.04).

In the evaluation of diabetic patients in the SIM group, we found that blood sugar measurement, compliance with the diabetic diet, regular use of diabetes medications, blood sugar amount, lipodystrophy due to injections, and patient's cooperation with nutritionist were significant with wound healing of patients ($P<0.05$). More details are shown in **Table 4**.

Table 4: Relation between diabetes variables with wound healing in the intervention group.

Variables		Wound healing		*P*-value
		Yes (n (%))	No (n (%))	
Blood sugar measurement	Appropriate	4 (80)	1 (5)	0.01
	Inappropriate	0 (0)	5 (100)	
Compliance with the diet	Yes	4 (66.7)	2 (33.3)	0.03
	No	0 (0)	4 (100)	
Regular use of diabetes medications	Yes	4 (55.7)	2 (33.3)	0.03
	No	0 (0)	4 (100)	
Blood sugar amount	Appropriate	0 (0)	4 (100)	0.03
	Inappropriate	4 (66.7)	2 (33.3)	
Lipodystrophy	Yes	3 (66.7)	1 (33.3)	0.01
	No	0 (0)	6 (100)	
The patient's cooperation with nutritionist	Yes	0 (0)	4 (100)	0.03
	No	4 (66.7)	2 (33.7)	

In **Figures 1** and **2**, we randomly selected bedsores pictures of diabetic and non-diabetic patients, which show the healing process. It should be noted that better wound healing was observed in the non-diabetic patients.

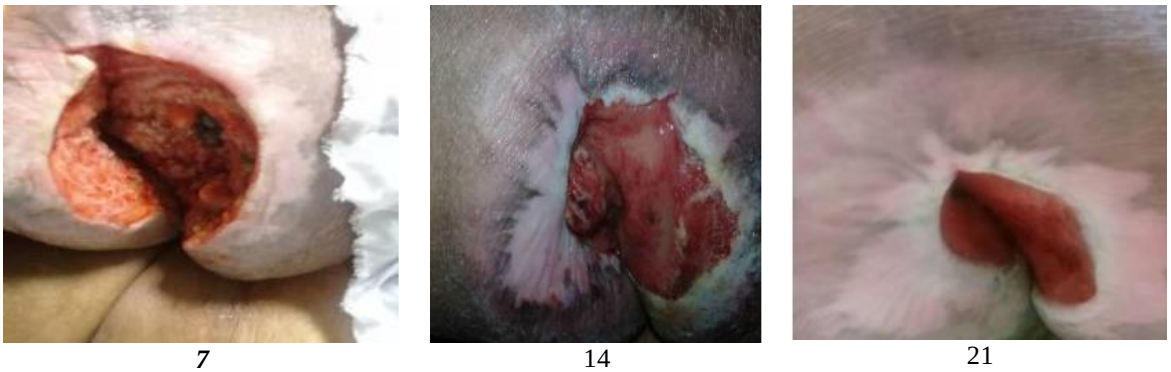
Because bedsores are one of the common and preventable patient injuries [2] and because of their importance, we investigated the effect of 3% SIM on the healing of second and third-degree bedsores in this study. Our findings revealed that age, gender, and statin use in the SIM group significantly impacted the wound's depth and the impact diabetes had on the length of the wound. Overall, we found a positive impact of SIM on bedsores.

The study of Ramhormozi et al., which evaluated the healing process of burn wounds by SIM, suggested that topically applied SMV can be used as an alternative therapeutic approach to manage deep second-degree burn wounds in rats [5]. In this way, in another study by Mousavi-Simakani et al., they investigated the SIM-loaded nanostructured (NLCs) lipid process of wound healing, it was shown that this combination is more effective in treating pressure ulcers than both drug-free NLCs and conventional SIM gels and it can also significantly reduce inflammation and promote skin regeneration [13].

Moreover, another study on diabetic wounds in mice found that topical use of combined Phyllanthus emblica Linn. and SIM can enhance wound healing by upregulating angiogenesis and reducing neutrophil infiltration [12] regarding further study results and our findings. SIM has properties beyond cholesterol lowering and is considered a promising candidate for enhancing the healing process by improving angiogenesis and epithelialization. One review study revealed that the topical use of SIM gels and hydrogel can be effective for wound healing by promoting epithelialization and antibacterial activity [7].

7 14 21

Figure 1. Grade 2 bedsores in a diabetic patient after 7, 14, and 21 days from the start of treatment.



7 14 21

Figure 2. Grade 3 bedsores in a non-diabetic patient after 7, 14, and 21 days from the start of treatment.

Our findings show that SIM topical cream works better on non-diabetic patients than on diabetic ones. It should be noted that we did not find any relevant study that evaluated topical SIM cream in these two groups. In a study, Asai et al. showed the effectiveness of topical use of SIM on diabetic wound healing [14]. Another study that investigated the role of SIM on the healing of blood vessels confirmed the generation and increase of nitric oxide bioavailability and the reduction of oxidative stress in diabetic mice and considered SIM as a hope for healing diabetic wounds [15].

One of the limitations of this study was its small sample size, which may have affected the results. Moreover, the patient's refusal to participate in the application of topical cream was the other one.

4. Conclusion

Based on our findings, the topical cream of SIM is an angiogenesis-stimulating, anti-inflammatory, and antibacterial agent. It also appears that in people with diabetes who suffer from vascular and wound repair disorders, topical simvastatin can be used as a therapeutic agent in the wound healing process and speed up it. In diabetic patients with bedsores, blood sugar control through nutritional counseling and consumption of regular diabetic medication seems to be very effective and efficient.

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Conflict of interest

The authors declare to have no conflict of interest.

References

[1] Wei, W. and N. Ma, *Bedsore*, in *Encyclopedia of Gerontology and Population Aging* (2022), Springer. p. 606-611.

[2] Abd Elfattah Atia Elasrag, G., S. E Aboalizm, and A. Youniss Ahmed Elghiety, *Effect of Olive Oil Topical Application on Pressure Ulcer Among Patients in Intensive Care Unit.* Egyptian Journal of Health Care (2022). **13**(2): p. 1715-1725.

[3] Varaei, S., et al., *Comparison the effects of massage with olive oil and sweet almonds oil on prevention of pressure ulcer in hospitalized patients in ICU.* Avicenna Journal of Nursing and Midwifery Care (2019). **27**(5): p. 353-360.

[4] Karabey, T. and Ş. Karagözoğlu, *Using Beeswax, Olive Oil and Centaury Oil for Pressure Ulcers.* Turkiye Klinikleri J Case Rep (2019). **27**(3): p. 153-6.

[5] Ramhormozi, P., et al., *Simvastatin accelerates the healing process of burn wound in Wistar rats through Akt/mTOR signaling pathway.* Annals of Anatomy-Anatomischer Anzeiger (2021). **236**: p. 151652.

[6] Xie, P., et al., *Liposome‐encapsulated statins reduce hypertrophic scarring through topical application.* Wound Repair and Regeneration (2020). **28**(4): p. 460-469.

[7] Sameh, N., et al., *Prospective role of simvastatin on wound healing: review of the literature.* J Bioequiv Bioavailab (2018). **10**(2): p. 36-42.

[8] Tufail, S., et al., *Simvastatin nanoparticles loaded polymeric film as a potential strategy for diabetic wound healing: In vitro and in vivo evaluation.* Current drug delivery (2022). **19**(5): p. 534-546.

[9] Huang, P.-H., et al., *Simvastatin pretreatment enhances ischemia-induced neovascularization and blood flow recovery in streptozotocin-treated mice.* Journal of Vascular Surgery (2016). **64**(4): p. 1112-1120. e1.

[10] Gupta, S., M. Del Fabbro, and J. Chang, *The impact of simvastatin intervention on the healing of bone, soft tissue, and TMJ cartilage in dentistry: a systematic review and meta-analysis.* International journal of implant dentistry (2019). **5**(1): p. 1-11.

[11] Dolivo, D., et al., *Simvastatin cream alleviates dermal fibrosis in a rabbit ear hypertrophic scar model.* Journal of Cosmetic Dermatology (2023). **22**(2): p. 534-541.

[12] Liao, T.-T., et al., *Topical combined Phyllanthus emblica Linn. and simvastatin improves wound healing in diabetic mice by enhancing angiogenesis and reducing neutrophil infiltration.* Biomedical Reports (2023). **18**(4): p. 1-11.

[13] Mousavi-Simakani, S.M., et al., *Simvastatin-Loaded Nanostructured Lipid Carriers as Topical Drug Delivery System for Wound Healing Purposes: Preparation, Characterization, and in Vivo Histopathological Studies.* Advanced Pharmaceutical Bulletin (2023). **13**(4): p. -.

[14] Asai, J., et al., *Topical simvastatin accelerates wound healing in diabetes by enhancing angiogenesis and lymphangiogenesis.* The American journal of pathology (2012). **181**(6): p. 2217-2224.

[15] Farsaei, S., H. Khalili, and E.S. Farboud, *Potential role of statins on wound healing: review of the literature.* International wound journal (2012). **9**(3): p. 238-247.