

# The effect of nitric oxide releasing cream on healing pressure ulcers

Vahid Saidkhani<sup>1</sup>, Marziyeh Asadzaker<sup>2</sup>, Mohammad Javad Khodayar<sup>3</sup>, Sayed Mahmoud Latifi<sup>4</sup>

## ABSTRACT

**Background:** Pressure ulcer is one of the main concerns of nurses in medical centers around the world, which, if untreated, causes irreparable problems for patients. In recent years, nitric oxide (NO) has been proposed as an effective method for wound healing. This study was conducted to determine the effect of nitric oxide on pressure ulcer healing.

**Materials and Methods:** In this clinical trial, 58 patients with pressure ulcer at hospitals affiliated to Ahvaz Jundishapur University of Medical Sciences were homogenized and later divided randomly into two groups of treatment (nitric oxide cream;  $n = 29$ ) and control (placebo cream;  $n = 29$ ). In this research, the data collection tool was the Pressure Ulcer Scale for Healing (PUSH). At the outset of the study (before using the cream), the patients' ulcers were examined weekly in terms of size, amount of exudates, and tissue type using the PUSH tool for 3 weeks. By integrating these three factors, wound healing was determined. Data were analyzed using SPSS.

**Results:** Although no significant difference was found in terms of the mean of score size, the amount of exudates, and the tissue type between the two groups, the mean of total score (healing) between the two groups was statistically significant ( $P = 0.04$ ).

**Conclusions:** Nitric oxide cream seems to accelerate wound healing. Therefore, considering its easy availability and cost-effectiveness, it can be used for treating pressure ulcers in the future.

**Key words:** Cream, healing, nitric oxide, pressure ulcer, wound healing

## INTRODUCTION

In recent years, the problem of pressure ulcer has become one of the major concerns of medical staff at medical centers around the world, especially for the nursing team.<sup>[1]</sup> Despite the advances in the quality

of providing health care around the world, the number of patients with pressure ulcer has increased.<sup>[2,3]</sup> In Iran, statistics show that the incidence of pressure ulcers in general sectors is 5% and in special sectors is 10.1–21%.<sup>[4]</sup> The prevalence of pressure ulcers in hospitals of USA is 11.3%, in the Netherlands is 7.6–11.8%, and in Japan is 3.3–18%.<sup>[5-7]</sup> Pressure ulcers have caused increasing hospital costs and by increasing septicemia and bacteremia level, patients' mortality rate is increased.<sup>[8]</sup> Due to each pressure ulcer, the nursing staff workload is increased up to 50%.<sup>[7]</sup> Studies have shown that pressure ulcer increases hospitalization days to 4.31.<sup>[9]</sup>

If these ulcers can be well managed, many problems including the cost imposed on a patient and hospitalization duration can be decreased, free time of the nursing staff can be increased, and instead of dealing with pressure ulcer and its complications, the rest of the critical issues of the

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patients can be addressed. Thus, the quality of patient care is improved.<sup>[10]</sup> Today, various methods of care and treatment are used for the prevention and treatment of pressure ulcer, including skin care to maintain its cohesion, frequent change position, ensuring adequate nutrition, careful evaluation to avoid skin damage, the use of support and training tools for patients as preventive methods, honey, the use of electrical stimulation, fibroblast growth factor, fish oil, laser therapy, and topical oxygen therapy.<sup>[11-18]</sup> Although first prevention approach is considered, despite using the best methods of prevention, pressure ulcer occurs.<sup>[19]</sup> Various methods have been used in treatment of pressure ulcer and only few them have been reported. But most of these therapies have relative effects and are complementary to one another.<sup>[15-19]</sup> Defects of some of these methods include difficult access,<sup>[14]</sup> high cost,<sup>[14-16]</sup> lack of patient comfort,<sup>[16-17]</sup> and not being easy to use.<sup>[16]</sup> For this reason, for the treatment of this disorder more effectively, less expensive treatments that are easier to use and better tolerated by the patients are needed.

In recent years, nitric oxide (NO) has been proposed as an effective treatment method in ulcer healing.<sup>[20,21]</sup> Nitric oxide causes ulcer healing in animal models and a few studies have also been conducted in humans. Results of these studies have suggested that NO may be effective in treating ischemic tissues and chronic ulcers.<sup>[22-26]</sup> NO regulates ulcer healing through processes such as re-epithelialization, angiogenesis, fibroblast and collagen synthesis, increase inflammatory cells and growth factor.<sup>[27-33]</sup> Also, in animal studies, it has been found that NO heals diabetic ulcers, burns, and ischemia in mice and rabbits.<sup>[29,34,35]</sup> Hydrogels released by NO cause increase in blood flow in human skin and for this reason, they are effective in the treatment of ischemic tissues and ulcers.<sup>[36-38]</sup> Farsaei *et al.* showed that sildenafil cream (intensifies the activity of NO) causes healing pressure ulcer in patients hospitalized in intensive care unit (ICU).<sup>[39]</sup> Phillips *et al.* showed in their study that nitric oxide releasing cream heals ulcer due to *Mycobacterium* (buruli ulcer) in humans.<sup>[40]</sup> Various clinical trials are being carried out that investigate the effect of NO donor patch on healing diabetic foot ulcer and leishmaniasis skin lesions.<sup>[41,42]</sup> Nitric oxide gas was reported to heal chronic leg ulcer.<sup>[43]</sup> One of the therapeutic effects of hyperbaric oxygen on ulcer healing is caused by increased levels of nitric oxide in ulcer.<sup>[44,45]</sup> In addition to the effects of NO on ulcer healing, it has been observed that NO has high antibacterial effects due to which it decreases infection.<sup>[46-52]</sup> Therefore, conducting further studies in the field of healing chronic ulcers such as pressure ulcer in humans seems to be necessary.

Although eradication of pressure ulcer seems to be a challenge, with skilled nursing care and correct scientific prevention and treatment, a major step can be taken in

this regard and the quality of life of these patients can be improved. As a result, regarding the high prevalence of pressure ulcer and the increased time spent and cost of the treatment and nursing care on the one hand and the benefits listed for nitric oxide in healing ulcer on the other hand, the present study was conducted with an aim to determine the effect of nitric oxide on healing pressure ulcer.

## MATERIALS AND METHODS

The study was a double-blind clinical trial registered in IRCT2014041417268N1. The researcher was unaware of the group that the patient belonged to (treatment or control). The research assistant determined which cream (nitric oxide or placebo) was to be used for which patient. The samples were also unaware of the content of used cream. Studied population included all patients with pressure ulcer admitted in hospitals of Ahvaz Jundishapur University of Medical Sciences. PUSH tools were used as a data collection tool in this study. Using this tool, three criteria of the size of ulcer, exudates amount, or tissue type in the ulcer were evaluated and scored.

The ulcer size was specified using a scaled ruler and by measuring the ulcer length and width (cm), so that the greatest ulcer length (top-down) and the greatest ulcer width (side-side) were measured. Its different forms measure from zero to more than 24 cm<sup>2</sup> and it is scored between zero and 10.

Exudate amount: Amount of exudate (drainage) present on sterile gauze after removal of the dressing and before applying new dressing to the ulcer and is scored as follows: In the absence of exudates, it is scored zero; in the presence of low exudates amount, it is scored 1; in the case of average exudates amount, it is scored 2; and in the case of very high exudates amount, it is scored 3.

The type of tissue or ulcer color is also scored as follows: Absence of ulcer is given a score of zero, epithelial tissue a score of 1, granulation tissue a score of 2, slough tissue a score of 3, and necrotic tissue has score of 4.

Inclusion criteria included: subjects over 18 years of age, having pressure ulcer with grade 2 and above, no cancer, not using drugs, such as nitroglycerin, that lead to increased level of nitric oxide, not using immunosuppressives, no smoking, no chronic diseases such as diabetes that affect ulcer healing process, and lack of severe vascular disease, lupus, rheumatoid arthritis, or renal failure. Exclusion criteria included death of the patient during the study and unwillingness to continue participating in the study for any reason. Fifty-eight patients with pressure ulcer

grade 2 and above were identified and enrolled in the study by purpose-based sampling method and according to the inclusion and exclusion criteria. After explaining the purpose and methods, patients' written consent was obtained. In patients with loss of consciousness, consent of first-grade family members was obtained. Items such as age, body mass index (BMI), the ulcer site, the ulcer grade, and ward of patients were homogeneous. Then, by random allocation method, the samples were divided into two groups of treatment ( $n = 29$ ) and control ( $n = 29$ ). In practice, the sampling was gradual, which means that samples entered the study gradually. This means that for the first 29 patients who entered the study, 29 draws were done (once per person) which specified the group in which the patient is in (treatment or control). Then, matched Person each sample that were found placed in another group. In the control group, in addition to routine care (change positions, rinsing, and Comfeel dressing), placebo cream was used, i.e. when changing the dressing (before putting new Comfeel dressing), placebo cream (commercial cream base without additional substance) was used in the ulcer site. After 30 min, the ulcer site was rinsed and dried by physiological serum. Then, according to the ward routine, dressing was performed for each patient. In the treatment group, in addition to routine care (change positions, rinsing, and dressing) nitric oxide releasing cream [sodium nitrite 6% + citric acid (monohydrate) 9%] was used in the ulcer site. Each substance was prepared with a separate cream base. First, citric acid was applied on the ulcer surface and spread evenly over the ulcer. Then, equal amount of sodium nitrite was rubbed on the ulcer and gently mixed with citric acid.<sup>[32,40]</sup> By acidification of nitrite (NO<sub>2</sub>), nitric oxide is released from dinitrogen trioxide interface (N<sub>2</sub>O<sub>3</sub>).<sup>[32,33,40,53]</sup>

Nitric oxide that is released in this way is spread quickly in the tissue without causing tissue damage.<sup>[32,33,40,53]</sup>

After 30 min, the ulcer site was rinsed and dried. Then, according to the ward routine, dressing was performed for each patient. It should be noted that nitric oxide releasing cream was used for 3 weeks<sup>[40]</sup> (once per 2 days) and when changing dressing, in order to not disturb patients' routine treatment process. The researcher was unaware of the group that the patient belonged to (treatment or control). The research assistant determined which cream (nitric oxide or placebo) was used for which patient by drawing lots. Also, the samples were unaware of the content of the cream. In case of complete healing, the procedure was stopped early. Dressing change in both groups was performed by the researcher. In addition, every week at a specified time and before dressing change, the researcher visited the studied centers to determine patients' Pressure Ulcer Scale for Healing (PUSH) score. Also, using PUSH

every week for 3 weeks, the ulcer characteristics were measured. During the 3 weeks, all the information of patients in both the groups was recorded. In case of any complication, the procedure was stopped and the complication was completely treated. The researcher practically completed training of staging and scoring of the ulcer under the supervision of a specialist in ICU and skilled nurses in the field of pressure ulcer. In order to avoid any scientific and practical abuse of work in 10 ulcers, a specialist approved the PUSH score and it was compared with completed check list by researcher. Also, according to the equality ( $r = 91.5\%$ ), both checklists were prepared by the researcher. In the case of discharge, the patients were told to go to the hospital daily for dressing change and/or the treatment process was followed at home by the researcher. In the case of a patient's death before the second week, he was replaced by another patient; but when the patient died after the second week, he was not removed from the sample and the ulcer status comparison was done in the last week and week zero. Regarding patients' long-term follow-up, some changes might have happened in the dietary status, type of activity, and consciousness level that are inconsistent with their initial information. Therefore, regarding this, the dietary status, type of activity, and consciousness level more time experienced by a patient for a longer period of time during 3 weeks was considered for the patient. The ulcer status in different weeks was compared in both groups. Also, weekly changes in the ulcer were examined in both groups separately. Data were analyzed using software SPSS version 16. Descriptive and analytical statistics and *t*-test, chi-square, and repeated measure analysis of variance (ANOVA) were used for data analysis.

### Ethical considerations

Approval for this study was obtained from Ahvaz Jundishapur University of Medical Sciences ethics committee.

### RESULTS

In Table 1, the characteristics of studied units in terms of age, sex, ulcer site, ward, BMI, Glasgow Coma Score (GCS), mobility, nutrition method, and the ulcer stage are given. These items were similar in both groups and no significant difference was found between the two groups.

In Table 2, mean ulcer status scores (size, exudates amount, the type of tissue) of the two groups are given while they entered the study. Table 2 shows that at baseline (week zero), in terms of ulcer status (size, exudates amount, the type of tissue), no statistically significant difference was found between the two groups.

**Table 1: Demographic characteristics of the study subjects**

	Group (%)		P value	Description
	Intervention	Control		
Sex				
Male	48	52	0.75	-
Female	52	48		
Ulcer site				
Scapula	16	24	0.77	The most frequent ulcers in sacrum area
Sacrum	56	52		
Heel	28	24		
Ward				
General ICU	80	72	0.56	The most frequent ward was General ICU
Neurology ICU	20	28		
GCS				
3-5	52	44	0.83	The most frequent score 3-5
6-8	36	44		
9-12	12	12		
Mobility				
Complete immobility	88	84	0.71	Most people had complete immobility
Relative immobility	12	16		
Nutrition method				
Feeding tube	84	80	0.73	The most frequent method was using feeding tube
TPN	16	20		
Ulcer stage				
Grade 2	56	60	0.82	The most frequent grade 2 ulcers
Grade 3	32	24		
Grade 4	12	16		
Age mean (SD)	56.84 (12.15)	11.80 (55.60)	0.85	Most people were older than 55 years
BMI mean (SD)	32.88 (6.30)	32.12 (6.36)	0.91	Most had between 30 and 40

ICU: Intensive care unit, SD: Standard deviation, TPN: Total parital nutrition

**Table 2: Ulcer characteristics in the study groups (baseline)**

Ulcer characteristics	Group	Mean (SD) baseline	P value
Size (length × width)	Intervention	9.64 (2.49)	0.61
	Control	9.56 (2.59)	
Tissue type	Intervention	2.76 (0.72)	0.72
	Control	2.68 (0.50)	
Exudates amount	Intervention	2.45 (0.50)	0.57
	Control	2.35 (0.49)	
Total score	Intervention	14.84 (3.34)	0.53
	Control	14.60 (3.38)	

SD: Standard deviation

On using repeated measure ANOVA, it was found that changes in the mean of ulcer size scores in weeks zero and 1 were not significant in the treatment group, but during weeks 1 and 2 ( $P = 0.008$ ) and weeks 2 and 3 ( $P = 0.000$ ), they were significant. Also, changes in the mean of ulcer size scores in the control group during weeks zero and 1,

and 1 and 2 were not significant, but during weeks 2 and 3 ( $P = 0.01$ ), they were significant [Table 3]. The mean of ulcer size score in the treatment group before intervention was  $9.64 \pm 2.49$  and 3 weeks after using nitric oxide cream, the mean decreased to  $8.83 \pm 2.64$ . The mean of ulcer size score in the control group was  $9.56 \pm 2.59$  at baseline, and 3 weeks after using placebo cream, it reached  $9.20 \pm 2.62$ . Decrease in the mean of ulcer size score was higher in the treatment group compared to the control group.

Figure 1 shows that although the slope of PUSH score decrease related to the ulcer size is steeper in the nitric oxide cream treated group, no statistically significant difference was observed between the mean of ulcer size scores of the two groups.

Changes in the mean of score of ulcer exudates amount in the treatment group during weeks zero and 1 were not significant, but during weeks 1 and 2 ( $P = 0.01$ ) and weeks

2 and 3 ( $P = 0.005$ ), they were statistically significant. Changes in the mean of score of ulcer exudates amount in the control group were not significant during weeks zero and 1, and 1 and 2, but during weeks 2 and 3 ( $P = 0.02$ ), they were statistically significant [Table 4]. The mean of score of ulcer exudates amount in the treatment group before the intervention was  $2.44 \pm 0.5$  and 3 weeks after using nitric oxide cream, it decreased to  $1.84 \pm 0.62$ . The mean of score of ulcer exudates amount in the control group was  $2.36 \pm 0.49$  at baseline, and 3 weeks after using placebo cream, it reached  $1.92 \pm 0.70$ . The decrease in the mean of score of ulcer exudates amount was higher in the treatment group compared to the control group.

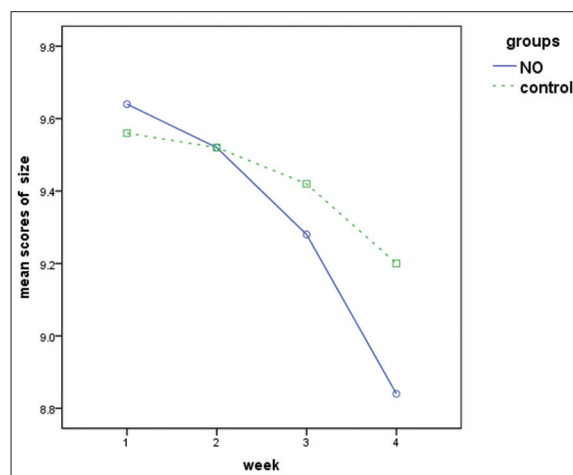
Figure 2 shows that although the slope of PUSH score decrease related to the ulcer exudates amount is steeper in the group using nitric oxide cream, no statistically significant difference was observed between the mean of scores of ulcer exudates amount in the two groups.

Changes in the mean of score of ulcer color (the tissue type) in the treatment group during weeks zero and 1, and weeks 1 and 2 were not significant, but during weeks 2 and 3 ( $P = 0.01$ ), they were statistically significant. Changes in the ulcer color mean score (the tissue type) in the control group were not significant during weeks zero and 1, and 1 and 2, but during weeks 2 and 3 ( $P = 0.04$ ), they were statistically significant [Table 5]. The mean of score of ulcer color (the tissue type) in the treatment group before the intervention was  $2.76 \pm 0.72$  and 3 weeks after using nitric oxide cream, it decreased to  $2.08 \pm 0.4$ . The mean of score of ulcer color (the tissue type) in the control group was  $2.68 \pm 0.5$  at baseline, and 3 weeks after using placebo cream, it reached  $2.40 \pm 0.62$ . Decrease in the mean of score of ulcer color (the tissue type) was higher in the treatment group compared to the control group.

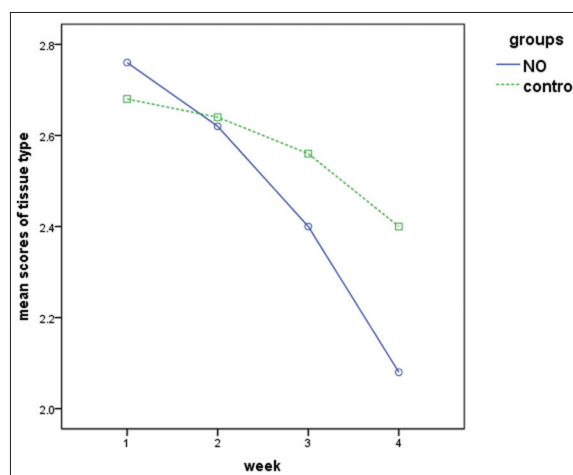
**Table 3: Results of post hoc test for ulcer size**

	<i>P</i>			
	Baseline	First week	Second week	Third week
Size (intervention group)				
Baseline	x	0.08	0.004	0.000
First week	0.08	x	0.008	0.000
Second week	0.004	0.008	x	0.000
Third week	0.000	0.000	0.000	x
Size (control group)				
Baseline	x	0.32	0.05	0.001
First week	0.32	x	0.09	0.002
Second week	0.05	0.09	x	0.01
Third week	0.001	0.002	0.01	x

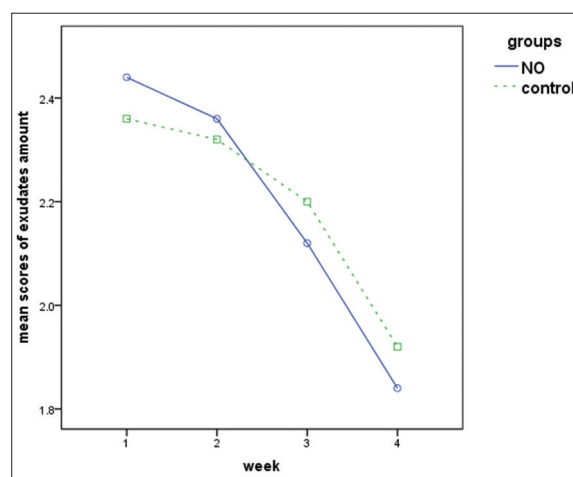
Figure 3 shows that although the slope of PUSH score decrease related to the ulcer color (the tissue type) is steeper



**Figure 1:** Comparison of mean scores of area (size) of the ulcer between the two groups



**Figure 2:** Comparison of mean scores of tissue type of ulcers between the two groups



**Figure 3:** Comparison of mean scores of exudates amount between the two groups

in nitric oxide cream group, no statistically significant difference was observed between the mean of score of ulcer color (the tissue type) in the two groups.

Changes in mean total scores of ulcer in the treatment group during weeks zero and 1 ( $P = 0.004$ ), weeks 1 and 2 ( $P = 0.00$ ), and weeks 2 and 3 ( $P = 0.000$ ) were statistically significant. Changes in mean total scores of ulcer in the control group were not significant during weeks zero and 1, but during weeks 1 and 2 ( $P = 0.009$ ) and weeks 2 and 3 ( $P = 0.001$ ), they were statistically significant [Table 6]. The mean total score of ulcer in the treatment group before the intervention was  $14.84 \pm 3.34$  and 3 weeks after using nitric oxide cream, it decreased to  $11.52 \pm 2.71$ . The mean total score of ulcer in the control group was  $14.60 \pm 3.38$  at baseline, and 3 weeks after using placebo cream, it reached  $12.91 \pm 2.90$ . Decrease in the mean total score of ulcer was significantly higher in the treatment group compared to the control group.

**Table 4: Results of *post hoc* test for ulcer exudates**

	<i>P</i>			
	Baseline	First week	Second week	Third week
Exudates (intervention group)				
Baseline	×	0.16	0.003	0.000
First week	0.16	×	0.01	0.000
Second week	0.003	0.01	×	0.005
Third week	0.000	0.000	0.005	×
Exudates (control group)				
Baseline	×	0.32	0.04	0.001
First week	0.32	×	0.08	0.001
Second week	0.04	0.08	×	0.01
Third week	0.001	0.001	0.01	×

**Table 5: Results of *post hoc* test for ulcer tissue**

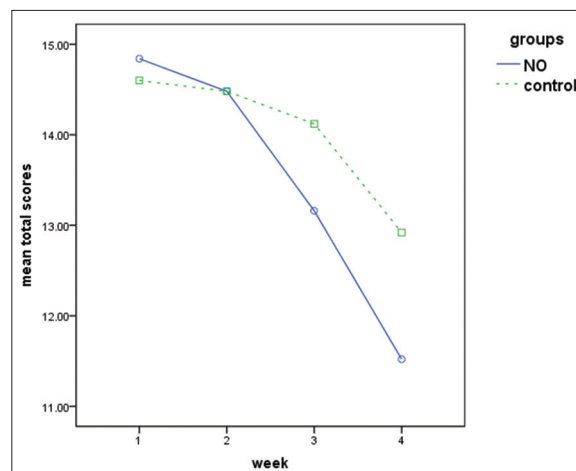
	<i>P</i>			
	Baseline	First week	Second week	Third week
Tissue (intervention group)				
Baseline	×	0.09	0.001	0.000
First week	0.09	×	0.06	0.001
Second week	0.001	0.06	×	0.01
Third week	0.000	0.001	0.01	×
Tissue (control group)				
Baseline	×	0.32	0.08	0.01
First week	0.32	×	0.16	0.03
Second week	0.08	0.16	×	0.04
Third week	0.01	0.03	0.04	×

Figure 4 shows that in nitric oxide cream group, the slope of PUSH score decrease related to total scores of ulcer is obviously steeper and healing status is better, and a statistically significant difference was observed between the mean total scores of ulcer in the two groups ( $P = 0.04$ ).

## DISCUSSION

This study was aimed to determine the effect of nitric oxide releasing cream on the size (size), the exudates amount, color (the tissue type), and finally the healing rate (combining all three criteria) of pressure ulcer. In the present study, it was found that decrease in ulcer size (size) during 3 weeks was higher in nitric oxide cream group compared to the control group. In Phillips *et al.*'s study, in the first 6 weeks, the ulcer size reduced quickly and significantly in the group receiving nitric oxide releasing cream. Of course, the greatest change in the ulcer size happened in the first 3 weeks.<sup>[40]</sup> Also, in Miller *et al.*'s case study, foot ulcer Miller *et al.*, in a case study, non-healing foot ulcers were exposed to nitric oxide; on day 14, its size was significantly decreased.<sup>[43]</sup> Farsaei *et al.* stated that sildenafil (intensifying NO activity) decreases the bed ulcer level significantly in patients hospitalized in ICU, 14 days after the intervention.<sup>[39]</sup> Animal studies have also confirmed this. In Jones *et al.*'s study, it was found that in the group receiving nitric oxide releasing patch, the rate of ulcer closure was more.<sup>[35]</sup> Weller and Finnen stated that there was a significant increase in diabetic ulcer closure percentage in the group of mice receiving nitric oxide cream, after 2 weeks.<sup>[32]</sup>

Also, decrease in the amount of ulcer exudates during 3 weeks was higher in the nitric oxide cream group compared to the control group. In other words, the amount of ulcer exudates from baseline to the end of the study showed a significant change in the nitric oxide cream



**Figure 4:** Comparison of mean total scores between the two groups

**Table 6: Results of *post hoc* test for ulcer healing**

	<i>P</i>			
	Baseline	First week	Second week	Third week
Healing (total score) (intervention group)				
Baseline	×	0.004	0.000	0.000
First week	0.004	×	0.000	0.000
Second week	0.000	0.000	×	0.000
Third week	0.000	0.000	0.000	×
Healing (total score) (control group)				
Baseline	×	0.18	0.005	0.000
First week	0.18	×	0.009	0.000
Second week	0.005	0.009	×	0.000
Third week	0.000	0.000	0.000	×

group. In Miller *et al.*'s case study, foot ulcer exposed to nitric oxide gas was not healed; after 3 days of treatment, its exudates amount decreased and the ulcer's bad smell also disappeared.<sup>[43]</sup> Also, in the studies conducted by Ghaffari *et al.*,<sup>[48]</sup> Englander and Friedman,<sup>[52]</sup> Hetrik,<sup>[49]</sup> kutner<sup>[50]</sup>, and Martinez *et al.*,<sup>[51]</sup> the ability of NO as an antimicrobial substance to treat infections in chronic ulcers and later in healing them has been approved.<sup>[46,47]</sup>

In the present study, it was found that the ulcer color (the tissue type) ulcer color mean is ulcer tissue type more during 3 weeks in the nitric oxide cream group compared to the control group. Zhu *et al.*'s study also found that nitric oxide, through processes such as angiogenesis, collagen synthesis, conducting the inflammatory mediators to the injury site, and regeneration of epithelium, heals burn ulcer in mice.<sup>[27]</sup> In Amadeu *et al.*'s study, it was found that the level of re-epithelialization and granulation tissue formation in the group receiving hydrogel containing S-nitrosoglutathione and glutathione (releasing NO) was much higher.<sup>[29]</sup> Also, Georgii *et al.* stated that S nitrous and glutathione (releasing NO) cause re-epithelialization, increasing the collagen fiber density and decreasing the level of inflammatory cells and angiogenesis in ischemic ulcers in mice.<sup>[28]</sup>

In this study, it was found that the ulcer healing process during 3 weeks in nitric oxide cream group was significantly higher than in the control group. Phillips *et al.* concluded that nitric oxide releasing cream accelerates the ulcer healing process.<sup>[40]</sup> Miller *et al.*, in a case study, stated that 90% of foot ulcer had not been healed; 6 weeks after treatment, it healed with nitric oxide gas.<sup>[43]</sup> Farsaei *et al.* stated that sildenafil (intensifying NO activity) causes healing of bed ulcer in ICU patients.<sup>[39]</sup> Studies conducted on animals confirm this. Weller stated that nitric oxide releasing cream accelerates diabetic ulcer healing process in mice.<sup>[33]</sup> In Han

study, it was found that nanoparticles releasing NO have the ability to set and accelerate the ulcer healing process.<sup>[34]</sup> Also, Jones *et al.*, in their study, stated that the patch releasing NO accelerates ulcer healing in rabbits.<sup>[35]</sup> Studies conducted by Zhu *et al.*<sup>[27]</sup> and Masters on burns, diabetic and ischemic ulcers in animals show similar results (ulcer healing).<sup>[29]</sup>

In Farsaei *et al.*'s study, the follow-up period was 2 years, but in the present study, treatment was continued for 3 weeks with nitric oxide cream. Perhaps, if a longer time had been spent for the therapeutic method, better results would have been obtained. The present study and Farsaei *et al.*'s study were double-blind clinical trials, while Phillips *et al.*'s study was not double blind. Miller *et al.*'s study was also a case report and was done only on an ulcer. In our study, three factors of ulcer size, exudates amount, and color (the tissue type) were examined, and by integrating these three factors, ulcer healing (the ulcer total score) was determined. While in Farsaei *et al.*'s study, the pressure ulcer's surface, grade, and healing were examined and in Phillips *et al.*'s study, only the ulcer size and the amount of its healing were examined. In Farsaei *et al.*'s study, sildenafil cream (intensifying NO activity) was compared with the ward routine method separately. While in the present study, due to respecting ethical issues and not depriving patients of the ward routine treatment (dressing), we had to use the dressing along with nitric oxide cream (the treatment group) and placebo cream (the control group). Perhaps, if nitric oxide cream and the ward routine method had been compared separately and independently, better results would have been obtained.

However, in the size, the ulcer exudates amount, and color (the tissue type), no significant difference was observed between the two groups. But in the group receiving nitric oxide cream, the slope of PUSH score decrease in relation to the three factors was steeper during the studied weeks. This indicates that nitric oxide cream (size) decreased the ulcer exudates amount more than the control group and the ulcer color (the tissue type) also further heals. The slope of PUSH score decrease related to the ulcer total score (healing) in nitric oxide cream group was clearly steeper and the healing status was better, and a significant difference was observed between the two groups in the mean of the total ulcer score (healing). This indicates that nitric oxide cream accelerates the pressure ulcer healing process. The researcher stated that possibly, the slope of PUSH score decrease is steeper in nitric oxide group, which indicates that further healing in the group may be due to the effect of NO on re-epithelialization, angiogenesis, synthesis of fibroblasts, inflammatory cells, and growth factors. Also, NO increases blood flow in the ulcer, which reinforces the healing process. The limitation of the present study was that the researcher had to use the dressing along with nitric oxide cream (treatment group) and placebo cream (control

group) in order to not deprive the patients from the ward routine treatment (Comfeel dressing).

## CONCLUSION

It can be concluded that nitric oxide cream can be used as a complementary method and facilitator of other therapeutic methods of pressure ulcer. It is recommended to compare nitric oxide cream and routine method in future studies separately and independently. May be by conducting further research in this field in the future, the therapeutic method may be considered as an independent and separate method. So, we can use this therapeutic method for better and faster healing of pressure ulcer in hospitals, nursing homes, and home. We can prevent the development of pressure ulcer and the complications and deaths caused by it, and also, the nurses' role as one of the most effective treatment team members in healing and caring pressure ulcer can be highlighted. Also, regarding the convenience of preparation and cost-effectiveness of nitric oxide releasing cream compared to current therapeutic methods, wastage of time, cost, and resources can be prevented and level of patients' health and finally community health can be further promoted.

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## Conflicts of interest

There are no conflicts of interest.

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