Caspian Journal of Dental Research
e-ISSN: 2322-2395 p-ISSN: 2251-9890
Babol University Of Medical Sciences

Investigating the effect of nifedipine mucosal adhesive on the wound healing process in the palate: A clinical trial study

Mohadeseh Emampanahi [1✉], **Mina Motallebnejad** [2*], **Niloofar Jenabian** [2✉], **Ali Akbar Moghadamnia** [3✉], **Sohrab Kazemi** [4✉]

1. Assistant Professor, Oral Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
2. Professor, Oral Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
3. Professor, Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
4. Associate Professor, Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

Article type
Research Paper

Received: 9 Oct 2022
Revised: 5 Dec 2022
Accepted: 14 Dec 2022
Pub. online: 14 Feb 2023

ABSTRACT

Introduction: Nifedipine (NF) is a calcium channel blocker that accelerates wound healing and subsequently relieves pain and discomfort. The aim of the present study was to investigate the local effect of this drug on the wound healing process of the palate.

Materials & Methods: In this triple-blind clinical trial study, 31 patients who were referred to the Periodontology Department of Babol Dental School (14 in the experimental group and 17 in the control group) were examined. They were candidates for gingival surgery and needed a palate transplant. Mucotom was used to create identical wounds in the palate (transplant donor). After a free gingival grafting, the active ingredient of 0.3% NF was applied as a mucosal adhesive (made of chitosan) in the area of the graft (palate). Patients were examined and recorded on days 2, 4, 7, 14, and 30 after surgery for wound closure and healing criteria (Landry & Manchester scar scale) and pain (VAS). Sutures were removed on day 7 of the study. Data were analyzed with SPSS 20 and chi-square, Kruskal-Wallis and Mann-Whitney tests. The significance level was set at 0.05.

Results: Based on Landry and Manchester criteria, wound healing process in the two groups was not significant (p=0.125). There was no significant difference between mean wound size reduction and VAS in both treatment and control groups (p=0.253).

Conclusion: Topical NF has no effect on the natural process of healing oral mucosal ulcers and reducing pain.

Keywords: Nifedipine, Oral Ulcers, Wound Healing

Cite this article: Emampanahi M, Motallebnejad M, Jenabian N, Moghadamnia AA, Kazemi S. Investigating the effect of nifedipine mucosal adhesive on the wound healing process in the palate: A clinical trial study. Caspian J Dent Res 2023; 12: 20-7.

* **Corresponding Author:** Mina Motallebnejad, Department of Oral Medicine, Faculty of Dentistry, Babol University of Medical Sciences, Babol, Iran.
Tel: +98 1132291408
E-mail: mmotallebnejad@yahoo.com

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]

Introduction

Dental treatments, surgeries and biopsies produce wounds in the environment (apart from infectious and malignant wounds), which must be taken care of in the best possible way. Therefore, it is useful that there are some substances that can facilitate the wound healing process. [1] Wound healing is a dynamic and biological process that occurs in three phases of inflammation, proliferation and maturation. [2] During repair, the primary collagen fibers cross-link together to form fibrillar bundles that increase the tensile strength and stiffness of the repaired tissue. [3, 4] Despite extensive advances in diagnosis and treatment, incomplete wound healing remains a serious clinical problem.

Calcium channel antagonists have gained widespread use since the 1980s because of their tolerable side effects. [5] Voltage-gated calcium channels play an important role in controlling cellular functions in various tissues such as the heart, arteries, and nerves. [6, 7] Although the importance of calcium channels in pain has not been clearly established, there is evidence that they are useful in the treatment of visceral and somatic pain. [8,9]

Nifedipine (NF) is a calcium channel blocker that blocks the membrane passage of calcium ions (ca) into muscle cells, resulting in dilation of blood vessels and reduced peripheral resistance, which reduces systemic hypertension.[10] A recent study [11] showed that NF enhances skin wound healing by increasing the tensile strength of 10-day granulation tissue in shearing wounds. Similarly, oral administration of NF increases the stability of the colony anastomosis during the first week after ingestion and deposition of collagen fibers in the wound area. Rashidi et al. (2016) showed that periodontal indices in patients with moderate to severe chronic periodontitis were significantly reduced by 1% after three weeks of use of phenytoin mucosal adhesive.[12]

In 2018, Mojiri investigated the mechanism of calcium channel blockers in wound healing. The potential of dihydropyridine and non-dihydropyridine calcium channel blockers in wound healing has been investigated in various animal models in previous experiments. Amlodipine, verapamil, diltiazem, NF, and azelnidipine are calcium channel blockers that promote wound healing. These drugs usually have relatively low side effects and provide good patient satisfaction in different clinical conditions. In addition, they may be introduced in the future as a promising new treatment for wound healing. [2]

In 2016, Rajesh et al. investigated the regenerative effect of NF on skin burns in white Wistar rats. They concluded that topical application of NF promoted wound healing, especially in cases where the healing process was suppressed by steroids. [13] Considering the effect of NF in promoting wound healing and the associated relief of patient pain and discomfort, and the lack of a similar study investigating the effect of topical NF in oral wound healing, this study investigated the topical effect of this drug on the healing process of wounds on the palate.

Materials & Methods

This triple-blinded (patient, investigator, and analyzer) clinical study with IRCT20190430043431N1 code and MUBABOL.HRI.REC.1396.209 code of ethics evaluated patients referred to the Department of Periodontology at Babol Dental School who were candidates for gingival surgery and needed to have a transplant from the palate. Given the preliminary nature of this study and the lack of previous studies on the efficacy of NF 0.3% in the oral mucosa, and taking into account ethical considerations, in the

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]

opinion of the statistical consultant of this research project, the minimum sample size was set at 31 patients, 14 and 17 of whom were assigned to the experimental and control groups, respectively.

The inclusion criteria were age 20-50 years, no systemic diseases affecting the wound healing process, such as diabetes or immunosuppressive diseases, no smoking, and no use of immunosuppressive drugs such as azathioprine or cyclosporine. If subjects developed the above diseases, started taking the above medications or smoked, they were excluded from the study. [12] Participants were initially selected using simple random sampling. For this purpose, any patient who met the inclusion criteria was included in the study. The participants were divided into the experimental and control groups. The pharmacologist, who was the only person who knew the contents of each mucosal adhesive, prepared 20 cards with the code for the NF gel and 20 cards with the code for the NF-free gel, and then the patients were randomly assigned to the experimental or control group by selecting a card.

Identical wounds were created in the palate (graft donor) with the mucotome (Medesy, Milano,Italy). All procedures were performed by a periodontist. After free gingival grafting, the active ingredient of NF 0.3%, manufactured by the (Kimidaro Company,Tehran,Iran), was applied to the area of the graft donor (palate) as a mucosal adhesive (made of chitosan). Patients were then instructed to smear the area with NF gel twice daily for 2 weeks [14] and then not to eat or drink for 30 minutes to allow the drug to work. All patients were prescribed amoxicillin, acetaminophen and chlorhexidine mouthwashes to reduce pain and infection.

Preparation of Nifedipine polymer film: 95 cc of distilled water was poured into a 500 cc beaker on a hot plate, the required amount of carbapol was added and heated, then, a certain amount of methylparaben (Nanosany,Tehran, Iran) and propylparaben was dissolved in 95% alcohol and added to the beaker sample. Finally, the required amount of glycerin was added to the sample. To add active ingredients to the gel (NF), 0.3 grams of NF was added per 100 g of dry film. To prepare the polymer film, the gel was placed in the oven to remove the solvent.

Criteria: The Turnbull and Howley index was used to evaluate the Landry repair criterion. [15] This criterion is evaluated and graded based on five criteria (tissue color, bleeding on contact, granular tissue, epithelialization of incision lines, presence of pus), which are classified into five groups: very bad, bad, good, very good, and excellent (Table. 1).

Manchester criteria are: Color compared to color of surrounding mucosa (zero: same color, one: minor difference, two: major differences). Contour (zero: similar to surrounding mucosa, one: slightly protruding or depressed to surrounding mucosa, two: hypertrophic). Distortion (zero: none, one: mild to moderate, two: severe). The numbers obtained are summarized in each section. The range of variation is from 0 to 6 with lower values indicating more severe repair. [15]

Follow-up: Patients were assessed for wound closure, Landry & Manchester scar scale, and pain (VAS) on days 2, 4, 7, 14, and 30 after surgery. Sutures were removed on the 7th day of referral. Data were analyzed using SPSS 20 and Chi-square, Kruskal-Wallis and Mann-Whitney tests. The significance level was set at 0.05.

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]

Table 1. Landry repair criterion

Repair 1 (very bad) If there were 2 or more of these features exist	**Repair 2(bad)** If there is only one of these features	**Repair 3(good)** If there is only one of these features	**Repair 4(very good)** If there is only one of these features	**Repair 5(excellent)** If there is only one of these features
Texture color: 50% or more redness of the surrounding tissue	Texture color: 50% or more redness of the surrounding tissue	Texture color: Between 25% and 50% redness of the surrounding tissue	Texture color: Less than 25% redness of the surrounding tissue	Texture color: uniform and pink
Bleeding on touch	Bleeding on touch	No bleeding on touch	No bleeding on touch	No bleeding on touch
Granular texture	Granular texture	Absence of granular tissue	Absence of granular tissue	Absence of granular tissue
Epithelialization of incision lines	Epithelialization of incision lines	Incision lines: Connective texture is not visible.	Incision lines: Connective texture is not visible.	Incision lines: Connective texture is not visible.
Existence of pus	Existence of pus			

Results

In the treatment group, 85.7% of patients and in the control group, 70.6% were women. There was no significant difference in the frequency of males and females in the two groups (p=0.316). The mean age of patients in the treatment group (38.28 ±11.57 years) and in the control group (32.17 ±6.84 years) was statistically similar (p=0.078). Tables 2 and 3 show a comparison of the wound healing processes according to Landry and Manchester criteria in the two treatment and control groups during the 30-day follow-up. As a result, the wound healing process in each study group was significant on different days of follow-up (p<0.05), but no significant difference in wound healing was observed between the two groups on any of the follow-up days. Tables 4 and 5 show a comparison of wound size reduction (mm2) and VAS levels in the two treatment and control groups during the 30-day follow-up. As a result, wound size and VAS level decreased significantly in each group during the 30-day follow-up (p<0.05), but there was no significant difference between the mean wound size reduction and the mean level of VAS in the two groups on any of the follow-up days.

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]

Table 2. Comparison of wound healing process according to Landry criteria in two treatment groups during the 30-day follow-up

Landry criteria	Treatment Group					Control Group				
	Follow-Up (Day)					Follow-Up (Day)				
	2	4	7	14	30	2	4	7	14	30
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Very Bad	3 (21.4 %)	2 (31.4 %)	1 (7.1 %)			5 (29.4%)	3 (17.6%)	1 (5.9%)		
Bad	11 (78.6%)	11 (78.6%)	8 (57.1%)	2 (14.3%)	1 (7.1%)	12 (70.6%)	12 (70.6%)	11 (64.7%)	3 (17.6%)	1 (5.9%)
Good		1 (7.1%)	4 (28.6%)	10 (71.4 %)	11 (78.6 %)	.	2 (11.8 %)	5 (29.4%)	14 (82.4%)	14 (82.4%)
Very Good			1 (7.1%)	2 (14.3%)	2 (14.3%)					2 (11.8%)
P value			0.06					0.101		

P-value: Chi-square test

Table 3. Comparison of the wound healing process according to Manchester criteria in the treatment and control groups during the 30-day follow-up

Manchester criteria	Follow-up (day)				
	2	4	7	14	30
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Treatment	3.5 (0.65)	3.14 (0.77)	2.85 (1.29)	1.71 (1.54)	1.14 (1.06)
Control	3.58 (0.79)	3.17(0.52)	2.64(0.99)	2.11 (1.31)	1(1.41)
P value	0.88	0.57	0.73	0.49	0.69

P-value: Mann-Whitney test

Table 4. Comparison of wound size reduction (mm2) in treatment and control groups during the 30-day follow-up

wound size reduction	Follow-up (day)			
	2_4	4_7	7_14	14_30
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Treatment	5.36(12.49)	23(31.43)	25.71(42.20)	13.79(29.73)
Control	3.82(11.02)	26.82 (43.28)	15.35(24.78)	12.24 (25.97)
P value	0.719	0.790	0.402	0.878

P-value: Mann-Whitney test

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]

Table 5. Comparison of VAS between treatment and control groups during the 30-day follow-up

VAS	Follow-up (day)				
	2	4	7	14	30
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Treatment	1.78(1.92)	1.00 (1.70)	0.50 (1.28)	0.07 (0.26)	0.00
Control	3.35 (3.01)	1.94 (3.11)	0.70 (1.44)	0.00	0.00
P value	0.411	0.534	0.710	0.739	

P-value: Mann-Whitney test

Discussion

The results of this study showed that topical NF had no effect on the natural healing process of oral mucosal ulcers, for which two separate Landry and Manchester repair criteria were used for closer examination.Literature review of several study results shows that NF has a positive effect on the wound healing process in skin wounds in animal models. Bhaskar et al. (2005) concluded that NF promoted the natural healing process of skin wounds in animal specimens by increasing the tensile strength of 10-day-old granulation tissue. [16] Rajesh et al. (2016) concluded that topical application of NF improves the healing of skin burns in mice, especially when the healing process is suppressed by steroids. [13] As can be seen, the results of this study do not indicate the effect of NF on the healing of oral ulcers. The reason for this difference may be the difficulty of using the adhesive containing the drug in the mouth and the short shelf life of the drug in place. In animal studies, the placement of the drug on the animal's skin is more controllable and easier.

A wound is a ruptured tissue that has lost its natural cohesion due to various factors. [3] The restoration of health and consistency to the damaged tissue during the healing process depends on factors such as the production, storage and binding of collagen, the function of various cells of the epithelial tissue and connective tissue, and the amount of collagenase secretion.[15] NF increases blood flow, which provides blood to the ischemic cells and heals the wound.[7] Research has also shown that NF has the property of dilating blood vessels and selectively acting on the vascular bed of the area, which promotes blood flow and the wound healing process.[6,7]

In the present study, there was no significant difference between the two treatment and control groups in terms of VAS values in the follow-up days. One of the reasons that NF may not provide effective pain relief despite its expected pharmacologic effect is the masking effect of mucosal adhesives used. As the pain caused by wounds in the mouth is triggered by secondary infections or mechanical and chemical stimuli, NF mucilage glue can provide analgesia in addition to its medicinal properties as a covering and protective substance. [17] This subject also leads to pain reduction in the control group; consequently, there is no significant difference in pain reduction between the two groups. The analgesic effect of mucosal adhesive was also confirmed in the study of Motallebnejad et al. (2003).[18] In general, calcium inhibitors have analgesic properties, so some studies came to contradictory results.[19]

Martín et al. (1996) showed in their study that calcium channel antagonists inhibit pain in mice. [6] Khayatnouri et al. (2009) showed that NF had a reducing effect on inflammatory pain (stage II) in formalin pain in mice but no significant effect on neurogenic pain (stage I). These effects are likely due to blockade of calcium channels and decreased calcium flow, resulting in decreased release of

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]

neurotransmitters and other mediators of pain and inflammation. [20] because it is not possible to create the same experimental wounds in human models for ethical reasons, in this study, the size of the wounds in the two groups was not the same on the first day, so the reduction in wound size compared with the first day was examined, and this limitation may be one of the reasons why the potential effects of NF were not observed in human studies. Other limitations of this study include the different age and sex of the two groups and the small sample size.

Conclusion

Topical NF has no effect on the natural process of healing oral mucosal ulcers and reducing pain.

Acknowledgments

The authors would like to thank Babol University of Medical Sciences for financial support.

Funding

This study was a research project (Grant No: 9645210), supported and funded by Babol University of Medical Sciences.

Conflicts of Interest

The authors certify that they have no conflict of interest.

Author's Contribution

M.Emampanahi assisted with data collection. M.Motallebnejad assisted in drafting and editing the manuscript. N.Jenabian , A.Moghadamnia and S.Kazemi helped with study design and data analysis. All authors read and approved the final manuscript.

References

1. Brasileiro ACM, de Oliveira DC, da Silva PB, Rocha JKSL. Impact of topical nifedipine on wound healing in animal model (pig). J Vasc Bras 2020; 19:e20190092.
2. Mojiri-Forushani H. The role of calcium channel blockers in wound healing. Iran J Basic Med Sci 2018;21:1198-9.
3. Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res 2010; 89: 219–29.
4. Prajapati V, Bansal M, Sharma PK. Mucoadhesive buccal patches and use of natural polymer in its preparation-Areview. Inter J Pharm Tech Res 2012; 4: 582-9.
5. Kułak W, Sobaniec W, Wojtal K, Czuczwar SJ. Calcium modulation in epilepsy. Pol J Pharmacol 2004; 56: 29-41.
6. Martín MI, del Val VL, Colado MI, Goicoechea C, Alfaro MJ. Behavioral and analgesic effects induced by administration of nifedipine and nimodipine. Pharmacol Biochem Behav 1996; 55: 93-8.
7. Pathirathna S, Brimelow BC, Jagodic MM, Krishnan K, Jiang X, Zorumski CF, et al . New evidence that both T-type calcium channels and $GABA_A$ channels are responsible for the potent peripheral analgesic effects of 5-reduced neuro active steroids. Pain 2005; 114: 429-43.
8. Ryan SG. Ion channels and the genetic contribution to epilepsy. J Child Neurol 1999; 14: 58-66.

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]

9. Shutov L, Kruglikov I, Gryshchenko O, Khomula E, Viatchenko-Karpinski V, Belan P, et al. The effect of nimodipine on calcium homeostasis and pain sensitivity in diabetic rats. Cell Mol. Neurobiol 2006; 26: 1541-57.
10. Zbuzek VK, Cohen B, Wu W. Anti-nociceptive effect of nifedipine and verapamil tested on rats chronically exposed to nicotine and after its withdrawal. Life Sci 1997; 60: 1651-8.
11. Grossman E, Messerli FH. Calcium antagonists. Prog Cardiovasc Dis 2004; 47: 34-57.
12. Rashidi Maybodi F, Haerian-Ardakani A, Nabi-Maybodi M, Nasrabadi N. Effect of 1% Phenytoin Muco Adhesive Paste on Improvement of Periodontal Status in Patients with Chronic Preiodontitis: A Randomized Blinded Controlled Clinical Study. J Dent (Shiraz) 2016; 17: 256-61.
13. Rajesh B, Ameena Khatoon Koralli, Rajasekhar CH, Manohar Herle PN, Savin CG. Evaluation of dermal burn healing activity of nifedipine in wistar albino rats. Int J Exp Pharmacol 2016; 6: 65-71.
14. de Rosa M, Cestaro G, Vitiello C, Massa S, Gentile M. Conservative versus surgical treatment for chronic anal idiopathicfissure: a prospective randomized trial. Updates Surg 2013; 65:197–200.
15. Kleinman DV, Swango PA, Niessen LC. Epidemiologic studies of oral mucosal conditions methodologic issues. Community Dent Oral Epidemiol 1991; 19: 129-40.
16. Bhaskar HN, Udupa SL, Udupa AL. Effect of nifedipine and amlodipine on dead space wound healing in rats. Indian J Exp Biol 2005; 43: 294-6.
17. Carr MP, Horton JE. Evaluation of a transoral delivery system for topical anesthesia. J Am Dent Assoc 2001;132:1714-9.
18. Motallebnejad M, Moghadamnia A, Mohammadi E. The effect of bioadhesive in reduction of pain and healing time of Aphtha. J Babol Univ Med Sci 2003; 5: 12-6. [In Persian]
19. Farid RM, Wen MM. Promote Recurrent Aphthous Ulcer Healing with Low Dose Prednisolone Bilayer Mucoadhesive Buccal Film. Curr Drug Deliv 2017;14:123-35.
20. Khayatnori M, Nasirzadeh M R, Norazar A R. Effect of dihydropyridine calcium channel blockers on formalin-induced pain response in mice. Feyz 2009; 13: 1-7.[In Persian]

[DOR: 20.1001.1.22519890.2023.12.1.3.6]
[DOI: 10.22088/cjdr.12.1.20]