Agri 2018;30(3):116-122
doi: 10.5505/agri.2018.43815

ORIGINAL ARTICLE

Effect of applying reflexology massage on nitroglycerin-induced migraine-type headache: A placebo-controlled clinical trial

Nitrogliserine bağlı migren tipi baş ağrısı üzerine refleksoloji masajının etkisi: Plasebo kontrollü bir klinik çalışma

Nima IMANİ, Shams Aldin SHAMS, Moloud RADFAR, Haleh GHAVAMİ, Hamid Reza KHALKHALİ

Summary

Objectives: Nitroglycerin (NTG)-induced migraine-type headache is the most prominent side effect of nitrate therapy. Therefore, the aim of this study was to clarify the effectiveness of reflexology massage on intravenous NTG-induced headache in coronary care unit (CCU) inpatients.

Methods: This was a randomized clinical trial. The study sample included 75 patients that were randomly divided into three groups: control, intervention, and placebo groups. The intensity of baseline headache in patients who received NTG was measured by the numeric rating scale for pain (NRS Pain). Patients in the intervention group received reflexology massage two times for 20 min (at 3-h interval), wherein the upper part of patient's both foot thumbs, which is the reflection point of the head, was massaged. In the placebo group, an unspecified point on the foot (heel), which was not related to the head, was massaged. Patients in the control group did not receive any massage.

Results: No baseline differences existed among the three groups for the mean pain scale score (p=0.66) before the study; but the difference between the groups after the application was statistically significant (p=0.000).

Conclusion: Reflexology massage can reduce the intensity of NTG-induced headache.

Keywords: Migraine; nitroglycerin-induced headache; reflexology massage.

Özet

Amaç: Nitrogliserin (NTG) ile oluşan migren tipi baş ağrısı, nitrat tedavisinin en belirgin yan etkisidir. Bu nedenle, bu çalışmanın amacı, koroner yoğun bakım ünitesinde tedavi gören hastalarda refleksoloji masajının, intravenöz nitrogliserine bağlı baş ağrısı üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Bu çalışma randomize bir klinik araştırmadır. Çalışma örnekleri rastgele yöntemi ile üç gruba ayrıldı ve 75 hasta; kontrol grubunu, plasebo grubunu ve müdahale grubunu oluşturdu.Nitrogliserin alan hastalarda baş ağrısı yoğunluğu Ağrı için Sayısal Değerlendirme Ölçeği (NRS) ile ölçüldü. Müdahale grubundaki hastalara 20 dakika boyunca iki kez refleksoloji masajı yapıldı. (İkinci masaj, birinciden 3 saat sonra yapıldı.), ayak başparmağının üst kısmı başın refleksoloji noktası olarak belirlenmiş bunun için refleksoloji masaji grubunda hastaların her iki ayak baş parmaklarının ust kısmına masaj uygulandı. Plasebo grubunda baş ağrısı ile ilişkili olmayan bir noktaya (ayak topuğuna) masaj yapıldı. Kontrol grubundaki hastalara herhangi bir masaj yapılmadı.

Bulgular: Çalışma öncesi ağrı skalası ortalamaları açısından üç grup arasında başlangıç farkı yoktu (p=0.66); ancak uygulama sonrası gruplar arasındaki fark istatistiksel olarak yüksekti (p=0.000).

Sonuç: Refleksoloji masajı, nitrogliserine bağlı baş ağrısının yoğunluğunu azaltabilir.

Anahtar sözcükler: Migren; nitrogliserine bağlı baş ağrısı; refleksoloji masajı.

Introduction

Organic nitrates, such as nitroglycerin (NTG), are still widely used for the treatment of acute and chronic angina and congestive heart failure.[1] NTG-induced headache is the most prominent side effect of nitrate therapy in patients with chest pain and has a detrimental effect on the quality of life.[2, 3] NTG-induced headache may be associated with vasodilation of the cerebral arteries due to direct activation of the nitric oxide-cyclic guanosine monophosphate pathway.[4] Nitrate-induced severe headache occurs in over 80% of patients. Indeed, approximately 10% of patients

Department of Nursing and Midwifery, Urmia University of Medical Sciences, Urmıa, Iran

Submitted *(Başvuru tarihi)* **02.10.2017 Accepted after revision** *(Düzeltme sonrası kabul tarihi)* **13.04.2018 Available online date** *(Online yayımlanma tarihi)* **26.06.2018**

Correspondence: Dr. Haleh Ghavami. Urmia University of Medical Sciences, Urmıa, Iran.
Phone: +98 - 914 - 341 6092 **e-mail:** haleh_ghavami@yahoo.co.uk

cannot tolerate nitrate therapies due to unbearable headache.[5]

Reflexology is considered to be a type of complementary and alternative medicine (CAM). CAM refers to treatments used either as an adjunct to or instead of conventional medical care. The House of Lords Select Committee for Science and Technology has placed reflexology in group two, categorized as therapies used mostly to complement conventional medicine. Its popularity has increased in recent years because people are seeking more holistic ways to maintain good health and improve their well-being.[6, 7] Reflexology is categorized as a system based on the massage of the feet which purports to have invisible lines connected vertically throughout the body to all organs, and that each organ has a corresponding place on the foot. Reflexology incorporates the use of specific pressure techniques to the feet, hands, or ears. It is one of the complementary therapies, which has been more commonly used in healthcare.[8]

Accordingly, this study evaluated the effectiveness of reflexology massage on intravenous NTG-induced headache in coronary care unit (CCU) inpatients. We hypothesized that reflexology massage reduces NTG-induced headache intensity.

Material and Methods

Research setting and sample

This was a randomized clinical trial study, and its Iranian Registry of Clinical Trials (IRCT) code is IRCT2015042922010N1. The study subjects included 75 males who were admitted in CCU of Urmia University of Medical Sciences, Urmia, Iran. The subjects were randomly divided into three groups: control, intervention, and placebo groups. We used a random numbers table to assign the participants who met all the criteria into the intervention, control, or placebo group in equal numbers.

Details of power calculations and sample size

As there is no study on the effects of reflexology massage on migraine-type headache in CCU inpatients, the appropriate information was not available to calculate it. However, in the study on the effect of foot reflexology on sternotomy pain after coronary artery bypass graft surgery,[9] the mean intensity of pain after reflexology massage was 3.34±1.5 in the intervention group and 5±1.9 in the control group. Our sample size was calculated using the following formula:

$$n = \frac{(s_1^2 + s_2^2)^2 (z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2}{(\bar{x}_1 - \bar{x}_2)^2}$$

$$n = \frac{(1/96+0/84)^2 (1/5^2+1/9^2)}{(5-3/34)^2}$$

Finally, we recruited 25 patients in each group for achieving 90% power to detect a difference in the intensity of headache at α level of 0.05. Thus, we registered a total of 75 patients (25 for each group).

Patient inclusion criteria

CCU male inpatients on intravenous NTG, having full consciousness, not having any problems in their feet (especially in the fingers), not having any movement disorders, not received any reflexology massage to date, not using any neuromuscular blocking drug, and not consuming alcohol, opioids, or analgesics were included. Patients willing to and able to participate in reflexology massage were included. Furthermore, they were adult (age, 19–49 years) and were able to express their headache intensity based on the numeric rating scale for pain (NRS Pain).

Patient exclusion criteria

Patients with diabetes (as diabetic neuropathy can led to bias in this study), those with physical/psychiatric impairment that would seriously impair their physical mobility, those who were suffering from severe diseases affecting their health (e.g., arthritis and multiple sclerosis), those who were unable to continue to participate in this study due to other reasons, and those with head trauma, migraine, or allergy to NTG were excluded.

Data collection and measures

The data were obtained from the patient information form (a researcher-made form) and NRS Pain. The NRS is a measure of pain intensity in adults. Although various iterations exist, the most commonly used is the 11-item NRS. It is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10)

that best reflects the intensity of his/her pain. It is anchored by terms describing pain severity. NRS Pain is a single 11-point numeric scale, with 0 representing no pain and 10 representing severe pain ("as bad as you can imagine" and "worst pain imaginable").[10]

All the patients were asked to complete the patient information questionnaire before the intervention. NRS was administered three times: just before the intervention and two times after the reflexology massage in the intervention group.

Ethical considerations and procedures

The study was approved by the Urmia University of Medical Sciences Ethics Committee (Ethical code of this study is IR.UMSU.REC 1394028). Participants were informed of the study, and consents were obtained. Also, the researcher had received a reflexology certification from an international reflexology academy before this study.

Initially, a total of 75males (according to the inclusion and exclusion criteria of the study) were randomized into three groups: the reflexology massage, placebo, and control groups. For randomization in this study, an independent researcher prepared random allocation cards using computer-generated random numbers. The allocator kept the original random allocation sequences at an inaccessible place and worked with a copy. Instead of the letters A, B, and C, he used the codes I, P, and C (I for intervention, P for placebo, and C for control) to avoid further confusion. He then continued randomization until 25 samples were allocated to each group of the study.

The patients in the placebo group received an ineffective massage (not reflexology massage) by the researcher to avoid any bias in the research related to researcher attendance at the study environment. Patients in the control group did not receive any massage. Patients in the reflexology massage group received the following manipulations: first, their feet were cleaned with a wet towel. Then, foot reflexology massage based on the Ingham method of reflexology was applied by the researcher. The patients' heel was held with the left hand by the researcher, and reflexology massage was given on points known as brain points (upper part of the thumb) for 10 min on each foot. The researcher applied continuous and uniform pressure in the upper part of the thumb of the patients' foot using his right hand thumb.

In the placebo group, all the above procedures were performed, but instead of patients' thumb of the foot, an unspecified point on the foot (heel), which is not related to the head, was pressured by the researcher.

As reflexology massage is a process for achieving better outcomes, it has to be repeated. Therefore, for better results in headache management, the second intervention was performed 3 h after the first intervention, and the massage was repeated again in the same way mentioned above for both the reflexology and placebo groups.

The data were obtained from the patient information form and NRS Pain which was completed three times, just before the intervention and two times after the intervention in all the groups. The data were calculated and analyzed.

Statistical procedures

The Statistical Package for Social Sciences (SPSS) software, version 21, was used for statistical analysis. The numbers are shown as percentage and average for identifying characteristics of patients. The chi-square, one-way ANOVA, and repeated measurement tests were used for evaluating the statistical significance in the sociodemographic data, medical characteristics, and headache intensity in the three groups before the study and two times after the intervention. Results were accepted at the confidence interval of 95% and statistical significance level of $p<0.05$.

Results

Demographic or medical characteristics

Patients included in the study were compared for variables, such as age, marital status, education level, employment status, smoking, and chronic headache that might affect the results of the research. No baseline differences existed between the three groups for either demographic or medical characteristics ($p>0.05$, Table1).

Headache intensity

Headache intensity was statistically similar ($p=0.66$) between the three groups just before the inter-

Table 1. Sociodemographic and medical characteristics of the groups (n=75)

Characteristics	Reflexology massage (n=25)		Placebo (n=25)		Control (n=25)		
	n	%	n	%	n	%	
							F=0.01 df1=2 df2=72 p=0.98
Age (Mean ±SD)	62±1.2		62.6±1.2		62.1±1.2		
Marital status							
Single	3	12	5	20	3	12	X^2=0.85 df=2 p=0.68
Married	22	88	20	80	22	88	
Level of education							
Illiterate	6	24	5	20	6	24	X^2=0.66
High school	16	64	15	60	15	60	df=4
University	3	12	5	20	4	16	p=0.95
Working Status							
Goverment	11	44	10	40	10	40	
employee							X^2=1.16
Retired	4	16	3	12	5	20	df=6
Workless	4	16	5	20	3	12	p=0.97
Private sector employee	6	24	7	28	7	28	
Smoking history							
Yes	11	44	8	32	10	40	X^2=0.78
No	14	56	17	68	15	60	df=2
							p=0.67
History of chronic headache							
Yes	1	4	2	8	1	4	X^2=0.52
No	24	96	23	92	24	96	df=2
							p=0.76

F=F test in the analysis of variance (ANOVA); d.f=degree of freedom; X^2=Chi-square test.

vention (after receiving intravenous NTG; Table 2), but the differences were statistically significant after the intervention (p=0.000; Table 4). The results showed reduced intensity of headache in the reflexology massage group comparted with the two other groups after the intervention (Tables 3 and 4).

In Table 4 (on the intensity of headache), three effects have been tested:

A. Interaction between time and intervention: The statistical test indicated that the interaction between time and intervention from the first to second intervention was significant on the mean of headache intensity (p=0.000), and pain intensity decreased with time.

B. Main effect of time: There was a statistically significant difference in the mean of headache intensity at different times (p=0.000).

C. Main effect of intervention: The main purpose of this research was to investigate this effect. ANOVA results showed that the mean headache intensity in the first to second intervention significantly differed between the reflexology massage, placebo, and con-

Table 2. Comparison of mean and standard deviation of headache intensity in each of the studied groups just before the intervention (after intravenous NTG injection)

Headache intensity	Reflexology Massage Group (Mean±SD)	Placebo Group (Mean ±SD)	Control Group (Mean±SD)	One-way ANOVA Results
Just before the intervention	7.2±1.7	7±1.4	6.8±1.5	F=0.41 df1=2 df2=72 p=0.66

F= F test in the analysis of variance (ANOVA); d.f = degree of freedom.

Table 3. Comparison of mean and standard deviation of headache intensity in each of the studied groups in the first, second, and third measurements

Group	Mean and standard deviation of headache intensity		
	First measurement (before the intervention)	Second measurement (first time after intervention)	Third measurement (second time after intervention)
Reflexology	7.2±1.7	5±1.4	3±1.2
Placebo	7±1.4	6.6±1.3	6.4±1.2
Control	6.8±1.5	7.4±1.1	7.2±1.5

Table 4. Analysis of measured headache intensity

Headache intensity	Total squared error	Degree of freedom	Average squared error	F	p	Partial Eta Squared
Main effect of time	80.88	2	40.44	28.92	0.001	0.287
Interaction of time with reflexology intervention	149.11	4	37.27	26.66	0.000	0.425
Component of time effect error	201.33	144	1.39			
Main effect of intervention	58.74	2	29.37	27.5	0.001	0.423
Component of intervention effect error	76.88	72	1.068		-	

F= F test in the analysis of variance (ANOVA).

trol groups (p=0.000), indicating that reflexology massage was effective in reducing headache intensity.

Discussion

This randomized controlled trial study was planned to clarify the effectiveness of reflexology massage on intravenous NTG-induced headache in CCU male inpatients. Our study findings supported our priori hypothesis that reflexology massage reduces NTG-induced headache intensity.

Numerous studies have indicated that reflexology massage can improve physical functioning, quality of life, and disease-related symptoms, such as back pain, seizure frequency, fatigue, anxiety, nausea, vomiting, and retching.[9, 11-19]

In our study, headache intensity after receiving intravenous NTG was statistically similar between the three groups before the reflexology intervention, but the differences were statistically significant after

the intervention. The results showed reduced intensity of headache in the reflexology massage group compared with the other two groups after the reflexology intervention. Headache intensity in the reflexology group was decreased to 5±1.4 at the first measurement and to 3±1.2 at the second measurement from the baseline score of 7.2±1.7. The headache intensity in the control group was 6.8±1.5 at baseline and increased to 7.4±1.1 at the first measurement and 7.2±1.5 at the second measurement. On the other hand, headache intensity in the placebo group was 7±1.4 at baseline, 6.6±1.3 at the first measurement, and 6.4±1.2 at the second measurement.

Similar to our study, as a nonpharmacological treatment for headache, NICE has published guidelines regarding the use of vagus nerve stimulation for the management of cluster headache and migraine in March 2016. The aim was to stimulate the cervical branch of the vagus nerve to relieve pain and reduce the frequency of attacks of migraine and cluster headache. A handheld device is used, and two stimulators are placed in front of the sternocleidomastoid muscle over the carotid artery. The patient is able to control the stimulation strength and should increase it slowly until he feels muscle contractions under the skin and continue stimulation for approximately 90s. It has been found to be effective in treating acute attacks and as prophylaxis between attacks.[20]

Furthermore, our study was consistent with the research carried out by Launsø et al.[21] on the application of reflexology massage for headache in 220 patients with migraine and/or tension headache from 1993 to 1994 to evaluate which patients with headache underwent a course of reflexology massage, why patients sought reflexology massage, what were the previous experiences of patients on medications for headache, and whether patients achieved favorable outcomes from reflexology massage. Their results showed that at 3-month follow-up, 81% of patients reported that they benefited from reflexology massage or that their headache problems were cured. Also, 19% of those who had formerly taken drugs to manage their headaches were able to discontinue the drugs following reflexology massage. The study concluded that reflexology massage results in the improvement of the general well-being, energy level, ability to interpret their own body signals, and ability to understand the reasons for headache.

Limitations

It is important to note the limitations of this study, such as relatively small sample size.

Conclusion

This study showed that CCU male inpatients with intravenous NTG-induced migraine-type headache may show reduction in their headache intensity by participating in reflexology massage programs. Furthermore, this simple, effective, comfortable, and low-cost program may be used for other types of migraine. Additional research in reflexology massage along with natural aromatherapy may be beneficial. The results of this study may contribute to the growing knowledge which will support the feasibility and effectiveness of reflexology massage as a nonpharmacological option for enhancing headache management in patients.

Conflict-of-interest issues regarding the authorship or article: None declared.

Peer-rewiew: Externally peer-reviewed.

References

1. Hink U, Alhamdani MS, Münzel T. Nitroglycerin hits the nerve: role for mitochondrial aldehyde dehydrogenase? J Am Coll Cardiol. 2008;52(11):961–3. [CrossRef]
2. Juhász G, Zsombók T, Gonda X, Bagdy G. Nitroglycerin-induced headaches. [Article in Hungarian]. Orv Hetil 2004;145(46):2323–8.
3. Cho SH, Jeong MH, Sim DS, Hong YJ, Park HW, Kim JH, et al. Diagnostic value of nitroglycerin-induced headache as a negative predictor of coronary atherosclerosis. Chonnam Med J 2011;47(1):14–9. [CrossRef]
4. Erkan H, Kırış G, Korkmaz L, Ağaç MT, Çavuşoğlu IG, Dursun I, et al. Relationship between Nitrate-Induced Headache and Coronary Artery Lesion Complexity. Med Princ Pract 2015;24:560–4. [CrossRef]
5. Gonzalez A, Hyde E, Sangwan N, Gilbert JA, Viirre E, Knight R. Migraines Are Correlated with Higher Levels of Nitrate-, Nitrite-, and Nitric Oxide-Reducing Oral Microbes in the American Gut Project Cohort. mSystems 2016;1(5). pii: e00105–16.
6. McCullough JEM, Liddle SD, Sinclair M, Close C, Hughes CM. The Physiological and Biochemical Outcomes Associated with a Reflexology Treatment: A Systematic Review. Evidence-Based Complementary and Alternative Medicine 2014;502123:16. [CrossRef]
7. Karakurum Göksel B, Coşkun Ö, Ucler S, Karatas M, Ozge A,

Ozkan S. Use of complementary and alternative medicine by a sample of Turkish primary headache patients. Agri 2014;26(1):1–7. [CrossRef]

8. Samuel C. An investigation into the efficacy of reflexology on acute pain in healthy human subjects. [PhD Thesis]. University of Portsmouth; 2011. p. 5, 36. Available at: https://researchportal.port.ac.uk/portal/files/6060909/Carol_Samuel_Thesis_2011.pdf. Accessed Jun 21, 2018.
9. Sadeghi Shermeh M, Bozorgzad P, Ghafourian AR, Ebadi A, Razmjoei N, Afzali M, et al. Effect of foot reflex massage on sternotomy pain after coronary artery bypass graft surgery. Iranian Journal of Critical Care Nursing 2009;2(2):51–4.
10. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S240–52. [CrossRef]
11. Dalal K, Devarajan E, Pandey RM, Subbiah V, Tripathi M. Role of reflexology and antiepileptic drugs in managing intractable epilepsy--a randomized controlled trial. Forsch Komplementmed 2013;20(2):104–11. [CrossRef]
12. Wyatt G, Sikorskii A, Rahbar MH, Victorson D, You M. Health-related quality-of-life outcomes: a reflexology trial with patients with advanced-stage breast cancer. Oncol Nurs Forum 2012;39(6):568–77. [CrossRef]
13. Quattrin R, Zanini A, Buchini S, Turello D, Annunziata MA, Vidotti C, et al. Use of reflexology foot massage to reduce anxiety in hospitalized cancer patients in chemotherapy treatment: methodology and outcomes. J Nurs Manag 2006;14(2):96–105. [CrossRef]
14. Wilkinson S, Lockhart K, Gambles M, Storey L. Reflexology for symptom relief in patients with cancer. Cancer Nurs 2008;31(5):354–60. [CrossRef]
15. Stephenson NL, Weinrich SP, Tavakoli AS. The effects of foot reflexology on anxiety and pain in patients with breast and lung cancer. Oncol Nurs Forum 2000;27(1):67–72.
16. Stephenson N, Dalton JA, Carlson J. The effect of foot reflexology on pain in patients with metastatic cancer. Appl Nurs Res 2003;16(4):284–6. [CrossRef]
17. Ketut N. Effect of foot massage on nausea, vomiting and retching in women with cervical cancer undergoing chemothrapy, in Bali, Indonesia. Nurse Media Journal of Nursing 2012;2(2)467–81.
18. Hughes CM, Smyth S, Lowe-Strong AS. Reflexology for the treatment of pain in people with multiple sclerosis: a double-blind randomised sham-controlled clinical trial. Mult Scler 2009;15(11):1329–38. [CrossRef]
19. Bagheri-Nesami M, Zargar N, Gholipour-Baradari A, Khalilian A. The effect of foot reflexology massage on pain and Fatigue in patients undergoing coronary artery bypass surgery. Mazandaran Univ Med Sci 2012;22(92):52–62.
20. NICE. Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine. IPG552. March 2016. Available at: https://www.nice.org.uk/guidance/ipg552. Accessed Jun 21, 2018.
21. Launsø L, Brendstrup E, Arnberg S. An exploratory study of reflexological treatment for headache. Altern Ther Health Med 1999;5(3):57–65.