



The Effect of Hand and Foot Surface Stroke Massage on Pain Intensity and Anxiety Level in Hospitalized Patients with Acute Coronary Syndrome: A Randomized Clinical Trial

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ABSTRACT

Background: Considering the high prevalence of cardiovascular diseases, angiography is important for diagnosis of diseases, pain, and fatigue following complete bed rest after percutaneous coronary intervention.

Objectives: This study aimed to evaluate the effects of hand and foot surface stroke massage on pain intensity and anxiety level in hospitalized patients with acute coronary syndrome.

Methods: This clinical trial was conducted on 70 patients with acute coronary syndrome referred to Hajar Hospital, Shahrekord, Iran. The patients were randomly divided into an intervention and a control group (n = 35 for each). Anxiety level was measured using Spielberger's Anxiety Inventory. Additionally, pain intensity was assessed by a visual analog scale 30 min before and 15 min after the intervention. The data were entered into the SPSS software and were analyzed using descriptive and inferential statistics (t-test, paired t-test, and chi-square test).

Results: Descriptive statistics included frequency and percentage for qualitative variables and mean ± Standard Deviation (SD) for normally distributed quantitative variables. The results revealed a significant decrease in the mean intensity of pain and the mean level of anxiety in the intervention group five minutes after massage. However, no significant difference was observed in this regard in the control group after the intervention. Additionally, no significant difference was observed between the two groups in terms of pain intensity and anxiety level before the intervention ($P \leq 0.05$).

Conclusions: Hand and foot massage was useful as a part of a nursing intervention in attenuating the pain intensity and decreasing the anxiety level in the patients with acute coronary syndrome.

1. Introduction

Cardiovascular disease remains a common chronic disease and a leading cause of mortality in developed countries, which accounts for more than 33% of deaths in people over 35 years of age (1-3). Due to the increasing prevalence of cardiovascular disease worldwide and the decline in the age at the disease onset (2), it has been considered an ongoing health concern. The American Heart Association (AHA) has referred to coronary artery disease as a common cause of death worldwide, accounting for 35 – 60% of deaths

per year (4). According to the statistics provided by Iran's Ministry of Health and Medical Education in 2012, cardiovascular disease was responsible for 39% of deaths (2). However, this measure has been predicted to reach 44.8% by 2030 (5).

Coronary angiography is a primary diagnostic method for heart patients, which has been considered the gold standard in the detection of heart diseases (6). However, this technique is invasive and can lead to adverse effects such as arrhythmia, vascular complications (e.g., bleeding hematoma and thrombosis), myocardial ischemia, arterial rupture, transient ischemic attacks, allergies, and kidney failure following the use of contrast agents. Previous studies showed that complete bed rest, leg immobilization, and

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use of sandbags could partly prevent these complications (7), but they could lead to other unwanted side effects such as back pain following bed rest (7, 8). In addition, the pain experienced by patients affected their physical health and mental health through stress, anxiety, and hemodynamic imbalance (9). The importance of controlling and managing pain is often referred to as the fifth vital sign by the American Pain Society (10). In these patients, pain and fatigue may be attenuated by drug therapy, but it is reasonable to identify and use non-pharmacological methods to control pain due to drug-related complications and the risks of drug interactions (11).

One of the most popular complementary therapies is massage therapy (12). Massage is considered a standard nursing intervention and an important part of health care. It is used to help patients meet their physical and psychological needs (5). Massage therapy refers to soft tissue manipulation (13) as well as a technique that can improve hemodynamic status and the nervous system (4, 5).

There are many documented complications associated with narcotic and other pain-relieving medications. On the other hand, nursing interventions can be used to control pain and reduce reliance on medications (7). Nevertheless, there is a paucity of studies on the evaluation of the effects of hand and foot massage on pain intensity and the anxiety levels amongst patients with Acute Coronary Syndrome (ACS). Thus, this gap has been addressed in the current study. Arms and legs have many neural receptors (14) and Manual Lymphatic Drainage (MLD) can reduce the recurrence of deep vein thrombosis (15).

2. Objectives

The aim of this study is evaluating the effects of hand and foot surface stroke massage on pain intensity and anxiety level in hospitalized patients with acute coronary syndrome.

3. Materials and Methods

3.1. Study Design and Sampling

This clinical trial was conducted on 70 patients suffering from ACS admitted to Hajar Hospital affiliated to Shahrekord University of Medical Sciences from 6 July to 16 August 2017. The patients were selected via convenience sampling and were randomly divided into an intervention and a control group. Based on the following equation, a 66-subject sample size was estimated for the study ($n=33$ in each group):

$$n = \frac{(z_{1-\alpha} + z_{1-\beta})^2 (s_1^2 + s_2^2)}{d^2}$$

Where $S_1=5$, $d=4$, $S_2=5$, $1 - \alpha=0.95$, and $1 - \beta=0.90$. Considering a 10% drop-out, the sample size was increased to 35 patients in each group (16).

3.2. Inclusion Criteria

The inclusion criteria of the study were aging over 18 years, consciousness, diagnosis of ACS by a physician based on the clinical symptoms, Electrocardiogram (ECG) changes, and laboratory tests, absence of severe anxiety according to the physician, having no history of mental disorders, not taking warfarin, Pulse Rate (PR) > 60 bpm

and < 110 bpm, no history of respiratory arrest in the past 72 h, not using a pacemaker because of hemodynamic instability, no amputations, diastolic blood pressure < 110 mmHg, systolic blood pressure < 180 mmHg, no history of cardiac arrhythmias including ventricular tachycardia or fibrillation, and willingness to cooperate. The patients who had bone fractures in the past two months, clotting disorder, deep vein thrombosis, and dialysis fistula in the upper limbs as well as those who had a history of taking hypnotic drugs, opioids, benzodiazepines, or alcohol were excluded from the study. It is worth mentioning that the patients had not undergone spinal anesthesia in the past four hours. In addition, the patients had healthy massage-related areas that were not characterized by redness, swollen skin, skin lesions, and healing wounds (10, 12, 13).

3.3. Exclusion Criteria

The exclusion criteria of the study were not being willing to participate in the study and obtaining a Spielberger's Anxiety Inventory score > 65, which indicated severe and very severe anxiety levels (4, 12).

3.4. Data Collection Tools

The study data were collected using three tools. Firstly, the demographic information form included age, sex, education level, marital status, occupation, and history of hospitalization. The second instrument was the standard Spielberger's Anxiety Inventory approved by Tehran University whose reliability was confirmed by Cronbach's alpha coefficient of 94 – 99% (17, 18). This 20-item questionnaire consisted of 10 positive attitude questions (1, 2, 5, 8, 10, 11, 15, 16, 17, 18) and 10 negative attitude questions (3, 4, 6, 7, 9, 12-14, 19, 20), which could be scored as 4 = not at all, 3 = somewhat, 2 = moderately, and 1 = very much. Thus, the total scores of 20 – 42, 43-64, and 65 - 80 represented mild, moderate, and severe anxiety, respectively (21, 22). Thirdly, the pain intensity was measured by a Visual Analog Scale (VAS) whose reliability and validity were approved previously (11, 23). In this 10-cm ruler graded from 0 (no pain) to 10 (maximum imaginable pain), scores 1 – 3, 4 - 7, and 8 - 10 represented mild, moderate, and severe pain, respectively (4, 11).

3.5. The Intervention Methodology

After verbally taking the patients' medical history, the Spielberger's Anxiety Inventory was filled out 30 min before the intervention. The patients' pain intensity was also measured using the VAS 30 min before and 15 min after the intervention and was recorded in a checklist.

In the intervention group, the patients were checked for skin allergies to almond oil on their right arms 30 min before the intervention. They were also asked about their skin allergies to almond oil. Then, they were put in supine position and massage was started from the palms towards the shoulders (each for five min) followed by the soles towards the quadriceps femoris muscle (each for five min). This lasted for 20 min. Massages were performed by sex-matched trained personnel based on the principles of the Islamic Republic of Iran and in compliance with an audit approved by the Islamic Consultative Assembly

on 1 November 1998. After 15 min, the participants were required to complete the Spielberger's Anxiety Inventory.

In the control group, a verbal interview was conducted to record the patients' medical history. Additionally, pain intensity was recorded in a checklist.

3.6. The Study Techniques

In this research, use was made of the Stroke and Swedish (tight strokes) massages. Hand and foot surface stroke massages were performed with no pressure by manipulating the soft tissues using nearly 60 movements per min for 3 – 10 min in order to increase the local blood circulation and lymphatic drainage. In doing so, the hands were positioned on the desired limb and were slowly and rhythmically moved from the end to the beginning with no pressure on the muscles (19, 20). It should be noted that sweet almond oil was applied to the patients' skin (20).

3.7. Ethical Considerations

This study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1396.83) and was registered in the Iranian Registry of Clinical Trials (code: IRCT2017070134830N1). Informed consent forms were obtained from all the participants. In fact, the patients' privacy was maintained and they were ascertained that they could leave the research at any stage.

3.8. Statistical Analysis

The data were described using frequency and percentage for the qualitative variables and mean \pm Standard Deviation

(SD) for the normally distributed quantitative variables. The normal distribution of the variables was evaluated by the Kolmogorov-Smirnov test. Additionally, the differences between the study groups was assessed using Fisher's exact test and chi-square test for the qualitative variables and using independent t-test and paired t-test for the quantitative variables. All analyses were done through the SPSS 23 software, and $P < 0.05$ was considered statistically significant.

4. Results

The results showed the normal distribution of the demographic and clinical characteristics in the intervention and control groups (Table 1). The mean age of the patients was 62.16 ± 10.47 years, ranging from 42 to 84 years (Table 2).

The results of independent t-test revealed no significant difference between the two groups regarding the anxiety level before the intervention ($P > 0.36$). The results also showed no significant difference between the two groups in terms of pain intensity before the intervention (Table 2). The results of paired t-test showed a significant difference in the intervention group's pain intensity and anxiety level before and after the intervention. However, no significant difference was observed in this regard in the control group (Table 3). The intervention group's mean level of anxiety was 30.00 ± 3.74 at baseline and 21.86 ± 1.68 15 min after the intervention ($P < 0.001$). These measures were respectively obtained as 29.17 ± 3.77 and 28.14 ± 5.59 in the control group ($P > 0.198$) (Table 3). The results of independent t-test demonstrated that the difference in the mean level of anxiety

Table 1. Demographic and Clinical Characteristics of the Participants in the Intervention and Control Groups

Variable	Total Number of Participants		Intervention Group		Control Group		P-value
	Number	Percentage	Number	Percentage	Number	Percentage	
Education level							
Illiterate	34	48.6	20	57.1	14	40	0.202
Below diploma	23	32.9	9	25.7	14	40	
Diploma	9	12.9	5	14.3	4	11.4	
Higher education	4	5.7	1	2.9	3	8.6	
Total	70	100	35	100	35	100	
Occupation							
Homemaker	27	38.6	15	42.9	12	34.3	0.215
Self-employed	18	25.7	11	31.4	7	20	
Civil servant	3	4.3	0	0	3	8.6	
Retired	21	30	9	25.7	12	34.3	
Unemployed	1	1.4	0	0	1	2.9	
Sex							
Female	28	60	16	45.7	12	34.3	0.333
Male	42	40	19	54.3	23	65.7	
History of taking blood pressure suppressants							
Yes	44	62.9	20	57.1	24	68.6	0.326
No	26	37.1	15	42.9	11	31.4	

Table 2. Data Analysis Using Independent T-Test before the Intervention

Variable	Group	Mean \pm SD	P-value
Age	Intervention	63.08 \pm 11.16	0.46
	Control	61.22 \pm 9.81	
Anxiety level	Intervention	30.00 \pm 3.74	0.36
	Control	29.17 \pm 3.77	
Pain level	Intervention	3.8 \pm 1.60	0.60
	Control	3.34 \pm 1.49	

Table 3. Changes in the Anxiety Levels and Pain Intensity in the Intervention and Control Groups at Specified Intervals using Paired T-Test

Variable	Before the Intervention		15 Min after the Intervention		P-value
	Group	Mean \pm SD	Group	Mean \pm SD	
Anxiety level	Intervention	30.00 \pm 3.74	Intervention	21.86 \pm 1.68	0.000
	Control	29.17 \pm 3.77	Control	28.14 \pm 5.59	
Pain intensity	Intervention	3.8 \pm 1.60	Intervention	1.54 \pm 1.09	0.000
	Control	3.6 \pm 1.63	Control	3.34 \pm 1.49	

Table 4. Comparison of the Mean Changes in the Anxiety Scores and Pain Intensity of the Participants in the Intervention and Control Groups before and 15 Min after the Intervention Using Independent T-Test

Variable	Group	Mean Difference	T-Test Result
Anxiety score	Intervention	-8.14 \pm 3.20	P = 0.000
	Control	-1.03 \pm 4.64	
Pain score	Intervention	-2.26 \pm 1.17	P = 0.000
	Control	-0.26 \pm 0.08	

before and 15 min after the intervention was -8.14 ± 3.20 in the intervention group and -1.03 ± 4.64 in the control group ($P < 0.001$), suggesting a significant difference between the two groups concerning the anxiety level (Table 4).

4. Discussion

The study results showed that hand and foot massage significantly decreased the pain intensity and anxiety level in the intervention group. Additionally, the results of paired t-test revealed a significant difference between the two study groups in terms of pain intensity and anxiety level. Similar studies also indicated that massage reduced anxiety levels and pain intensity in patients (17, 18, 21-23). For instance, CiptoSusilo et al. detected a significant relationship between the occurrence of chest pain and massaging or rubbing with oil in the pre-hospital phase (24). Bahrami et al. also disclosed a significant difference between the study groups regarding the levels of anxiety and depression after the intervention. Moreover, aromatherapy massage could alleviate psychological responses in older women with ACS (25).

There are different theories about how massage affects anxiety and vital signs. As an instance, the hypothalamic-pituitary axis has been theoretically found to be related to sympathetic and epinephrine systems. Massage can reduce the levels of stress hormones and improve the vital signs balance via parasympathetic stimulation and decreasing the sympathetic activity (26-28). Another issue is related to the release of oxytocin, which creates feelings of comfort, relaxation, and wellness (12). Massage results in the release of peptides for an analgesic effect, increased serotonin, and a feeling of comfort (14). Overall, massage brings about the feelings of comfort and well-being through the induction of physical and mental relaxation characterized by increase in blood, oxygen, and nutrient flow to tissues as well as through the stimulation of the parasympathetic system, elevation of endorphin secretion, reduction in localized inflammation, secretion of catecholamines, reduction in muscle spasms, and closure of pain gate (9). However, different results were obtained by Najafi et al. (9), which might be attributed to the high severity of burns, the utilized techniques, or damage to the sensory receptors in hands and feet. Other effective factors in cortisol levels could also lead to different results from those

of the present investigation (29). All in all, future studies are recommended to be conducted on larger sample sizes.

There is no doubt that a motivation for conducting a research is to use the results to attenuate pain intensity and anxiety level, which reduces the use of narcotic medicines. In fact, an increasing emphasis has been put on the lower utilization of medicine worldwide (10). Non-pharmacological methods can decrease the use of narcotic medicines, reduce patients' pain intensity and anxiety levels, and minimize the pain and anxiety cycles (9).

5.1. Conclusions

The present study utilized a non-pharmacological, simple, and low-cost method in a short time (a 20-minute session) to reduce the pain intensity and anxiety level among the patients with ACS. The results indicated that hand and foot massage reduced the patients' pain intensity and anxiety level. Considering this intervention's ease of use and low cost, it can be used as a complementary therapy to relieve pain and anxiety. Nonetheless, the drawbacks of this method include time constraints, lack of manpower, use of advanced technology, and increased complexity of the required care. This therapeutic approach and its importance can be taught through nursing education courses.

5.2. Suggestions

Future studies with larger sample sizes are required to evaluate the impacts of hand and foot surface stroke massage on patients' outcomes.

5.3. Ethical Approval

IR.SKUMS.REC.1396.83.

5.4. Informed Consent

Written informed consent was obtained from the patients.

5.5. Clinical Trial Registration Code

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Authors' Contribution

Study concept and design: Z.Gh., A.Kh., and A.H.; Analysis and interpretation of data: Z.Gh. and M.S.; Drafting of the manuscript: Z.Gh., A.H., Sh.S., and A.Kh.; Critical revision of the manuscript for important intellectual content: Z.Gh., A.Kh., Sh.S., and A.H. All authors have read and approved the final manuscript.

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The authors have no financial interests related to the material in the manuscript.

References

- Yosae S, Soltani S, Sekhavati E, Jazayeri S. Adropin-a novel biomarker of heart disease: a systematic review article. *Iranian journal of public health*. 2016;**45**(12):1568.
- Ahmadi A, Soori H, Mehrabi Y, Etemad K, Samavat T, Khaledifar A. Incidence of acute myocardial infarction in Islamic Republic of Iran: a study using national registry data in 2012. *Eastern Mediterranean health journal*. 2015;**21**(1):5-12.
- Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Annals of translational medicine*. 2016;**4**(13).
- Alimohammad HS, Ghasemi Z, Shahriar S, Morteza S, Arsalan K. Effect of hand and foot surface stroke massage on anxiety and vital signs in patients with acute coronary syndrome: A randomized clinical trial. *Complementary therapies in clinical practice*. 2018;**31**:126-31.
- Oshvandi K, ABDI S, Karampourian A, Moghimbaghi A, HOMAYOUNFAR S. The effect of foot massage on quality of sleep in ischemic heart disease patients hospitalized in CCU. 2014.
- Valiee S, Fathi M, Hadizade N, Roshani D, Mahmoodi P. Evaluation of feasibility and safety of changing body position after transfemoral angiography: A randomized clinical trial. *Journal of Vascular Nursing*. 2016;**34**(3):106-15.
- Abdollahi AA, Mehranfar S, Behnampour N, Kordnejad AM. Effect of positioning and early ambulation on coronary angiography complications: a randomized clinical trial. *Journal of caring sciences*. 2015;**4**(2):125.
- Mohammady M, Heidari K, Sari AA, Zolfaghari M, Janani L. Early ambulation after diagnostic transfemoral catheterisation: a systematic review and meta-analysis. *International Journal of Nursing Studies*. 2014;**51**(1):39-50.
- Ghezalje TN, Ardebili FM, Rafii F. The effects of massage and music on pain, anxiety and relaxation in burn patients: Randomized controlled clinical trial. *Burns*. 2017;**43**(5):1034-43.
- Levy N, Sturgess J, Mills P. "Pain as the fifth vital sign" and dependence on the "numerical pain scale" is being abandoned in the US: why? *British journal of anaesthesia*. 2018;**120**(3):435-8.
- Ghezalje TN, Ardebili FM, Rafii F, Manafi F. The effect of massage on anticipatory anxiety and procedural pain in patients with burn injury. *World journal of plastic surgery*. 2017;**6**(1):40.
- Cronfalk BS, Strang P, Ternstedt B-M, Friedrichsen M. The existential experiences of receiving soft tissue massage in palliative home care—an intervention. *Supportive care in cancer*. 2009;**17**(9):1203-11.
- Braun LA, Stanguts C, Casanelia L, Spitzer O, Paul E, Vardaxis NJ, et al. Massage therapy for cardiac surgery patients—a randomized trial. *The Journal of thoracic and cardiovascular surgery*. 2012;**144**(6):1453-9. e1.
- Kordi M, Tara F, Bahrami HR, Shariati Nejad K. The effect of hand and foot massage on post-cesarean pain and anxiety. *Journal of Midwifery and Reproductive Health*. 2015;**3**(4):465-71.
- van Vuuren TM, van Laanen JH, de Geus M, Nelemans PJ, de Graaf R, Wittens CH. A randomised controlled trial comparing venous stenting with conservative treatment in patients with deep venous obstruction: research protocol. *BMJ open*. 2017;**7**(9).
- Adib-Hajbaghery M, Rajabi-Beheshtabad R, Ardjmand A. Comparing the effect of whole body massage by a specialist nurse and patients' relatives on blood cortisol level in coronary patients. *ARYA atherosclerosis*. 2015;**11**(2):126.
- Kordi M, Irani M, Bahrami HR, Ghaffari Sardasht F. Effect of hand and foot massage on vital signs of women after caesarean section. *The Iranian Journal of Obstetrics, Gynecology and Infertility*. 2016;**19**(15):8-15.
- Saatsaz S, Rezaei R, Alipour A, Beheshti Z. Massage as adjuvant therapy in the management of post-cesarean pain and anxiety: A randomized clinical trial. *Complementary therapies in clinical practice*. 2016;**24**:92-8.
- Eguchi E, Funakubo N, Tomooka K, Ohira T, Ogino K, Tanigawa T. The effects of aroma foot massage on blood pressure and anxiety in Japanese community-dwelling men and women: A crossover randomized controlled trial. *PLoS one*. 2016;**11**(3):e0151712.
- Shafie Z, Nourian K, Babae S, Nazari A. Effectiveness of light pressure stroking massage on pain and fatigue of patients after coronary artery bypass graft surgery-A randomized clinical trial. *Journal of Clinical Nursing and Midwifery*. 2013;**2**.
- Adib-Hajbaghery M, Rajabi-Beheshtabad R, Abasi A, Azizi-Fini E. The Effect of Massage Therapy by a Nurse and the Patient's Companion on the Anxiety of Male Patients Hospitalized in CCU: A Clinical Trial. *Iran Journal of Nursing (2008-5923)*. 2012;**25**(78).
- Gholami-Motlagh F, Jouzi M, Soleymani B. Comparing the effects of two Swedish massage techniques on the vital signs and anxiety of healthy women. *Iranian journal of nursing and midwifery research*. 2016;**21**(4):402.
- Vahedian-Azimi A, Ebadi A, Jafarabadi MA, Saadat S, Ahmadi F. Effect of massage therapy on vital signs and GCS scores of ICU patients: a randomized controlled clinical trial. *Trauma monthly*. 2014;**19**(3).
- Susilo C, Qomaruddin MB, Fahrera MP. Acute Coronary Syndrome and patient behavior factors in overcoming the event of chest pain in pre hospital phase. *Journal of Public Health Research*. 2020;**9**(2).
- Bahrami T, Rejeh N, Heravi Karimooi M, Vaismoradi M, Tadrissi SD, Sieloff C. Effect of aromatherapy massage on anxiety, depression, and physiologic parameters in older patients with the acute coronary syndrome: A randomized clinical trial. *International journal of nursing practice*. 2017;**23**(6):e12601.
- Adib-Hajbaghery M, Rajabi-Beheshtabad R, Abasi A. Effect of whole body massage by patient's companion on the level of blood cortisol in coronary patients. *Nursing and midwifery studies*. 2013;**2**(3):10.
- Kim I-H, Kim T-Y, Ko Y-W. The effect of a scalp massage on stress hormone, blood pressure, and heart rate of healthy female. *Journal of physical therapy science*. 2016;**28**(10):2703-7.
- Lindgren L, Lehtipalo S, Winsö O, Karlsson M, Wiklund U, Brulin C. Touch massage: a pilot study of a complex intervention. *Nursing in critical care*. 2013;**18**(6):269-77.
- Kanitz JL, Reif M, Rihs C, Krause I, Seifert G. A randomised, controlled, single-blinded study on the impact of a single rhythmical massage (anthroposophic medicine) on well-being and salivary cortisol in healthy adults. *Complementary therapies in medicine*. 2015;**23**(5):685-92.