

Physical therapy intervention in patients with non-cardiac chest pain following a recent cardiac event: A randomized controlled trial

SAGE Open Medicine
3: 2050312115580799
© The Author(s) 2015
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/2050312115580799
smo.sagepub.com


Astrid T Berg¹, Signe N Stafne^{1,2}, Aud Hiller³, Stig A Slørdahl⁴ and Inger-Lise Aamot^{1,4}

Abstract

Objectives: To assess the effect of two different physical therapy interventions in patients with stable coronary heart disease and non-cardiac chest pain.

Methods: A randomized controlled trial was carried out at a university hospital in Norway. A total of 30 patients with known and stable coronary heart disease and self-reported persistent chest pain reproduced by palpation of intercostal trigger points were participating in the study. The intervention was deep friction massage and heat pack versus heat pack only. The primary outcome was pain intensity after the intervention period and 3 months after the last treatment session, measured by Visual Analogue Scale, 0 to 100. Secondary outcome was health-related quality of life.

Results: Treatment with deep friction massage and heat pack gave significant pain reduction compared to heat pack only (−17.6, 95% confidence interval: −30.5, −4.7; $p < 0.01$), and the reduction was persistent at 3 months' follow-up (−15.2, 95% confidence interval: −28.5, −1.8; $p = 0.03$). Health-related quality of life improved in all three domains in patients with no significant difference between groups.

Conclusion: Deep friction massage combined with heat pack is an efficient treatment of musculoskeletal chest pain in patients with stable coronary heart disease.

Keywords

Deep friction massage, myofascial trigger point, chest pain

Date received: 28 November 2014; accepted: 3 March 2015

Introduction

Non-cardiac chest pain in patients with coronary heart disease is a common complaint in general practice and accident- and emergency units.¹ Musculoskeletal causes are common, but frequently overlooked with estimations showing that 20%–25% of non-cardiac chest pain has a basis in the musculoskeletal system.¹ In primary care, intercostal tenderness has been reported to be the most common origin of pain, comprising almost 50% of all patients with chest pain.² In addition, chest pain often occurs following cardiac surgery. One study found that 11% reported pain at 6 and 12 months after surgery,³ and another study found that persistent pain was reported by 28%–61% 1–3 years after surgery with pain being moderate to severe in 11%–37% of the patients.⁴

Chest pain represents a major, but often unrecognized, clinical problem which is an important health-care issue.³

¹Department of Clinical Services, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

²Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway

³Department of Cardiology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

⁴Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

Corresponding author:

Astrid T Berg, Department of Clinical Services, St. Olavs Hospital, Trondheim University Hospital, 7006 Trondheim, Norway.
Email: astrid.tarlebo.berg@gmail.com



The symptom generates anxiety and is often followed by various examinations.

Myofascial trigger points may lead to complex pain symptoms, and one traditional physical therapy intervention in patients presenting musculoskeletal pain is inactivating myofascial trigger points and eliminating factors that perpetuate them. Thermal heat is another common treatment modality used by physical therapists in the management of painful musculoskeletal disorders.⁵ Wright and Sluka⁵ state that therapeutic heat might relieve muscle spasm, reduce pain and increase blood flow to the injured area.

Clinical experience from the first author (A.T.B.) is that trigger points are found in the intercostal muscles in patients presenting non-cardiac chest pain and that deep friction massage relieves this pain. In systematic searches in various databases, no trials concerning the effect of treatment of chest pain from the intercostal muscles were identified. Therefore, the aim of the present trial was to evaluate the effect of two different physical therapy interventions in patients with known heart disease and persistent chest pain from the intercostal muscles. The hypothesis was that deep friction massage combined with moist heat pack was more effective in relieving pain than moist heat pack only.

Method

Design

The study is a prospective randomized controlled trial with an open parallel-group design and was carried out in a daily clinical setting.

Participants

Participants were recruited from an exercise-based cardiac rehabilitation programme at St. Olavs Hospital, Trondheim University Hospital, from October 2003 to January 2008. Participants were referred to the cardiac rehabilitation programme due to a recent cardiac event (<3 months), were revascularized and clinically stable. Criteria for inclusion in the present trial were known and stable coronary heart disease, age 18–80 years and persistent and increasing chest pain reproduced by palpation of intercostal trigger points. Exclusion criteria were misuse of drugs or alcohol, participation in other ongoing studies or unable to participate for other reasons. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 066-03) in accordance with the Helsinki Declaration. Written informed consent was obtained before entering the study.

Intervention

Participants were randomly assigned into two intervention groups comprising deep friction massage and moist heat pack or moist heat pack only (Figure 1). The combined intervention (deep friction massage and moist heat pack) has

been standardized as treatment for these patients at St. Olavs Hospital, Trondheim University Hospital for many years, but the intervention has not been evaluated in a randomized controlled trial until now. However, a pilot study showed promising results.⁶ Concealed randomization was performed at the Unit for Applied Clinical Research, Norwegian University of Technology and Science, by a web-based computerized procedure. The staff involved with training or outcome assessments had no influence on the randomization procedure. The computerized randomization procedure was conducted immediately after the patient had provided written informed consent.

Participants attended cardiac rehabilitation which is offered to all patients with a stable coronary heart disease discharged from St. Olavs Hospital, Trondheim University Hospital. They were given a maximum of eight individual treatments, and the treatments were given immediately after the exercise training classes. Individual treatment was given twice a week if tolerated, otherwise once per week. Participants in the combined treatment group received 15 min of deep friction massage followed by 15 min of moist heat pack (Standard Hydrocollator Moist Heat HotPac; Chattanooga Medical Supply, Inc.), and participants in the control group received 25 min of heat pack. All participants were treated in a supine position in a relaxed posture with a pillow under the head and knees. The moist heat pack was a reusable hot pack of clay in canvas kept in a container of hot water. Intensity of heat and size of heat pack were individually adapted as to the patient's comfort level and anatomical differences. After the heat pack was applied over the chest, participants were wrapped in blankets and made comfortable. Before leaving the treatment bench, participants in both groups were instructed to elevate the arms and expand the chest as much as they could while taking a deep breath. In addition, participants in both groups received thorough oral information concerning the condition of myofascial trigger points (explain pain). Deep friction massage often extends the pain-threshold but not the tolerance-threshold. From experience, the pain will decrease after a few minutes of treatment. In the combined treatment group, participants were instructed to focus on deep, calm respiration in order to relax the respiratory muscles during the deep friction massage.

Outcome measures

Primary outcome. The primary outcome measure was change in pain, evaluated by the Visual Analogue Scale (VAS). VAS is a psychometric response scale frequently used and a validated tool for pain measurement, consisting of a line of 0–100 mm where 0 mm is no pain and 100 mm intolerable pain.⁷ When responding to VAS, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points.⁸ VAS score was registered at inclusion, post treatment and 3 months after the last treatment session. Three different scores were

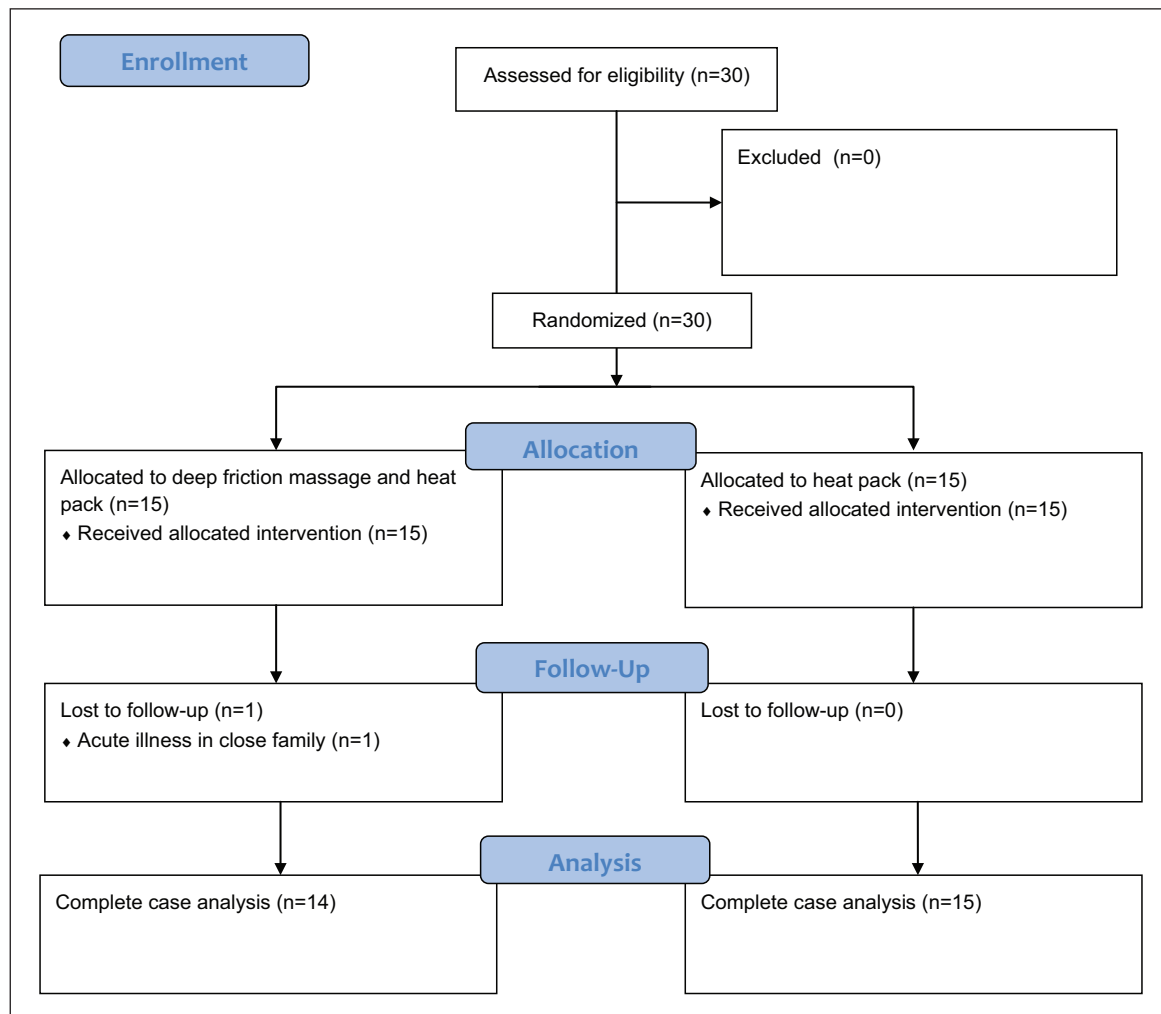


Figure 1. CONSORT flow diagram of study participants.

recorded: (1) present pain, (2) mean pain last week and (3) worst pain attack last week.

Secondary outcome. Secondary outcome measure was health-related quality of life (HRQL) measured by MacNew Heart Disease Health-Related quality-of-life instrument (MacNew)⁹ and Short Form-36 (SF-36).¹⁰ MacNew is a disease-specific questionnaire with a validated translation in Norwegian.¹¹ The questionnaire assesses three different domains: emotional, social and physical quality of life. The scores range from 1 to 7 where higher score indicates better quality of life. A change in score of 0.5 is set to be clinically significant.⁹ SF-36 is a generic questionnaire assessing eight domains, and higher scores (0–100) indicate better quality of life.¹⁰ HRQL was measured at inclusion and at 3 months' follow-up.

Data analysis

Sample size calculation was performed a priori based on the results from the pilot study.⁶ To achieve a statistical power of

0.8 with a significance level of $p < 0.05$, it was calculated that a minimum of 30 patients were needed, assuming a pain reduction of more than 20% between groups. The data analysis was done with complete cases ($N = 29$) using Statistical Package for Social Science (SPSS Inc., Chicago, IL) version 15. We used a mixed linear model with the VAS score as the dependent variable, intervention and time (baseline, post intervention and 3 months' follow-up) as fixed effects and subjects as the random effect. Linear contrast estimates were performed when effects were significant for the dependent variable. HRQL was analysed by analysis of covariance (ANCOVA), adjusting for baseline values with Bonferroni corrections for multiple analysis. A p value ≤ 0.05 was considered significant. Values are referred to as mean (\pm standard deviation (SD)) or 95% confidence interval (CI).

Results

All participants in the study presented pain in the anterior chest wall with increasing limitation of chest expansion by

pain when exercising at high intensity or on specific movements involving stretching of muscles in the chest. On palpation, they had one or more trigger points, mostly in the anterior chest wall in the third, fourth, fifth and sixth intercostal space. Participants presented a specifically painful trigger point in the fifth intercostal space, approximately two fingerbreadths medial to the nipple. When asked to describe the quality of the pain, they all used the word ‘stinging’ sensation. Both right and left chest walls were represented, with a strong overrepresentation of pain in the left hemi-thorax. Some also presented additional trigger points in m.supraspinatus, m.infraspinatus, m.rhomboides, m.pectoralis minor, m.pectoralis major and m.serratus anterior.

Treatments were well tolerated, and no adverse effects were recorded at any time. After randomization, 1 participant was lost to follow-up because of acute illness in close family, and we were left with 29 participants to analyse (Figure 1), 6 women and 23 men, all Norwegians. Participants analysed completed all the individual treatment sessions they were offered.

At study entry, there were no significant differences between the groups in baseline characteristics (Table 1), pain and HRQL (Tables 2 and 3). Out of 29 participants, 12 reported persistent pain for more than 3 months, and 2 participants reported pain for more than 2 and 5 years, respectively, following previous surgery.

Treatment with deep friction massage combined with heat pack was significantly more efficient than heat pack only in pain reduction (Table 2), both immediately after intervention and at 3 months’ follow-up. HRQL increased in both groups, and no between-group differences was found at baseline or 3 months’ follow-up. However, within-group analysis showed increased HRQL measured with MacNew disease-specific questionnaire in the combined treatment group (Table 3).

Discussion

To our knowledge, this is the first randomized controlled trial to evaluate the effect of deep friction massage and heat pack versus heat pack only, in the treatment of non-cardiac chest wall pain in patients with known coronary heart disease. Deep friction massage combined with heat pack was superior to heat pack only in pain reduction, in short and long term. Also interesting, pain reduction was found even in those participants who reported pain over several years.

The strengths of the present trial are the prospective design, the consecutive inclusion of participants and the use of validated tools for pain and HRQL measurements. Despite this, there are some limitations. One limitation of the study is lack of a control group receiving no treatment. However, this was considered unethical since deep friction massage and heat pack is established as standard treatment for these patients at St. Olavs Hospital, Trondheim University Hospital. Ideally, time with heat pack should be equal in both groups, still this was not possible since the trial was done in

Table 1. Baseline characteristics of the study population.

	Heat pack + deep friction massage (n = 14)	Heat pack (n = 15)	p value
Mean age (years)	61.2 ± 9.4	57.4 ± 4.8	0.19
Gender (male/female)	9/5	14/1	0.08
BMI (kg/m ²)	25.9 ± 3.9	27.5 ± 3.1	0.25
Duration of pain (months)	6.7 ± 15.3	4.2 ± 5.6	0.55
Diagnosis, n (%)			
Myocardial infarction	1 (7)	0 (0)	0.48
Coronary artery bypass graft	9 (64)	13 (87)	0.22
Percutaneous coronary intervention	4 (29)	2 (13)	0.39

BMI: body mass index.

Data are presented as mean ± standard deviation (SD) or n (%) unless stated otherwise.

a clinical setting with a time schedule and limited room facilities. Anyhow, achieving the thermal effect of heat pack is assumed to be reached both with 15 and 25 min due to the superficial tissues being treated. Instead, total time with treatment was believed to be more important. The physiotherapist was present near the patient during the whole treatment session, limiting the possible role of verbal interaction with the physical therapist on the treatment effect. Participants in both groups were given the same instruction on elevating arms and expanding the chest as much as they could while taking a deep breath. Inclusion and treatments were done by the same physiotherapist and thereby not blinded.

There is strong evidence that exercise-based cardiac rehabilitation is effective in reducing total and cardiac mortality,¹² and all participants were in an exercise-based cardiac rehabilitation programme according to guidelines. The exercise groups were held in an outpatient hospital setting and led by competent physiotherapists. Besides improving cardiovascular fitness, patients were assured that their hearts were working well. Patients with non-cardiac chest pain were given support and information regarding their chest-pain condition and given an option to be treated. They experienced increased assurance as to their chest pain being non-cardiac, when the physiotherapist could reproduce the pain by palpation. This may explain the increased HRQL in both groups. Compliance in the present trial was excellent confirming that the intervention was well tolerated.

Myofascial pain associated with trigger points has been studied; however, various aspects of its pathophysiology, clinical manifestation and treatment remain unclear. In the present trial, we have used Simons and Travell’s definition of myofascial pain; a non-inflammatory disorder of musculoskeletal origin, associated with local pain and muscle stiffness, characterized by the presence of hyperirritable palpable nodules in the skeletal muscle fibers.¹³

Table 2. Primary outcomes estimated in a Linear Mixed-Effects Model.

	Groups		Difference between groups corrected for baseline values*	
	Heat pack + deep friction massage	Heat pack	Mean (95% CI)	p value
Baseline VAS (0–100)				
Present pain	46.9 (37.7, 55.9)	35.3 (22.3, 56.0)	–	0.13
Average pain last week	52.1 (43.3, 60.9)	42.1 (30.5, 53.6)	–	0.16
Worst pain last week	62.6 (51.2, 74.0)	62.2 (48.1, 76.3)	–	0.97
After intervention VAS (0–100)				
Present pain	8.3 (–1.6, 18.2)	25.9 (16.3, 35.6)	–17.6 (–30.5, –4.7)	<0.01
Average pain last week	10.5 (0.2, 20.7)	27.9 (18.0, 37.8)	–17.4 (–31.1, –3.8)	0.01
Worst pain last week	15.3 (3.2, 27.4)	33.9 (22.2, 45.7)	–18.7 (–34.5, –2.8)	0.02
3 months' follow-up VAS (0–100)				
Present pain	7.1 (–3.5, 17.7)	22.3 (12.6, 31.9)	–15.2 (–28.5, –1.8)	0.03
Average pain last week	7.9 (–3.1, 18.8)	28.2 (18.2, 38.1)	–20.3 (–34.5, –6.2)	<0.01
Worst pain last week	11.2 (–1.7, 24.1)	32.8 (21.0, 44.5)	–21.5 (–38.0, –5.1)	0.01

CI: confidence interval; VAS: Visual Analogue Scale.

*The baseline-adjusted differences between groups were estimated using the interaction between treatment group and time (using baseline and follow-up values as dependent variables).

Table 3. Health-related quality of life at baseline and follow-up.

	Heat pack + deep friction massage			Heat pack			ANCOVA between-group differences at 3 months' follow-up
	Baseline	3 months' follow-up	Paired samples t-test	Baseline	3 months' follow-up	Paired samples t-test	
MacNew							
Emotional	5.0 ± 1.0	5.7 ± 0.8	0.05	5.3 ± 0.8	5.4 ± 0.9	0.51	0.21
Social	5.5 ± 0.7	6.2 ± 0.6	0.001	5.3 ± 0.8	5.9 ± 0.7	0.15	0.14
Physical	5.1 ± 0.9	5.7 ± 0.9	0.03	5.3 ± 0.8	5.6 ± 1.1	0.16	0.64
SF-36							
Mental health	68.8 ± 15.6	76.7 ± 11.0	0.12	74.4 ± 15.4	75.7 ± 14.2	0.49	0.81
Vitality	45.7 ± 20.4	54.0 ± 21.6	0.37	50.0 ± 17.9	52.9 ± 22.7	0.62	0.90
Bodily pain	45.0 ± 14.0	57.8 ± 24.0	0.08	38.9 ± 18.5	60.8 ± 22.3	0.001	0.73
General health	60.9 ± 21.3	66.9 ± 21.2	0.52	66.6 ± 21.3	59.9 ± 25.9	0.34	0.33
Social function	75.0 ± 18.9	85.2 ± 16.4	0.07	81.7 ± 20.0	87.0 ± 12.9	0.18	0.73
Physical function	78.3 ± 12.1	79.0 ± 17.4	0.53	73.3 ± 14.0	83.8 ± 14.1	0.05	0.38
Role physical	18.8 ± 32.2	46.5 ± 44.3	0.09	23.3 ± 30.6	44.7 ± 39.2	0.07	0.91
Role emotional	58.9 ± 38.2	70 ± 41.8	0.46	64.4 ± 38.8	68.3 ± 36.7	0.73	0.91

ANCOVA: analysis of covariance; SF-36: Short Form–36.

Summary of within and between-group results, presented as mean ± standard deviation.

In systematic searches, no previous studies on treatment of intercostal trigger points were found. However, Janet G Travell, who was the White House physician to President Kennedy, started her academic career in the 1930s and was a pioneer in understanding and treating myofascial trigger points. Her aim was that some day

cardiology residents would be taught how to identify and treat myofascial trigger points. She stressed the importance of learning how to find which muscle or muscles needed to be palpated, learn what to palpate for and either develop the skill to treat the pain or find a therapist with that skill.¹⁴

Intervention studies of pain experience reporting less than 13-mm change in VAS score, although statistically significant, may have no clinical importance.¹⁵ In our study, no change in VAS score was less than 39 mm from baseline to immediately after the intervention period, and no change in VAS score was less than 25 mm from baseline to 3 months after the end of the intervention period. The major pain reduction and that the effect was found to be persistent 3 months after the intervention period are of high clinical importance. Our sample size calculation was based on an estimate of 20% difference in pain reduction between groups, requiring 15 participants in each group. Only 29 participants completed the study; however, the effect size of treatment was higher than estimated (28%–45% difference). Additionally, a more powerful statistical analysis was used;¹⁶ thus, the study maintained sufficient power to detect differences between the treatment groups.

Wright and Sluka⁵ state that several types of physical therapy are used in the management of painful musculoskeletal disorders and that there seems to be evidence from basic science research to suggest that many of the therapies could have potentially therapeutic effects. However, there appears to be limited high-quality evidence from randomized clinical trials to support these findings. In a study, 44% of the patients thought that they still had cardiac pains 1 year after negative angiographies and 50% reported that they were unable to work because of chest pains.¹⁷ McPartland and Simons¹⁷ state further that ‘patients with known heart disease and non-cardiac chest pains often are difficult to investigate and treat having already the knowledge of a life-threatening disease and anxiety of worsening of it’. In our study, the same physiotherapist, with long experience in cardiac rehabilitation, including treatment of intercostal pain, performed all the treatments in both groups. However, interventions used are well known to most physiotherapists and should be easy to reproduce in many settings. In patients presenting reproducible chest pain by intercostal palpation, it is not always necessary to carry out a detailed cardiological assessment including electrocardiography, exercise testing and cineangiography.¹⁸ As for now, most patients are being told that their chest pain is not of a coronary origin, thereby not life-threatening and that they must learn to live with the pain. However, living with chronic pain is known to reduce quality of life.³ Vigorous massage of the chest combined with injection of Xylocaine into trigger points in the intercostal muscles has been suggested previously, but as far as we know, no randomized controlled trial has investigated the possible effect. Nevertheless, this treatment needs a skilled doctor in order to avoid causing pneumothorax.

At our hospital, intercostal pain has been treated with deep friction massage and heat pack for more than 20 years with good results as to reduce or remove chest pain. Our findings suggest that for patients with persistent pain from the intercostal muscles, deep friction massage and heat pack is a simple, non-invasive, low risk choice and may have

important clinical implications as to prevent chronic chest pain. For clinicians, deep friction massage and heat pack is an easy way of helping the patients.

Patients presenting with chest pain is a common problem to general practitioners and accident- and emergency units, and musculoskeletal causes are common. Despite being a recognized and frequent source of chest pain, musculoskeletal disorders remain poorly understood.¹⁹ No previous trials were found investigating treatment of chest pain from the intercostal muscles, and the present trial shows promising results, although needs to be confirmed in a larger trial. Furthermore, in future research, it would be interesting to see whether patients presenting chest pain of musculoskeletal origin at accident- and emergency units could avoid readmission to hospital with non-cardiac chest pain if they were treated with deep friction massage and heat pack and given some follow-up controls. If successful, this would save the patients from further pain and anxiety and save the health-care system from repeated examinations and expensive hospitalization.

In conclusion, deep friction massage and heat pack treatment reduced pain significantly compared to treatment with heat pack only. The results were persistent 3 months after the intervention period. Our findings suggest that for patients with persistent chest pain from the intercostal muscles, deep friction massage and heat pack is a simple, non-invasive, low risk choice and may have important clinical implications to prevent chronic chest pain.

Acknowledgement

The trial was registered with ClinicalTrials.gov (www.clinicaltrials.gov, NCT 01803529).

Declaration of conflicting interests

There are no conflicts of interest. The sponsor of the trial had no role in the study design, data collection, data analysis, data interpretation and writing of the article or decision to submit for publication.

Funding

Unimed Innovation AS supported the study.

References

1. Jensen S. Musculoskeletal causes of chest pain. *Aust Fam Physician* 2001; 30(9): 834–839.
2. Svavarsdottir AE, Jonasson MR, Gudmundsson GH, et al. Chest pain in family practice. Diagnosis and long-term outcome in a community setting. *Can Fam Physician* 1996; 42: 1122–1128.
3. Gjeilo KH, Klepstad P, Wahba A, et al. Chronic pain after cardiac surgery: a prospective study. *Acta Anaesthesiol Scand* 2010; 54(1): 70–78.
4. Bruce J, Drury N, Poobalan AS, et al. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. *Pain* 2003; 104(1–2): 265–273.
5. Wright A and Sluka KA. Nonpharmacological treatments for musculoskeletal pain. *Clin J Pain* 2001; 17(1): 33–46.

6. Berg A. Physiotherapy in treating intercostal pain [Norwegian]. *Fysioterapeuten* 2001; 8: 11–15.
7. Wewers ME and Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health* 1990; 13(4): 227–236.
8. Grant S, Aitchison T, Henderson E, et al. A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. *Chest* 1999; 116(5): 1208–1217.
9. Dixon T, Lim LL and Oldridge NB. The MacNew heart disease health-related quality of life instrument: reference data for users. *Qual Life Res* 2002; 11(2): 173–183.
10. Ware JE Jr. SF-36 health survey update. *Spine* 2000; 25(24): 3130–3139.
11. Hiller A, Helvik AS, Kaasa S, et al. Psychometric properties of the Norwegian MacNew Heart Disease health-related quality of life inventory. *Eur J Cardiovasc Nurs* 2010; 9(3): 146–152.
12. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011; 7: CD001800.
13. Simons DG, Travell JG and Simons LS. *Travell and Simons Myofascial pain and dysfunction. The trigger point manual, upper half of body*. 2nd ed. Baltimore, MD: Williams & Wilkins, 1999.
14. Simons DG. Cardiology and myofascial trigger points: Janet G. Travell's contribution. *Tex Heart Inst J* 2003; 30(1): 3–7.
15. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996; 27(4): 485–489.
16. Tu YK, Blance A, Clerehugh V, et al. Statistical power for analyses of changes in randomized controlled trials. *J Dent Res* 2005; 84(3): 283–287.
17. McPartland J and Simons D. Myofascial trigger points: translating molecular theory into manual therapy. *J Man Manip Ther* 2006; 14(4): 232–239.
18. Baldry P. Cardiac and non-cardiac chest wall pain. *Acupuncture in Medicine* 1997; 15(2): 83–90.
19. Stochkendahl MJ and Christensen HW. Chest pain in focal musculoskeletal disorders. *Med Clin North Am* 2010; 94(2): 259–273.