Effect of Continuous Compression Stimulation on Pressure-Pain Threshold and Muscle Spasms in Older Adults With Knee Osteoarthritis: A Randomized Trial

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Abstract

Objective: The purpose of this study was to assess the effect of continuous compression stimulation on pressure-pain threshold and muscle spasms in older adults with knee osteoarthritis.

Methods: Thirty-two older adults with knee osteoarthritis on outpatient visits were randomly divided into 2 groups. Those in the treatment group (n = 16) received 5-minute massage therapy (continuous compression stimulation), and those in the control group (n = 16) received sham massage therapy (touch without compression). Immediately before and after single-intervention sessions, the pressure-pain threshold, muscle spasm, and pain were quantified.

Results: The change in pain on walking in the treatment group exceeded 1.9 cm, corresponding to the minimum clinically important difference. In the treatment group, the pressure-pain threshold improved significantly for pain both at rest and while walking, but the improvement in muscle spasm was not significant.

Conclusions: Massage therapy resulted in minimal clinically important changes for pain relief. There was an increase in the pressure-pain threshold in the older adults with knee osteoarthritis. We propose that the improvements in pain may be related to the medial thigh muscle rather than knee osteoarthritis. (J Manipulative Physiol Ther 2018;41:315-322)

Key Indexing Terms: *Massage; Osteoarthritis; Knee; Pain*

Introduction

Osteoarthritis is a painful musculoskeletal disease[1] that results from breakdown of the joint cartilage and underlying bone. It affects an estimated 12.1% of the adult US population[2] and is a leading cause of disability in the elderly.[3] Symptomatic knee osteoarthritis is frequently diagnosed in the clinical setting, and treatment usually targets pain relief, prevention of disability, and improvement of quality of life.

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Cartilage loss, inflammation of the synovial membrane, mechanical stress within the joint, and stiffness of the peri-articular components are believed to cause pain. Muscle condition is one of the peri-articular components that has been targeted in massage therapy. Perlman et al reported the effect of massage therapy on pain relief in patients with knee osteoarthritis.[4,5] In addition, several studies have been performed to examine whether knee pain can be improved by acupressure and/or ischemic compression toward lower-extremity muscle.[6-10] One of the reasons for addressing these non-drug therapies is that these therapies are safer than drug therapies and have fewer side effects. However, the mechanism underlying the pain relief induced by massage therapy remains unclear. Understanding this mechanism would help in customizing massage therapy for each patient.

Recent studies have revealed that patients with knee osteoarthritis may have both peripheral and central sensitization of pain mechanisms, resulting in the spread of hyperalgesia.[11] Pain sensitization occurs in patients with knee osteoarthritis and may be associated with the severity of knee osteoarthritis symptoms.[12] A lower pressure-pain threshold, which is a sign of sensitization, has been observed in patients with osteoarthritis compared with healthy controls.[13] Lower pressure-pain thresholds have also been correlated with higher pain intensity, higher disability scores, and poorer quality of life.[14] These data suggest that an improvement in the pressure-pain threshold may partially relieve the pain in knee osteoarthritis. Other evidence indicates that massage therapy can improve the pressure-pain threshold[15-17] and muscle spasms.[18,19] However, this threshold has not been studied as a key factor in understanding the mechanism of pain relief in trials for patients with knee osteoarthritis.[4-10]

The purpose of this study was to test the hypothesis that an increase in the pressure-pain threshold and a decrease in muscle spasms induced by massage therapy can mediate pain relief in patients with knee osteoarthritis. Validating this hypothesis would help us to understand the mechanism(s) underlying pain relief induced by massage therapy.

Methods

Trial Design

In this randomized controlled trial, the treatment group received massage therapy and the control group received sham treatment. The allocation ratio was 1:1. This study was approved by the ethics committees of both Saiseikai Kure Hospital (No. 87) and Hiroshima International University (No. 13-100). All patients provided written informed consent after receiving complete information about the study objectives and content. The registration number of this trial is UMIN000022947.

Participants

Participants were outpatients who visited the Saiseikai Kure Hospital in Japan. The inclusion criteria were as follows: a positive diagnosis of knee osteoarthritis by an orthopedist based on plain radiography, knee pain either at rest or while walking, and age ≥50 years. The exclusion criteria were as follows: definitive neurological disorders, inability to respond to the questions unaided because of cognitive impairment (eg, dementia), and the presence of skin disease (eg, contact dermatitis). Because the change in pain derived from the peri-articular muscle condition was the focus of the present study, we did not investigate in detail whether the patient had an intra-articular prosthesis. At baseline, age, height, weight, severity of osteoarthritis (Kellgren-Lawrence grade), and comorbidities (diabetes and hypertension) were recorded.

Interventions

To evaluate the immediate effect of massage therapy, intervention was limited to 1 session. The second author (T.U.) took charge of therapeutic intervention, and the third author (Y.K.) measured outcomes. In both the treatment and control groups, intervention was performed on the anterior and distal portion of the medial thigh (Fig 1). The reasons for this were as follows: tenderness and pain were noted in this area while walking[20]; the location was easily accessible

Fig 1. *Continuous compression stimulation performed on the anterior and distal portion of the medial thigh. This photograph depicts application of stimulation at the right thigh.*

during massage therapy; and knee pain subsided on massaging this area according to our clinical experience. If the participants had undergone surgery in the past (eg, total knee arthroplasty), intervention was performed on the non-operated knee. If participants experienced pain in both knees and had not undergone any knee surgery, the more painful site was selected as the intervention target. We chose the continuous compression stimulation massage type, because the amount of compression stimulation applied could be converted into numerical values. To quantify the amount of compression stimulation applied, a manual load was provided via a hand-held dynamometer (Microfet2, Orsay, France).

In the treatment group, the participants maintained a lateral posture, with the knee pointing down. The therapist stood near the treatment bed and approached the participants from behind. The therapist applied continuous compression load at the target area with his hand. During treatment, the therapist used his body weight by keeping the elbow in extension. The compression stress was increased gradually and stopped just before the patient experienced pain. Based on the degree of compression stress at this time, the pressure for massage for each patient was determined. The therapist monitored regularly to maintain the degree of compression load as high as possible. The duration of continuous compression was 5 minutes.

In the control group, the therapist placed a handheld dynamometer over the surface of the target area only and did not subject the patient to any compression (the force was almost 0).

Outcomes

The primary outcomes in this study included the pressure-pain threshold, muscle spasm, and pain at both rest and on walking. These were measured immediately before and after intervention. The secondary outcome was the general rating of change.

The pressure-pain threshold was measured using an algometer (NEUTONE Hi-Precision Algometer TAM-1, TRY-ALL Corp, Chiba, Japan). The algometer was positioned vertically to the anterior and distal portion of the medial thigh of the participants, and a load was gradually applied. Pressure was recorded when the participants felt pain induced by the load. The reliability of the algometer had been validated in our preliminary experiment, and the intraclass correlation coefficient was 0.94 (n = 16 in healthy younger people).

Muscle spasm was measured using a muscle hardness tester (NEUTONE Muscle Hardness Tester TDM-Z1 (RB), TRY-ALL Corp). Muscle hardness measurement was performed on the anterior and distal portion of the medial thigh, the same area in which intervention and measurement of the pressure-pain threshold was performed. The reliability of the tester had been validated in our preliminary experiment, and the intraclass correlation coefficient was 0.94 (n = 16 in healthy younger people).

Pain was measured using a 10-cm visual analogue scale (VAS, 0 = no pain; 10 = unbearable pain). Participants rated the degree of pain both at rest and while walking. The general rating of change was assessed using a 15-point Likert scale.[21] The scale ranged from −7 (“a very great deal worse”) to +7 (“a very great deal better”). In this study, a rating ≥+3 signified excellent results from the intervention. The participants rated the general rating of change after evaluating pain while walking.

Sample Size

The required sample size was calculated using EZR 1.30.[22] Previous knee osteoarthritis trials[23,24] had revealed that pain reduction of 1.75 to 1.9 cm on the VAS is recommended as the minimum clinically important difference. With 11 participants, the study had 80% power to detect a difference in pain reduction of 1.9 cm between pre-intervention and post-intervention, assuming a standard deviation of 1.9 cm at a significance level of 5%. Patient numbers were increased to >15 per group to accommodate for dropouts.

Randomization and Blinding

To generate the random allocation sequence, the first author (R.T.) generated random numbers using Excel 2010 (Microsoft, Redmond, Washington). At that time, the restriction of randomization, such as blocking and block size, was not considered in detail. The random allocation sequence was revealed to the therapist, but not to the participants and the assessor. The second author enrolled participants and assigned participants to the different interventions. Although the therapist knew which participant was allocated to the treatment or control group, the participants and the assessor were blinded after assignment to each intervention such that they were unable to discriminate whether individual participants had or had not received the treatment. The intervention settings were the same for the 2 groups.

Statistical Methods

Data were subjected to an intention-to-treat analysis, accounting for those who did not complete the study. The distribution of patients with respect to sex and osteoarthritis grades was compared between the groups using the χ^2 test. Baseline values for the pressure-pain threshold, muscle spasm, and pain were compared between the groups using Student’s t test. A 2-way analysis of variance with time as the repeated factor was used to compare the effects of group (treatment and control) and time (pre-intervention and post-intervention). When interactions were detected, post hoc analyses using Bonferroni adjustment were performed. Statistical significance was set at $P < .05$.

Correlation analysis was performed to understand the relationships between measured outcomes. Path analysis was used to validate the model of pain relief caused by the change in the pressure-pain threshold and muscle spasm. The goodness-of-fit of models was compared between groups by using statistical parameters such as the χ^2 value, goodness-of-fit index (GFI), adjusted GFI (AGFI), comparative fit index (CFI), and root-mean-square error of approximation (RMSEA). A low χ^2 value relative to the degrees of freedom with an insignificant P value ($P > .05$), GFI >0.95, AGFI >0.95, CFI >0.95, or RMSEA <0.06 indicated good model fit.[25]

Results

Figure 2 is the flow diagram for this study. We started the recruitment process in November 2013 and ended in August 2014 until patient numbers exceeded 15 per group. Thirty-two participants completed this study. For each group, there were no losses or exclusions after randomization.

Table 1 outlines the baseline information for the 2 groups. For each group, the number of participants included in each analysis was determined, and the analysis was conducted according to the original assigned groups. There were no significant differences in age, sex distribution, body height, body weight, osteoarthritis grade distribution, total knee arthroplasty, side of involvement, or side of intervention between the 2 groups ($P > .05$). Significant harm or unintended effects were reported by patients in both groups.

Table 2 outlines the compression force exerted on participants in the treatment group. Although there was a variation, >5 N was manually loaded by the therapist toward the anterior and distal portion of the medial thigh.

Table 3 provides descriptive data on the pressure-pain threshold, muscle spasm, and pain both at rest and while walking before and after intervention. There were no significant intergroup differences in any of the measured variables in the pre-intervention stage. Both groups exhibited significant improvement in post-intervention

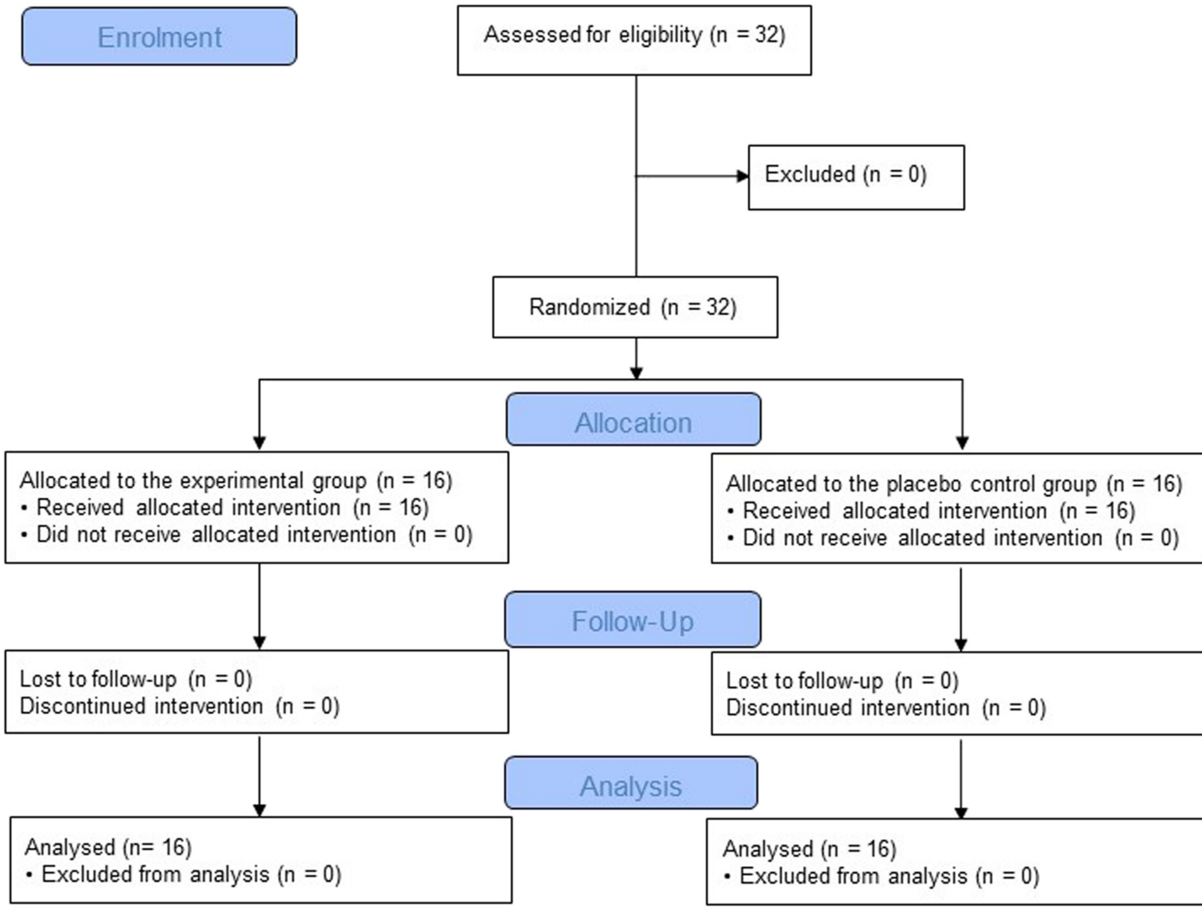

Fig 2. *Flow diagram.*

scores over pre-intervention scores, except for the variable pain at rest. The 2-way analysis of variance revealed no significant time-by-intervention interaction for any of the measured variables ($P > .05$).

In Table 4 are the results for general rating of change. Results of the χ^2 test indicated that the number of participants who gave excellent ratings was significantly higher in the treatment group than in the control group ($P < .05$).

Table 5 outlines the results of correlation analysis. In the treatment group, pain relief was moderately correlated with an increase in the pressure-pain threshold, but not in muscle spasm. In the control group, pain relief was not significantly correlated with either an increase in the pressure-pain threshold or the degree of muscle spasm.

The results of the path analyses are summarized in Table 6 and illustrated in Figure 3. The χ^2 values could not be calculated in the initial models. When the path from muscle spasm to pain on walking and covariance between muscle spasm and pressure-pain threshold were deleted, this problem could be eliminated. In the treatment group, the χ^2 values were not significant, and the GFIs were high, implying that the model was validated (GFI = 0.997, AGFI = 0.986, CFI = 1.000, RMSEA = 0.000). The pressure-pain threshold had a significant impact on pain both at rest and while walking, but the path coefficient of muscle spasm to pain was not significant. However, in the control group, all indices related to the goodness-of-fit indicated poor fitness of the model toward the data (GFI = 0.820, AGFI = 0.102, CFI = 0.408, RMSEA = 0.470). Unlike in the treatment group, the significance of the correlation of the pressure-pain threshold to pain could not be confirmed in the control group.

Discussion

In the current study, the pressure-pain threshold, muscle spasm, and pain both at rest and while walking in patients with knee osteoarthritis were investigated immediately before and after continuous compression stimulation. Although all measured variables exhibited improvement in the treatment group, no significant differences could be detected when compared with the control group. However, the extent of impact of the pressure-pain threshold on pain differed between groups, and a significant causal relationship was confirmed only in the treatment group. The change in muscle spasm did not significantly influence pain relief in the treatment group.

Table 1. *Baseline Information*

Characteristics	Treatment Group	Control Group	*P*
Age, y	80.8 ± 9.7	81.3 ± 6.3	.85
Gender, female	16 (100%)	13 (81.3%)	.06
Height (cm)	146.5 ± 8.3	150.9 ± 8.7	.15
Weight (kg)	51.3 ± 11.4	57.2 ± 8.9	.11
Kellgren-Lawrence grade			.13
1	1	0	
2	6	2	
3	5	7	
4	4	7	
Total knee arthroplasty	4 (26.7%)	5 (31.3%)	.50
Diabetes	6 (37.5%)	2 (12.5%)	.11
Hypertension	10 (62.5%)	8 (50%)	.36
Affected side			.50
Right	1	2	
Left	3	2	
Both	12	12	

Table 2. *Compression Force Exerted on Participants in the Treatment Group*

Force (N)	Number
5-10	1
10-15	0
15-20	1
20-25	3
25-30	2
30-35	3
35-40	3
40-45	1
45-50	0
50-55	1
55-60	1

Placebos are known to have the greatest effect on continuous subjective outcomes.[26] Placebo effects are common in knee osteoarthritis; reported improvements with sham intervention range from 16% to 40%.[27-30] Tubach et al reported that the minimum clinically important differences for absolute and relative changes were –19.9 mm and –40.8%, respectively, for knee osteoarthritis.[24] In our study, the observed improvement in pain while walking in the treatment group was >40% compared with the baseline, and the absolute value was larger than that in the control group, which was higher than the minimum clinically important differences recommended.[24] Moreover, the general rating of change in the treatment group was higher than that in the control group. On the basis of the above results, this study found that the continuous compression stimulation used in this study was equal to or better than the placebo treatment at relieving pain in patients with knee osteoarthritis while walking. Such massage therapy could be helpful in patients with knee osteoarthritis.

Patients with painful knee osteoarthritis also experience sensitization.[11] In several studies, it has been reported that the pressure-pain threshold was lower in osteoarthritis patients than in healthy individuals[13,14,31] and may be associated with knee osteoarthritis symptom severity.[12,14] Other studies have reported on the effect of massage therapy on the pressure-pain threshold and pain.[17-19] However, these studies[17-19] did not include patients with knee osteoarthritis. Previous trials have examined the effect of massage therapy, including acupressure, on pain in patients with knee osteoarthritis, but have not addressed the pressure-pain threshold.[6-10] To the best of our knowledge, a causal relationship between a change in the pressure-pain threshold induced by massage therapy and pain relief has not been validated, and the mechanism underlying the beneficial effects of massage therapy in patients with knee osteoarthritis remains unknown. Our results indicated not only the significant effect of continuous compression stimulation on the pressure-pain threshold and pain relief, but also its causal relationship in the treatment group. These findings may help us to understand the mechanism underlying the pain relief induced by massage therapy. Usually, repeated stimulation causes most sensory organs to become fatigued and less responsive.[32] Such "acclimatization" may have occurred in our study and may have increased the pressure-pain threshold, thereby causing pain relief.

Previous studies have found that pain in patients with knee osteoarthritis may be associated with generalized pain sensitization rather than peripheral inflammation and injury.[11,13,33] In addition to knee osteoarthritis, there are other musculoskeletal diseases that may decrease the pressure-pain threshold. For example, in tension-type headache or migraine, the pressure-pain threshold has been reported to be generally lower in patients than in healthy individuals.[34] Individuals with chronic nonspecific lower back pain have lower pressure-pain threshold values than healthy individuals.[35] Peripheral sensitization manifests consistently in those with musculoskeletal shoulder pathology.[36] Our findings may be applicable to the treatment of patients with these musculoskeletal diseases.

Limitations

First, it was difficult to establish that the groups were entirely similar at baseline. Specifically, the value of the pressure-pain threshold and pain while walking in the experimental group was worse than that in the control group, the differences being 3.7 and 17 mm, respectively, between groups. This was an error, but the source of this error may be the small sample size used. The effect of continuous compression stimulation on the pressure-pain threshold or pain may be limited for people with certain types of severe symptomatic knee osteoarthritis. Second, our results include

Table 3. *Descriptive Data on the Pressure-Pain Threshold, Muscle Spasm, and Pain*

Outcome	Pre-intervention	Post-intervention	Change Score (Rate)	P [a]
Treatment Group				
Pressure-pain threshold (N)	20.4 ± 7.9	24.5 ± 10.4 [b]	4.0 ± 4.3 (19.6%)	>.05
Muscle spasm (N)	0.75 ± 0.13	0.61 ± 0.12 [b]	–0.14 ± 0.11 (18.7%)	>.05
Pain at rest (cm)	2.8 ± 2.4	1.2 ± 1.2 [b]	–1.6 ± 2.2 (57.1%)	>.05
Pain on walking (cm)	4.7 ± 2.3	2.6 ± 1.9 [b]	–2.1 ± 1.9 (44.7%)	>.05
Control Group				
Pressure-pain threshold (N)	24.1 ± 7.9	27.9 ± 11.1 [b]	3.8 ± 5.5 (15.8%)	>.05
Muscle spasm (N)	0.73 ± 0.13	0.66 ± 0.11 [b]	–0.08 ± 0.14 (11.0%)	>.05
Pain at rest (cm)	1.0 ± 1.2	0.5 ± 0.4	–0.5 ± 1.0 (50.0%)	>.05
Pain on walking (cm)	3.0 ± 2.0	2.2 ± 1.2 [b]	–0.8 ± 1.5 (26.7%)	>.05

Pressure-pain threshold was measured using an algometer. Muscle spasm was measured using a muscle hardness tester. Pain at rest and at walking was measured using a 10-cm visual analogue scale.

[a] A 2-way analysis of variance with time as the repeated factor.

[b] A significant difference between pre-intervention and post-intervention ($P < .05$).

Table 4. *Results of General Rating of Change*

	General Rating of Change	
	<3	≥3
Treatment group	9	7
Control group	15	1

Table 5. *Results of Correlation Analysis*

	Pressure-Pain Threshold	Muscle Spasm	Pain at Rest
Treatment Group			
Muscle spasm	–0.068	–	–
Pain at rest	–0.457	–0.359	–
Pain on walking	–0.640 [a]	–0.103	0.627 [a]
Control Group			
Muscle spasm	–0.233	–	–
Pain at rest	–0.124	–0.053	–
Pain on walking	–0.009	0.417	0.646 [a]

[a] $P < .01$.

some bias; allocation was not concealed, and the therapists were not blinded. Additionally, it is likely that the patients in the control groups were not blinded because of the awareness related to the massage itself by their common knowledge and previous experience with "massage." As it was unknown to what extent these biases influenced our results, the effect size on the pressure-pain threshold and pain improvement by continuous compression stimulation should be considered with caution. The third limitation was the length of intervention. Our study tested only the immediate effect of massage; the effects of long-term intervention were not examined. If long-term intervention was performed, other factors might mediate the effect of massage (eg, psychological factors).[37] In addition, some researchers have indicated that the increased blood circulation to the muscles—which promotes gas exchange, delivery of nutrients, and removal of waste products—is the primary factor in pain relief induced by massage.[38-41] Future studies are needed to measure and control this factor to understand the mechanism of pain relief induced by massage in patients with knee osteoarthritis. The fourth limitation was the characteristics of the participants. The participants were older, with a mean age of 80 to 81 years. Our results may not be generalizable to patients with common knee osteoarthritis in other age groups. Clinicians should take note that our findings may not be applicable to younger populations. The final limitation was the range of effect. As functional outcome measures were not used, the effects of massage on functional ability are unknown. To examine the functional change after massage, outcome measures such as the Lower Extremity Functional Scale,[42] the McMaster Universities' Osteoarthritis Index,[43] or the short measure developed using the Knee Injury and Osteoarthritis Outcome Score[44] should be used in a future trial.

Table 6. *Goodness-of-Fit of Models*

	df	χ^2	*P*	GFI	AGFI	CFI	RMSEA
Treatment group	2	0.084	.959	0.997	0.986	1.000	0.000
Control group	2	8.637	.013	0.820	0.102	0.408	0.470

AGFI, adjusted goodness-of-fit index; *CFI*, comparative fit index; *df*, degrees of freedom; *GFI,* goodness-of-fit index; *RMSEA,* root-mean-square error of approximation.

Conclusion

In this study, massage therapy resulted in minimal clinically important changes for pain relief. There was an increase in the pressure-pain threshold in older adults with knee osteoarthritis. We propose that the improvements in pain may be related to the medial thigh muscle rather than knee osteoarthritis.

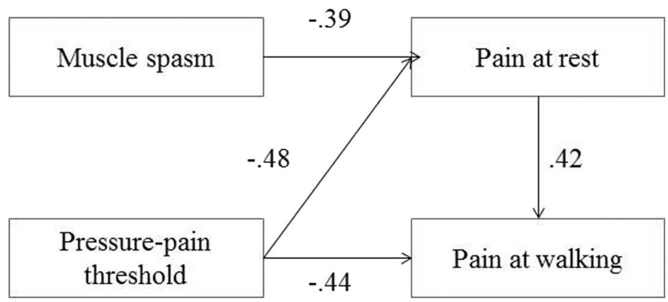

Fig 3. *Path coefficient in the treatment group.*

Funding Sources and Conflicts of Interest

No funding sources or conflicts of interest were reported for this study.

Contributorship Information

Concept development (provided idea for the research): R.T.
Design (planned the methods to generate the results): R.T.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): R.T.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): T.U., Y.K., T.S.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): R.T.
Literature search (performed the literature search): R.T.
Writing (responsible for writing a substantive part of the manuscript): R.T.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): R.T.

Practical Applications

- Knee pain in the elderly with knee osteoarthritis may be derived from muscle condition around the knee joint.
- Pain relief can be addressed by a simple 5-minute continuous compression stimulation performed on the anterior and distal portion of the medial thigh.
- Continuous compression stimulation relieves pain at rest and on walking.
- Improvement of muscle spasm does not correlate with the pressure-pain threshold.

References

1. Sharma L, Kapoor D, Issa S. Epidemiology of osteoarthritis: an update. *Curr Opin Rheumatol.* 2006;18(2):147-156.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008;58(1):26-35.
3. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. *Am J Phys Med Rehabil/Assoc Acad Phys.* 2006;85(11 Suppl):S2-S11 quiz S2-S4.
4. Perlman AI, Sabina A, Williams AL, Njike VY, Katz DL. Massage therapy for osteoarthritis of the knee: a randomized controlled trial. *Arch Intern Med.* 2006;166(22):2533-2538.
5. Perlman AI, Ali A, Njike VY, et al. Massage therapy for osteoarthritis of the knee: a randomized dose-finding trial. *PLoS One.* 2012;7(2)e30248.
6. Li LW, Harris RE, Murphy SL, Tsodikov A, Struble L. Feasibility of a randomized controlled trial of self-administered acupressure for symptom management in older adults with knee osteoarthritis. *J Altern Complement Med.* 2016;22(5):396-403.
7. Sorour AS, Ayoub AS, Abd El Aziz EM. Effectiveness of acupressure versus isometric exercise on pain, stiffness, and physical function in knee osteoarthritis female patients. *J Adv Res.* 2014;5(2):193-200.
8. Chiranthanut N, Hanprasertpong N, Teekachunhatean S. Thai massage, and Thai herbal compress versus oral ibuprofen in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *Biomed Res Int.* 2014;2014:490512.
9. Horng HC, Kuo CP, Cherng CH, et al. The effects of collateral meridian therapy for knee osteoarthritis pain management: a pilot study. *J Manipulative Physiol Ther.* 2013;36(1):51-56.
10. Zhang Y, Shen CL, Peck K, et al. Training self-administered acupressure exercise among postmenopausal women with osteoarthritic knee pain: a feasibility study and lessons learned. *Evid Based Complement Alternat Med.* 2012;2012:570431.
11. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain.* 2010;149(3):573-581.
12. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthr Cartil.* 2015;23(7):1043-1056.
13. Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis Rheum.* 2012;64(9):2907-2916.
14. Imamura M, Imamura ST, Kaziyama HH, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. *Arthritis Rheum.* 2008;59(10):1424-1431.

15. Buttagat V, Eungpinichpong W, Chatchawan U, Arayawichanon P. Therapeutic effects of traditional Thai massage on pain, muscle tension and anxiety in patients with scapulocostal syndrome: a randomized single-blinded pilot study. *J Bodyw Mov Ther.* 2012;16(1):57-63.
16. Gay CW, Alappattu MJ, Coronado RA, Horn ME, Bishop MD. Effect of a single session of muscle-biased therapy on pain sensitivity: a systematic review and meta-analysis of randomized controlled trials. *J Pain Res.* 2013;6:7-22.
17. Chatchawan U, Eungpinichpong W, Sooktho S, Tiamkao S, Yamauchi J. Effects of Thai traditional massage on pressure pain threshold and headache intensity in patients with chronic tension-type and migraine headaches. *J Altern Complement Med.* 2014;20(6):486-492.
18. Gatlin CG, Schulmeister L. When medication is not enough: nonpharmacologic management of pain. *Clin J Oncol Nurs.* 2007;11(5):699-704.
19. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. *J Pain Symptom Manag.* 2004;28(3):244-249.
20. Ikeuchi M, Izumi M, Aso K, Sugimura N, Tani T. Clinical characteristics of pain originating from intra-articular structures of the knee joint in patients with medial knee osteoarthritis. *Springerplus.* 2013;2:628.
21. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials.* 1989;10(4):407-415.
22. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* 2013;48(3):452-458.
23. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials. III. Setting the delta for clinical trials–results of a consensus development (Delphi) exercise. *J Rheumatol.* 1992;19(3):451-457.
24. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis.* 2005;64(1):29-33.
25. Hooper D, Coughlan J, Mullen M. Structural equation modelling: guidelines for determining model fit. *J Bus Res Methods*. 2008;6(1):53-60.
26. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med.* 2001;344(21):1594-1602.
27. Hassan BS, Doherty SA, Mockett S, Doherty M. Effect of pain reduction on postural sway, proprioception, and quadriceps strength in subjects with knee osteoarthritis. *Ann Rheum Dis.* 2002;61(5):422-428.
28. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med.* 2002;347(2):81-88.
29. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. *Ann Intern Med.* 2000;132(3):173-181.
30. Hughes R, Carr A. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatology.* 2002;41(3):279-284.
31. Kuni B, Wang H, Rickert M, Ewerbeck V, Schiltenwolf M. Pain threshold correlates with functional scores in osteoarthritis patients. *Acta Orthop.* 2015;86:215-219.
32. Bonica J. Applied anatomy relevant to pain. In: Bonica JJ, ed. *The Management of Pain*. Philadelphia: Lea & Febiger; 1990:133-158.
33. Suokas AK, Walsh DA, McWilliams DF, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthr Cartil.* 2012;20(10):1075-1085.
34. Andersen S, Petersen MW, Svendsen AS, Gazerani P. Pressure pain thresholds assessed over temporalis, masseter, and frontalis muscles in healthy individuals, patients with tension-type headache, and those with migraine–a systematic review. *Pain.* 2015;156(8):1409-1423.
35. Imamura M, Chen J, Matsubayashi SR, et al. Changes in pressure pain threshold in patients with chronic nonspecific low back pain. *Spine.* 2013;38(24):2098-2107.
36. Borstad J, Woeste C. The role of sensitization in musculoskeletal shoulder pain. *Braz J Phys Ther.* 2015;19(4):251-256.
37. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther.* 2009;14(5):531-538.
38. Kirby BS, Carlson RE, Markwald RR, Voyles WF, Dinenno FA. Mechanical influences on skeletal muscle vascular tone in humans: insight into contraction-induced rapid vasodilatation. *J Physiol.* 2007;583(Pt 3):861-874.
39. Sefton JM, Yarar C, Berry JW, Pascoe DD. Therapeutic massage of the neck and shoulders produces changes in peripheral blood flow when assessed with dynamic infrared thermography. *J Altern Complement Med.* 2010;16(7):723-732.
40. Cambron JA, Dexheimer J, Coe P, Swenson R. Side-effects of massage therapy: a cross-sectional study of 100 clients. *J Altern Complement Med.* 2007;13(8):793-796.
41. Nayak S, Matheis RJ, Agostinelli S, Shifleft SC. The use of complementary and alternative therapies for chronic pain following spinal cord injury: a pilot survey. *J Spinal Cord Med.* 2001;24(1):54-62.
42. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. *Phys Ther.* 1999;79(4):371-383.
43. Bellamy N. *WOMAC Osteoarthritis Index User Guide. Version V*. Brisbane, Australia: The University of Queensland; 2002.
44. Perruccio AV, Stefan Lohmander L, Canizares M, et al. The development of a short measure of physical function for knee OA KOOS-Physical Function Shortform (KOOS-PS) - an OARSI/OMERACT initiative. *Osteoarthr Cartil.* 2008;16(5):542-550.