Course Instructions

NOTE: The following two pages contain a preview of the final exam. The final exam is identical to the final exam that your will take online **after you purchase the course.**

After you purchase the course online, you will be taken to a receipt page online which will have a link to take the final exam. You will then click on this link to begin taking the exam. The link will also be emailed to you.

3 Easy Step to Complete the Course:

1.) **Read the Course Below**

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Massage Techniques for Specific Areas – Final Exam

1. With its popularity in pain relief, massage therapy has become a widely accepted treatment for neck and shoulder pain.

a. True
b. False

2. According to *Massage Therapy for Neck and Shoulder Pain, Figure 1*, the study selection process included 18 _____________:

a. abstracts screened
b. duplicate publications
c. major methodological flaws
d. full articles screened

3. Regarding *Massage Therapy for Neck and Shoulder Pain, 4.1. Limitations of the Review*, there were __________limitations in their review:

a. no
b. several
c. three
d. many

4. With respect to *Massage Therapy for Osteoarthritis of the Knee, Results*, WOMAC Global scores improved significantly (24.0 points, 95% CI ranged from 15.3–32.7) in the 60-minute massage groups compared to Usual Care (6.3 points, 95% CI 0.1–12.8) at the primary endpoint of 8-weeks.

a. True
b. False

5. Considering *Massage Therapy for Osteoarthritis, Participants*, eligible patients were _______________ with radiographically established OA of the knee:

a. women
b. men and women
c. children
d. men

6. As per Figure 1, *Participant Flow Diagram*, participants were analyzed at:

a. 8 weeks
b. 16 weeks
c. 24 weeks
d. all of the above

7. As per Table 1, *30- and 60-Minute Massage Protocols*, in a 30 minute protocol, 8 – 12 minutes were allocated to:

a. lower limbs
b. upper body
c. both a and b
d. none of the above

8. Considering *Comparative Effects of Acupressure*, chronic neck pain is a very common symptom, especially in males.

a. True
b. False

9. With regards to Comparative *Effects of Acupressure, 2.1 Subjects*, the subjects were randomly allocated to ______ groups:

a. three
b. two
c. four
d. none of the above

10. The study results demonstrated that acupressure on the local and the distal acupuncture points significantly reduced various parameters of the pain-associated conditions.

a. True
b. False

Section 3:
Massage Techniques for Specific Areas
(4 CE credits)

- *Massage Therapy for Neck and Shoulder Pain: A Systematic Review and Meta-Analysis*

- *Massage Therapy for Osteoarthritis of the Knee: A Randomized Dose-Finding Trial*

- *Comparative Effects of Acupressure at Local and Distal Acupuncture Points on Pain Conditions and Autonomic Function in Females with Chronic Neck Pain*

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Review Article

Massage Therapy for Neck and Shoulder Pain: A Systematic Review and Meta-Analysis

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Objective. To evaluate the effectiveness of massage therapy (MT) for neck and shoulder pain. *Methods.* Seven English and Chinese databases were searched until December 2011 for randomized controlled trials (RCTs) of MT for neck and shoulder pain. The methodological quality of RCTs was assessed based on PEDro scale. The meta-analyses of MT for neck and shoulder pain were performed. *Results.* Twelve high-quality studies were included. In immediate effects, the meta-analyses showed significant effects of MT for neck pain (standardised mean difference, SMD, 1.79; 95% confidence intervals, CI, 1.01 to 2.57; $P < 0.00001$) and shoulder pain (SMD, 1.50; 95% CI, 0.55 to 2.45; $P = 0.002$) versus inactive therapies. And MT showed short-term effects for shoulder pain (SMD, 1.51; 95% CI, 0.53 to 2.49; $P = 0.003$). But MT did not show better effects for neck pain (SMD, 0.13; 95% CI, −0.38 to 0.63; $P = 0.63$) or shoulder pain (SMD, 0.88; 95% CI, −0.74 to 2.51; $P = 0.29$) than active therapies. In addition, functional status of the shoulder was not significantly affected by MT. *Conclusion.* MT may provide immediate effects for neck and shoulder pain. However, MT does not show better effects on pain than other active therapies. No evidence suggests that MT is effective in functional status.

1. Introduction

Massage therapy (MT), as one of the complementary and alternative treatments, is defined as a therapeutic manipulation using the hands or a mechanical device, which includes numerous specific and general techniques that are often used in sequence, such as effleurage (stroking), petrissage (kneading), and percussion [1]. It may be the earliest and most primitive tool to improve pain. The most ancient references to the use of massage come from China (around 2700 BC). With the popularity of MT in the world, common types of MT include Swedish massage, Shiatsu, Rolfing, reflexology, myofascial release, and craniosacral therapy.

With its popularity in pain relief, MT has become a widely accepted treatment for neck and shoulder pain. There are, however, inconsistent conclusions on effects of MT for neck and shoulder pain. Most prior reviews maintained that there was inconclusive evidence on effects of MT for neck and shoulder pain [2–4]. Others suggested that MT is effective for neck and shoulder pain [5, 6]. But in prior reviews, MT usually was viewed as an adjunctive therapy to prepare for mobilization, spinal manipulation, or other interventions. In addition, it was rarely employed as the main treatment method. Consequently, it is difficult to draw accurate conclusions regarding the effectiveness of MT when multiple treatments are involved. What is more, most of these reviews were outdated.

Therefore, we performed an updated systematic review of all currently available data that included English and Chinese publications and conducted quantitative meta-analyses of MT on pain and functional status of patients with neck and shoulder pain to determine whether MT is a viable complementary and alternative treatment for neck and shoulder pain.

2. Methods

2.1. Search. We performed comprehensive computerized searches of the medical literature in 7 databases and reference lists through December 2011. English databases included PubMed, EMBASE, OVID-MEDLINE, and SPRINGLINK, and Chinese databases included China Knowledge Resource Integrated Database (CNKI), Weipu Database for Chinese Technical Periodicals (VIP), and Wan Fang Data. The main search terms were massage, manual therapy, Tuina, neck pain, neck disorders, cervical vertebrae, shoulder pain, and trapezius muscle. No restrictions on publication status were imposed. In addition, we performed hand searches at the library of Shanghai University of Traditional Chinese Medicine.

2.2. Study Selection. Randomized controlled trials (RCTs) of MT for patients with neck and/or shoulder pain were included. There were no limitations on the participant's age, gender, or nationality. The focused intervention was MT using the hands or mechanical devices. The control intervention included placebo, a wait list control, no treatment, standard care, and any active treatments not related to MT. The main outcomes of interest were pain and functional status. We did not set any restriction on the type of tool used in the studies to measure these outcomes as there were no universally accepted tools available. We found various validated tools for these outcomes in different countries. The effects of MT included immediate effects (immediately after treatments: up to one day) and followup effects (short-term followup: between one day and three months, intermediate-term followup: between three months and one year, and long-term followup: one year and beyond).

Trials were excluded if any of the following were identified: (1) if neck and/or shoulder pain was caused by fractures, tumors, infections, rheumatoid arthritis, and so forth; (2) if MT was combined with other manual therapies including spinal manipulation, mobilization, chiropractic, and; (3) if controlled interventions also contained MT, since it would be impossible to evaluate the specific effect of MT; and (4) if the language was neither English nor Chinese.

2.3. Data Abstraction. Two reviewers extracted data independently according to predefined criteria including the first author, the original country of the study, year of the study, pain location, pain duration, the sample size, the mean age of participants, the duration of treatments, the followup time, main outcome assessments, the intervention of experimental and control group, and main conclusion (mean improvement on pain). Any discrepancies were discussed until the authors reached consensus.

2.4. Methodological Quality Assessment. The methodological quality of RCTs was assessed independently by two reviewers based on PEDro scale, which is based on the Delphi list and has been reported to have a fair-to-good reliability for RCTs of the physiotherapy in systematic reviews. This scale consists of 11 criteria: (1) study eligibility criteria specified, (2) random allocation of subjects, (3) concealed allocation, (4) measure of similarity between groups at baseline, (5) subject blinding, (6) therapist blinding, (7) assessor blinding, (8) less than 15% dropouts, (9) intention-to-treat analysis, (10) between-group statistical comparisons, and (11) point measures and variability data. Criteria (2)–(11) were used to calculate the PEDro score. Each criterion was scored as either 1 or 0 according to whether the criteria was met or not, respectively. The scores are summed, and a higher score represents a better methodological quality. A cut point of 6 on the PEDro scale was used to indicate high-quality studies as this has been reported to be sufficient to determine high quality versus low quality in previous studies [7]. If additional data or clarification was necessary, we contacted the study authors. And disagreements were resolved by discussions among the reviewers.

2.5. Data Synthesis and Analysis. The mean change in outcomes between the end of final intervention and the baseline was used to assess the difference between experimental group and control group in the meta-analyses. Standardised mean difference (SMD) was used because the studies included in meta-analyses assessed the outcome based on different scales (e.g., VAS 0–10 and VAS 0–100). And the SMD and 95% confidence intervals (CI) were calculated in the meta-analyses. For studies with insufficient information, the reviewers contacted the primary authors to acquire and verify the data when possible. In studies that involved more than one control group, the reviewers restricted our analyses to MT and each control group. In order to get more accurate heterogeneity we used random effects model employing variation factors among studies as correction weight. The I^2 was used to assess statistical heterogeneity. The reviewers determined that heterogeneity was high when the I^2 was above 75%. The Review Manager 5.0 was used for the meta-analyses.

3. Results

3.1. Study Selection. We identified 865 abstracts from 7 English and Chinese databases. After initially screening 108 potentially relevant abstracts, we excluded 90 because they did not meet the inclusion criteria (e.g., systematic reviews, commentary, case report, technical report, not MT as a stand-alone treatment, participants were healthy, using psychosocial or biochemical outcome measures, and not in English or Chinese). We retrieved and reviewed 18 full articles. 12 RCTs [8–19] were eligible, including 10 English articles and 2 Chinese. In excluded studies, the trials were excluded due to duplicate publications ($n = 1$), major methodological flaws ($n = 2$), and insufficient data ($n = 3$). Two RCTs were excluded from meta-analyses due to unsuitable main outcomes [15, 17]. The study selection process is summarized in Figure 1.

3.2. Study Characteristics. Twelve eligible studies included 757 subjects with mean age of 42.3 ± 16.4, which, respectively, were conducted in US, Germany, Australia, UK, Spain, China,

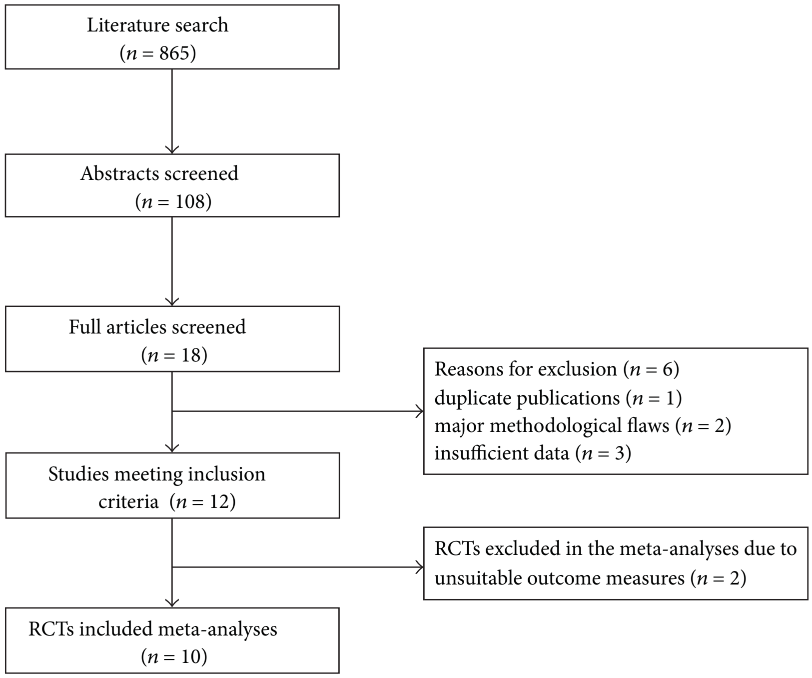


Figure 1: Study selection process. RCTs: randomized controlled trials.

Thailand, and HongKong between 2001 and 2011. The disease duration ranged from 4 weeks to 10.4 years. The study duration lasted from 1 day to 10 weeks. The mean ± SD number of the session and treat time, respectively, were 7.0 ± 4.9 (range 1–18) and 26.6 ± 10.6 minutes (range 10–45 minutes). The followup time ranged from 3 days to 24 weeks.

Of twelve RCTs, 8 RCTs [8, 10, 13–17, 19] assessed the effectiveness of MT for neck pain and 4 trials [9, 11, 12, 18] for shoulder pain. MT in the studies included Chinese traditional massage, common Western massage, traditional Thai massage, slow-stroke back massage, soft tissue massage, manual pressure release, classical strain/counterstrain technique, and myofascial band therapy. The control therapies contained inactive therapies (waiting list control, standard care, and sham therapies) and active therapies including acupuncture, traction, physical therapy, exercise, and activator trigger point therapy. The characteristics of all studies are summarized in Table 1.

3.3. Methodological Quality. The quality scores are presented in Table 2. The quality scores ranged from 6 to 8 points out of a theoretical maximum of 10 points. The predetermined cutoff 6 was exceeded by all the studies included, indicating that all of them were considered to be of high quality; however, four articles were at the limit of the cutoff with scores of 6. The most common flaws were lack of blinded therapists (92% of studies) and blinded subjects (83% of studies). But this situation cannot be considered a flaw because blinded therapists are impossible, and blinded patients can be difficult in this kind of trials, and most studies used blinded assessors (92% of studies). Although all studies adopted random assignment of patients, six trials did not use adequate method of allocation concealment. Four studies were lacking of analysis by intention-to-treat analysis because they cancelled the dropout data in the last results. In other items on PEDro scale, the studies included showed higher methodological quality involving measure of similarity between groups at baseline, less than 15% dropouts, between-group statistical comparisons, and point measures and variability data.

3.4. Quantitative Data Synthesis

3.4.1. Immediate Effects of MT on Pain. Eight RCTs examined the immediate effect of MT for neck pain versus inactive therapies or active therapies. Six of them were included in the meta-analysis [8, 10, 13, 14, 16, 19]. The results showed that MT may have been more effective than inactive therapies, but there were no differences between MT and other active therapies. In two RCTs excluded in the meta-analysis, one [15] tested the effect of myofascial band therapy versus activator trigger point therapy or sham ultrasound. With regard to pain reduction, the results showed that the odds of patients improving with activator trigger point therapy was higher than patients treated with myofascial band therapy or sham ultrasound. The other RCT [17] assessed the effectiveness of MT for chronic neck pain compared with standard care. The author found that participants in the massage group experienced clinically significant improvements on neck disability index (39% versus 14% of standard care group) and on the symptom bothersomeness scale (55% versus 25% of standard care group).

Table 1: Randomized controlled trials evaluating the effect of massage therapy for neck and shoulder pain.

First authors, year, country	Pain location, pain duration	Sample size, mean age (year),	Duration weeks	Follow-up weeks	Main outcome assessments	Experimental group intervention*	Control group intervention*	Main conclusion (mean improvements on pain)
Irnich 2001, Germany [8]	Neck pain 42% > 5 years	177 52	3	12	Pain VAS (0–100) Cervical mobility	Massage therapy (MT) (30 min/5 sessions)	(1) Acupuncture (AC) (2) Sham laser AC (30 min/5 sessions)	MT (12.70) < AC (25.30); MT (12.70) < Sham laser AC (19.20)
Dyson-Hudson 2001, US [9]	Shoulder pain 5.8 years	18 45	5	5	Pain WUSPI ROM	MT (45 min/10 sessions)	AC (20–30 min/10 sessions)	MT (28.80) > AC (26.70)
Cen 2003, US [10]	Neck pain NR	31 49	6	6	Pain NPQ (0–100) ROM	Chinese traditional massage (CTM) (30 min/18 sessions)	(1) Exercise (EX) (20 min/day) (2) Standard care (SC)	CTM (19.22) > EX (7.78) CTM (19.22) > SC (−4.13)
van den Dolder 2003, Australia [11]	Shoulder pain 28 weeks	29 64	2	—	Pain VAS (0–100) ROM	Soft tissue massage (STM) (15–20 min/6 sessions)	Waiting list (WL)	STM (26.60) > WL (0.10)
Mok 2004, Hong Kong [12]	Shoulder pain NR	102 73	1	3 days	Pain VAS (0–100) STAI	Slow-stroke back massage (SBM) (10 min/7 sessions)	SC	SBM (14.60) > SC (7.61)
Fryer 2005, Australia [13]	Neck pain NR	37 23	1 day	—	PPT	Manual pressure release (MPR) (1 session)	Sham myofascial release (SMR) (1session)	MPR (2.05) > SMR (−0.08)
Meseguer 2006, Spain [14]	Neck pain NR	54 40	1 day	—	Pain VAS (0–10)	Classical strain/counterstrain technique (CST) Modified strain/counterstrain technique (MST) (1 session)	SC	CST = MST (2.60) CST (2.60) > SC (0.03)
Blikstad 2008, UK [15]	Neck pain 4–12 weeks	45 24	1 day	—	Pain VAS (0–10) ROM	Myofascial band therapy (MBT) (1session)	(1) Activator trigger point therapy (ATPT) (2) Sham ultrasound (SU) (1 session)	MBT < ATPT MBT = SU
Zuo 2008, China [16]	Neck pain 10.4 years	60 42	2	—	Pain VAS (0–10) NDI	CTM (30 min/6 sessions)	Traction (TR) (20 min/14 sessions)	CTM (5.47) > TR (4.87)
Sherman 2009, US [17]	Neck pain 7.6 years	64 47	10	16	NDI CNFDS	MT (10 sessions)	SC	MT > SC (NDI)
Buttagat 2011, Thailand [18]	Shoulder pain 39 months	20 25	3	2	Pain VAS (0–10) STAI	Traditional Thai massage (TTM) (30 min/9 sessions)	Physical therapy (PT) (30 min/9 sessions)	TTM (4.50) > PT (1.60)
Zhang 2011, China [19]	Neck pain 1–3 years	120 23	10 days	24	Pain VAS (0–10) ASCS (0–29)	CTM (20 min/10 sessions)	TR (15 min/10 sessions)	CTM (5.56) > TR (3.85)

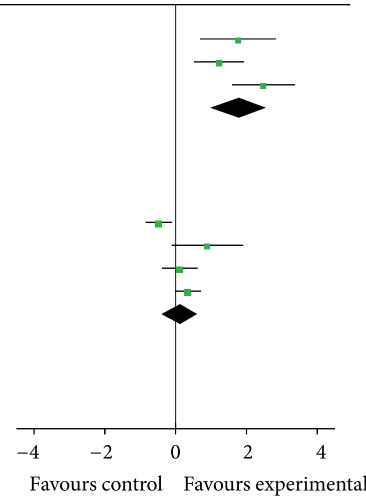
VAS: visual analog scale; WUSPI: wheelchair user's shoulder pain index; ROM: range of motion; NR: no reported; NPQ: Northwick park neck pain questionnaire; STAI: state-trait anxiety inventory; PPT: pressure pain threshold; NDI: neck disability index; CNFDS: Copenhagen neck functional disability scale; ASCS: Assessment scale for cervical spondylosis.
*Intervention/dose: number of intervention time/number of sessions.

Table 2: PEDro scale of quality for included trials.

Study	Eligibility criteria	Random allocation	Concealed allocation	Similar at baseline	Subjects blinded	Therapists blinded	Assessors blinded	<15% dropouts	Intention-to-treat analysis	Between-group comparisons	Point measures and variability data	Total
Irnich et al. [8]	1	1	0	1	0	0	1	1	1	1	1	7
Dyson-Hudson et al. [9]	1	1	1	1	0	0	1	1	0	1	1	7
Cen et al. [10]	1	1	0	1	0	0	1	1	0	1	1	6
van den Dolder and Roberts [11]	1	1	1	1	0	0	1	1	1	1	1	8
Mok and Woo [12]	1	1	0	1	0	0	1	1	0	1	1	6
Fryer and Hodgson [13]	1	1	0	0	1	0	1	0	1	1	1	6
Meseguer et al. [14]	1	1	0	1	0	1	1	1	1	1	1	8
Blikstad and Gemmell [15]	1	1	1	1	1	0	1	0	0	1	0	6
Zuo et al. [16]	1	1	0	1	0	0	1	1	1	1	1	7
Sherman et al. [17]	1	1	1	1	0	0	1	1	1	1	1	8
Buttagat et al. [18]	1	1	1	1	0	0	1	1	1	1	1	8
Zhang et al. [19]	1	1	1	1	0	0	0	1	1	1	1	7

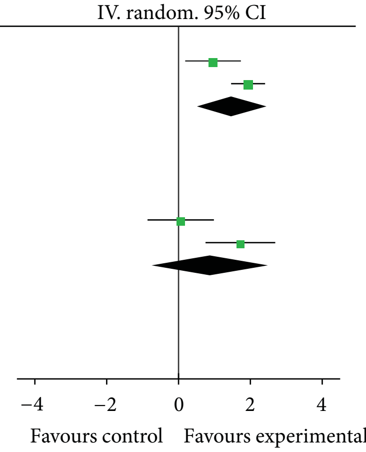
0 = not meet the criteria; 1 = meet the criteria.

Study or subgroup	Experimental group Mean	SD	Total	Control group Mean	SD	Total	Weight	Sandardised mean difference IV. random. 95% CI
1.1.1. Massage Therapy versus Inactive Therapy								
Cen 2003	19.22	11.54	9	−4.13	13.51	11	12%	1.76 (0.69, 2.84)
Fryer 2005	2.05	1.7	20	−0.08	1.7	17	14.4%	1.23 (0.52, 1.94)
Meseguer 2006	2.6	1.4	18	0.03	0.3	18	13.2%	2.48 (1.59, 3.37)
Subtotal (95% CI)			**47**			**46**	**39.5%**	**1.79 (1.01, 2.57)**
Heterogeneity: $\tau^2 = 0.27$; $\chi^2 = 4.67$, df = 2 ($P = 0.1$); $I^2 = 57\%$								
Test for overall effect: $Z = 4.52$ ($P < 0.00001$)								
1.1.2. Massage Therapy versus Active Therapy								
Irnich 2001	12.7	29.5	59	25.3	22.6	52	16.2%	−0.47 (−0.85, −0.09)
Cen 2003	19.22	11.54	9	7.58	13.12	8	12.4%	0.9 (−0.11, 1.91)
Zuo 2008	5.47	4.81	30	4.87	5.5	30	15.6%	0.11 (−0.39, 0.62)
Zhang 2011	5.56	4.72	60	3.85	5.03	60	16.3%	0.35 (−0.01, 0.71)
Subtotal (95% CI)			**158**			**150**	**60.5%**	**0.13 (−0.38, 0.63)**
Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 12.7$, df = 3 ($P = 0.005$); $I^2 = 76\%$								
Test for overall effect: $Z = 0.49$ ($P = 0.63$)								



(a) Neck pain

Study or subgroup	Experimental group Mean	SD	Total	Control group Mean	SD	Total	Weight	Sandardised mean difference IV. random. 95% CI
1.1.1. Massage Therapy versus Inactive Therapy								
Van den Dolder 2003	26.6	27.07	15	0.1	26.53	14	25.2%	0.96 (0.19, 1.74)
Mok 2004	14.6	7.56	51	−0.2	7.61	51	29.2%	1.94 (1.46, 2.41)
Subtotal (95% CI)			**66**			**65**	**54.4%**	**1.5 (0.55, 2.45)**
Heterogeneity: $\tau^2 = 0.37$; $\chi^2 = 4.43$, df = 1 ($P = 0.04$); $I^2 = 77\%$								
Test for overall effect: $Z = 3.09$ ($P = 0.002$)								
1.1.2. Massage Therapy versus Active Therapy								
Dyson-Hudson 2001	28.8	33.18	9	26.7	32.75	9	23.1%	0.06 (−0.86, 0.98)
Buttagat 2011	4.5	1.48	10	1.6	1.72	14	22.5%	1.72 (0.75, 2.69)
Subtotal (95% CI)			**19**			**23**	**45.6%**	**0.88 (−0.74, 2.51)**
Heterogeneity: $\tau^2 = 1.15$; $\chi^2 = 5.9$, df = 1 ($P = 0.02$); $I^2 = 83\%$								
Test for overall effect: $Z = 1.06$ ($P = 0.29$)								



(b) Shoulder pain

Figure 2: Forest plot of the immediate effect of massage therapy for (a) neck pain and (b) shoulder pain.

Four trials tested the immediate effect of MT for shoulder pain versus inactive therapies [11, 12] or active therapies [9, 18]. All studies were included in the meta-analysis. The result showed that MT may have been more effective than inactive therapies, but there were no differences between MT and other active therapies.

(1) *MT versus Inactive Therapies.* Three RCTs [10, 13, 14] assessed the immediate effect of MT on pain versus inactive therapies (including standard care or sham myofascial release) for neck pain. All studies showed significant effects of MT on pain relief compared with inactive therapies. The meta-analysis also showed favorable effects of MT ($n = 93$; SMD, 1.79; 95% CI, 1.01 to 2.57; $P < 0.00001$; heterogeneity: $\chi^2 = 4.67$, $P = 0.10$, $I^2 = 57\%$; Figure 2(a)). The study conducted by Irnich et al. [8] was excluded because it did not include the direct comparison between MT and sham laser acupuncture. Therefore, it is not possible to determine whether MT is superior to an inactive therapy.

Two RCTs [9, 12] compared the immediate effect of MT on pain with inactive therapies for shoulder pain. They reported favorable effects of MT on pain reduction. The meta-analysis also showed superior effects of MT on pain compared with inactive therapies ($n = 131$; SMD, 1.50; 95% CI, 0.55 to 2.45; $P = 0.002$; heterogeneity: $\chi^2 = 4.43$, $P = 0.04$, $I^2 = 77\%$; Figure 2(b)).

(2) *MT versus Active Therapies.* Four RCTs assessed the immediate effect of MT for neck pain compared with acupuncture [8], exercise [10], or traction [16, 19]. The meta-analysis did not show favorable effects of MT on pain reduction ($n = 308$; SMD, 0.13; 95% CI, −0.38 to 0.63; $P = 0.63$; heterogeneity: $\chi^2 = 12.70$, $P = 0.005$, $I^2 = 76\%$; Figure 2(a)).

Study or subgroup	Experimental group Mean	SD	Total	Control group Mean	SD	Total	Weight	Sandardised mean difference IV. random. 95% CI
1.1.1. Neck Pain								
Irnich 2001	14.4	21.9	59	17.4	29.7	52	21.8%	−0.12 (−0.49, 0.26)
Cen 2003	19.03	10.22	9	18.22	12.78	11	19.5%	0.07 (−0.81, 0.95)
Subtotal (95% CI)			**68**			**63**	**41.3%**	**−0.09 (-0.43, 0.26)**
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.14$, df = 1 ($P = 0.71$); $I^2 = 0\%$								
Test for overall effect: $Z = 0.5$ ($P = 0.62$)								
1.1.2. Shoulder Pain								
Dyson-Hudson 2001	37.1	32.99	9	20.7	35.42	9	19.1%	0.46 (−0.48, 1.4)
Mok 2004	14.6	6.91	51	−0.1	7.67	51	21.5%	2 (1.52, 2.48)
Buttagat 2011	4.5	1.28	10	1	2	10	18.1%	2 (0.88, 3.11)
Subtotal (95% CI)			**70**			**70**	**58.7%**	**1.51 (0.53, 2.49)**
Heterogeneity: $\tau^2 = 0.57$; $\chi^2 = 8.49$, df = 2 ($P = 0.01$); $I^2 = 76\%$								
Test for overall effect: $Z = 3.01$ ($P = 0.003$)								

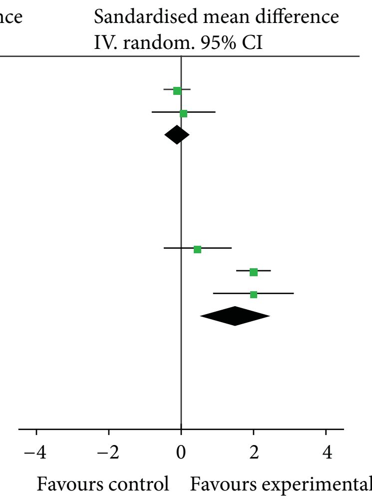


Figure 3: Forest plot of the followup effect of massage therapy for neck and shoulder pain.

Two RCTs tested the immediate effect of MT for shoulder pain compared with acupuncture [9] or physical therapy [18]. The MT group in two RCTs showed favorable effects versus control group. But the meta-analysis did not show superior effects of MT on pain reduction ($n = 42$; SMD, 0.88; 95% CI, −0.74 to 2.51; $P = 0.29$; heterogeneity: $\chi^2 = 5.90$, $P = 0.02$, $I^2 = 83\%$; Figure 2(b)).

3.4.2. The Followup Effects of MT on Pain. In studies with followup, two RCTs assessed short-term effects of MT for neck pain. The authors reported that MT did not experience significant improvements on pain compared with acupuncture after a 12-week followup [8] or exercise after a 6-week followup [10]. The meta-analysis did not show significant effects of MT on pain in followup ($n = 131$; SMD, −0.09; 95% CI, −0.43 to 0.26; $P = 0.62$; heterogeneity: $\chi^2 = 0.14$, $P = 0.71$, $I^2 = 0\%$; Figure 3).

Three trials tested short-term effects of MT on shoulder pain compared with acupuncture [9], standard care [12], or physical therapy [18]. Two RCTs reported significant pain reduction, respectively, compared with standard care after 3-day followup [12] and physical therapy after a 2-week followup [18], while the other did not versus acupuncture after a 12-week followup [9]. The meta-analysis showed superior short-term effects of MT on pain reduction in followup ($n = 140$; SMD, 1.51; 95% CI, 0.53 to 2.49; $P = 0.003$; heterogeneity: $\chi^2 = 8.49$, $P = 0.01$, $I^2 = 76\%$; Figure 3).

3.4.3. Effects of MT on Functional Status. Two studies tested the effectiveness of MT for shoulder range of motion compared with acupuncture [9] and waiting list control [11]. And the meta-analyses did not show significant immediate effects of MT on shoulder flexion ($n = 47$; SMD, 0.38; 95% CI, −0.69 to 1.45; $P = 0.49$; heterogeneity: $\chi^2 = 3.17$, $P = 0.08$, $I^2 = 68\%$; Figure 4) or shoulder abduction ($n = 47$; SMD, 0.53; 95% CI, −0.94 to 2.00; $P = 0.48$; heterogeneity: $\chi^2 = 5.71$, $P = 0.02$, $I^2 = 83\%$; Figure 4).

Six trials reported the effectiveness of MT on functional status of patients with neck pain; however, the quantitative meta-analysis had not been conducted due to the serious heterogeneity in assessment methods and ineligible reported data. Four of these studies reported favourable immediate effects compared with standard care [17], exercise (or standard care) [10], and traction [16, 19]. In the other two studies, MT did not show better immediate effects than acupuncture (or sham laser acupuncture) [8] or activator trigger point therapy [15]. Only two studies reported the followup effects of MT on functional status. One showed the short-term effects compared with exercise after a 6-week followup [10]. The other reported that MT showed less relapse rates compared with traction after a 24-week followup [19].

4. Discussion

The results suggested that MT may have been more beneficial than inactive therapies in immediate effects for neck and shoulder pain, but there were no differences between MT and other active therapies. On followup effects, the meta-analysis only showed the short-term benefit of MT for shoulder pain. With regard to the improvement of functional status, there was not valid evidence of MT for neck and shoulder pain.

We analyzed studies comparing MT with inactive therapies and active therapies separately because different control comparators address different questions. In addition, each control has advantages and limitations that must be considered in interpreting the analysis results. The inactive therapy control is intended to address the following question: is MT an effective therapy for neck and shoulder pain? Inactive therapies included standard care, waiting list, and sham treatment control in our review. Sham treatment control has advantages with regard to the blinding of patients, evaluators, or both to the treatment compared with other inactive

Study or subgroup	Experimental group Mean	SD	Total	Control group Mean	SD	Total	Weight	Sandardised mean difference IV. random. 95% CI
1.1.1. Flexion								
Dyson-Hudson 2001	2.7	12.69	9	5	8.88	9	23.7%	−0.2 (−0.13, 0.73)
Van den Dolder 2003	15.1	23.87	15	−7.46	25.25	14	26.7%	0.89 (0.12, 1.66)
Subtotal (95% CI)			**24**			**23**	**50.4%**	**0.38 (−0.69, 1.45)**
Heterogeneity: $\tau^2 = 0.41$; $\chi^2 = 3.17$, df = 1 ($P = 0.08$); $I^2 = 68\%$								
Test for overall effect: $Z = 0.69$ ($P = 0.49$)								
1.1.2. Abduction								
Dyson-Hudson 2001	1.4	18.7	9	5.7	14.74	9	23.6%	−0.24 (−1.17, 0.69)
Van den Dolder 2003	33.4	29.24	15	−8.9	36.06	14	26%	1.26 (0.45, 2.06)
Subtotal (95% CI)			**24**			**23**	**49.6%**	**0.53 (−0.94, 2)**
Heterogeneity: $\tau^2 = 0.93$; $\chi^2 = 5.71$, df = 1 ($P = 0.02$); $I^2 = 83\%$								
Test for overall effect: $Z = 0.7$ ($P = 0.48$)								

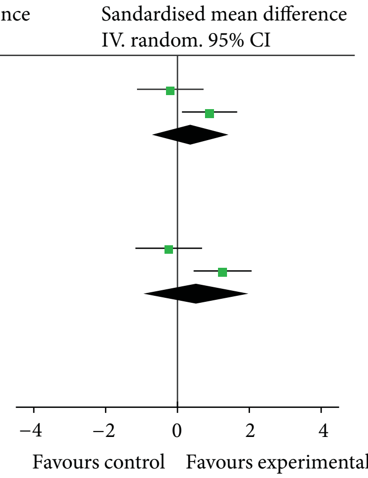


Figure 4: Forest plot of the effect of massage therapy in improving functional status related to shoulder pain.

therapies. The meta-analyses showed that MT is an effective therapy on relieving neck and shoulder pain. And the meta-analyses results from active therapy controlled RCTs address the question of whether MT is more effective than other active therapies for neck and should pain. No evidence suggested that MT was better than active therapies. In addition, we also paid attention to the immediate and followup effects of MT for neck and shoulder pain.

Our positive results concur with those from systematic reviews. Ottawa panel evidence-based clinical practice guidelines [6] suggested that MT is effective for relieving immediate posttreatment neck pain symptoms, but data is insufficient to estimate followup effects. This systematic review included 5 RCTs published from 2003 to 2009, which demonstrated high methodological quality (≥3) according to the Jadad scale. And Tsao' systematic review [5] provided moderate support for the use of MT for shoulder pain, which qualitatively analyzed three RCTs of MT for shoulder pain. However, our systematic review included four new RCTs [14, 16, 18, 19] (three for neck pain and one for shoulder pain). Of notes, our review contained two Chinese RCTs [16, 19] of MT for neck pain with high methodological quality. And we quantitatively examined the effectiveness of MT for neck and shoulder pain. In our meta-analyses, we separately compared MT with inactive therapies and active therapies. We also paid attention to the immediate and followup effects of MT. So our update provides stronger evidence of MT for neck and shoulder pain.

Our results differ from those of Ezzo and colleagues' systematic review [3] of MT for mechanical neck disorders, which concluded that the effectiveness of MT for neck pain remained uncertain. One suspected reason for this difference is that 6 high-quality RCTs [13–17, 19] have been published since 2003, of which 5 favored MT. Another possible explanation for the difference in the finding is that we used a different data analysis approach than Ezzo and colleagues. While we used meta-analyses, Ezzo' review declined to combine the trials because of trial heterogeneity. Any strictly qualitative approach may be problematic since it can be more subjective than meta-analyses. In addition, only six studies published from 1997 to 2003 examined MT alone as a treatment group in Ezzo' review. Four of those received low-quality scores. Two studies used treatments related to MT in control group. These were limited to evaluate the specific effect of MT because any individual study might affect the review's overall conclusions. More high-quality RCTs, classification of quantitative data synthesis, and the homogeneity of results of inactive therapy controlled RCTs and active therapy controlled RCTs in meta-analyses strengthen our confidence in our systematic review.

4.1. Limitations of the Review. There are several limitations in our review. First, the distorting effects of publication and location bias on systematic reviews and meta-analyses are well documented [20, 21]. We are confident that our search strategy located all relevant studies. However, some degree of uncertainty remains. Another possible source of bias is that the more negative trials of MT for neck and shoulder pain may be never published in the peer-reviewed literature, so there were only two negative studies in our review [8, 15]. Our review also may be affected by the heterogeneity in characters of different MTs including frequency, duration, number of sessions, and massage technique. Our review contained many types of MT (e.g., Swedish massage, Chinese traditional massage, soft tissue massage, slow-stroke back massage, manual pressure release, myofascial band therapy, and traditional Thai massage). These are very different in characters of MT. As a result, the basic standard of MT is very important in further studies, especially in a mechanism of influence. In addition, there were less eligible trials due to strict eligibility criteria for considering studies in our review, so some meta-analyses were performed on the bases of two trials. It may influence combining results, but low eligibility criteria would generate more doubtful results. In order to get stronger evidence, we will update our review as soon as new eligible RCTs of MT for neck and shoulder pain are reported.

4.2. The Possible Rationale of MT for Relieving Pain. Assuming that MT was beneficial on relieving pain related to the neck and shoulder, the complex interplay of both physical and mental modes may provide a possible rationale. MT delivered to soft and connective tissues may induce local biochemical changes that modulate local blood circulation, improve muscle flexibility, intensify the movement of lymph, and loosen adherent connective tissue, which may alternately improve reuptake of local nociceptive and inflammatory mediators [22]. These local effects may subsequently influence neural activity at the spinal cord segmental level, thereby modulating the activities of subcortical nuclei that influence pain perception [23].

5. Conclusion

MT is an effective intervention that may provide immediate effects for neck and shoulder pain. However, MT does not show better effects than other active therapies on pain relief. Additionally, MT only showed short-term effects for shoulder pain in followup. No evidence suggests that MT was effective in improving functional status related to neck and shoulder pain.

Future studies of MT for neck and shoulder pain should adhere to large-scale and high-quality RCTs with long followup for better quantitative meta-analysis. Even though it is difficult to blind subjects and therapists for treatments, employing assessor blinding and allocation concealment are important for reducing bias. The RCT should adopt validated primary outcome measures, adequate statistical tests, applicable comparison groups, and standard MT. This comprehensive review of MT for neck and shoulder pain acts to provide guidelines for future researches.

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Massage Therapy for Osteoarthritis of the Knee: A Randomized Dose-Finding Trial

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Abstract

Background: In a previous trial of massage for osteoarthritis (OA) of the knee, we demonstrated feasibility, safety and possible efficacy, with benefits that persisted at least 8 weeks beyond treatment termination.

Methods: We performed a RCT to identify the optimal dose of massage within an 8-week treatment regimen and to further examine durability of response. Participants were 125 adults with OA of the knee, randomized to one of four 8-week regimens of a standardized Swedish massage regimen (30 or 60 min weekly or biweekly) or to a Usual Care control. Outcomes included the Western Ontario and McMaster Universities Arthritis Index (WOMAC), visual analog pain scale, range of motion, and time to walk 50 feet, assessed at baseline, 8-, 16-, and 24-weeks.

Results: WOMAC Global scores improved significantly (24.0 points, 95% CI ranged from 15.3–32.7) in the 60-minute massage groups compared to Usual Care (6.3 points, 95% CI 0.1–12.8) at the primary endpoint of 8-weeks. WOMAC subscales of pain and functionality, as well as the visual analog pain scale also demonstrated significant improvements in the 60-minute doses compared to usual care. No significant differences were seen in range of motion at 8-weeks, and no significant effects were seen in any outcome measure at 24-weeks compared to usual care. A dose-response curve based on WOMAC Global scores shows increasing effect with greater total time of massage, but with a plateau at the 60-minute/week dose.

Conclusion: Given the superior convenience of a once-weekly protocol, cost savings, and consistency with a typical real-world massage protocol, the 60-minute once weekly dose was determined to be optimal, establishing a standard for future trials.

Trial Registration: ClinicalTrials.gov NCT00970008

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Introduction

Osteoarthritis (OA) is a slowly progressive degenerative disease of the joints that at present afflicts approximately 27 million Americans [1,2]. With the aging of the "baby boom" population and increasing rates of obesity, the prevalence of OA is estimated to increase 40% by 2025 [3]. Conventional therapies for OA have limited effectiveness, and toxicities associated with suitable drugs thus often limit utilization, leaving many facing surgery or chronic, often debilitating, pain, muscle weakness, lack of stamina, and loss of function [3,4,5,6,7,8,9,10]. In 2005, US costs from OA related absenteeism alone were estimated at $10.3 billion, and in 2007, OA increased aggregate annual medical care expenditures by $185.5 billion (in 2007 dollars) [11]. Well-publicized events such as the multiple lawsuits associated with rofecoxib and potential cardiac toxicity, as well as the removal of additional COX-2 inhibitors from the market, have lessened the public's confidence in pharmaceuticals and led to increased interest in therapeutic interventions believed to be safer [12,13,14].

Massage therapy and certain other complementary and alternative medicine (CAM) interventions are being utilized by OA sufferers, and represent attractive, potentially effective options to manage pain [12,13,14,15,16,17,18]. Massage is one of the most popular CAM therapies in the US [14]. Between 2002 and 2007, the 1-year prevalence of use of massage by the US adult population increased from 5% (10.05 million) to 8.3% (18.07 million) [14]. Massage is generally used to relieve pain from musculoskeletal disorders [19,20,21,22], cancer, and other conditions; rehabilitate sports injuries; reduce stress; increase relaxation; decrease feelings of anxiety and depression; and aid general wellness [12,21,23,24,25,26,27,28,29,30,31,32,33,34,35]. However, only a relatively small body of research exists exploring the efficacy of massage therapy for any condition.

In 2006, we reported results of a pilot study of massage therapy for OA of the knee [18]. Subjects with OA of the knee meeting American College of Rheumatology Criteria [36] were randomized to biweekly (4 weeks), then weekly (4 weeks) Swedish massage (1 hour sessions) or wait list. Subjects receiving massage therapy demonstrated significant improvements in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [37,38,39] pain, stiffness, and physical functional disability domains ($p<0.001$) and visual analog pain scale [39] ($p<0.01$) [18], compared to usual care. Notably, the benefits persisted up to 8 weeks following the cessation of massage [40]. Despite these promising results, there was no data to determine whether the dose utilized in the pilot study was optimal.

Here, we report the results of our Phase 2 dose-finding study to identify a dose and treatment regimen of an 8-week course of a standardized Swedish massage therapy for OA of the knee that is both optimal (providing greatest effectiveness) and practical (minimizing patient cost and inconvenience). To our knowledge, this was the first dose-finding study of massage therapy for OA, and for OA of the knee specifically. This trial employed a more diverse subject population at two clinical sites, and assessed longer-term residual effects, than did our earlier pilot study. In addition, a formally manualized massage protocol was developed and utilized [18]. Results of the trial reported herein will inform the dosing regimen for future clinical trials designed to confirm the efficacy of massage therapy for osteoarthritis of the knee and define its place in clinical practice.

Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

Ethics Statement

The study protocol, consent form and all recruitment materials were approved by the Institutional Review Boards of the University of Medicine and Dentistry of New Jersey (Newark, NJ), Griffin Hospital (Derby, CT), and the Saint Barnabas Medical Center (Livingston, NJ). The study was conducted in accordance with the Declaration of Helsinki.

Participants

Eligible patients were men and women with radiographically-established OA of the knee who met American College of Rheumatology criteria [36], were at least 35 years of age, and had a pre-randomization score of 40 to 90 on the visual analog pain scale. Patients with bilateral knee involvement had the more severely affected knee (determined by the patient) designated as the study knee. Subjects using NSAIDS or other medications to control pain were included if their doses remained stable three months prior to starting the intervention.

Subjects were excluded if they suffered from rheumatoid arthritis, fibromyalgia, recurrent or active pseudogout, cancer, or other serious medical conditions. Subjects were also excluded if they had signs or history of kidney or liver failure; unstable asthma; knee replacement of both knees; reported recent use (4 weeks–1 year prior to enrollment) of oral or intra-articular corticosteroids or intra-articular hyaluronate; or knee arthroscopy or significant knee injury one year prior to enrollment. A rash or open wound over the knee and regular use of massage therapy (greater than once a month) also resulted in exclusion from the study.

Those passing telephone screening ($n = 125$), agreeing to the study protocol, and providing a written physician confirmation of OA were scheduled for an on-site evaluation to provide written informed consent and undergo clinical eligibility screening. All subjects received nominal compensation (consisting of gift certificates for future massages) for their participation. The intervention was delivered at two sites; St. Barnabas Ambulatory Care Center (Livingston, NJ), and the Integrative Medicine Center at Griffin Hospital (Derby, CT). Subject participation and flow are shown in Figure 1.

Recruitment and screening commenced in July 2009 in Livingston, New Jersey and Southern Connecticut through flyers, newspaper advertisements, and press releases. Information letters were sent to patients identified with OA, as well as physicians in the rheumatology and internal medicine practices at Saint Barnabas Medical Center (Livingston, NJ) and Griffin Hospital (Derby, CT). Of the 430 persons screened for eligibility, 168 did not meet eligibility criteria, 43 refused to participate, and 94 were not screened for other reasons (Figure 1). The most common reasons for ineligibility were 1) no documented confirmation of OA of the knee, 2) recent history of cortisone and hyaluronate injections, and 3) history of knee replacement. Enrollment continued until July 2010. 125 subjects were randomized to receive one of four active massage arms (Groups 1–4) and one Usual Care/control arm.

Randomization

Participants were block randomized using a permuted block design (blocks of 5 or 10) in a 1:1:1:1:1 ratio and stratified by site and body mass index (BMI) to ensure balance between the intervention and Usual Care groups across the two performance sites.. The study statistician (VYN) generated the random allocation sequence using SAS Software version 9.1. Each eligible and consented subject (identified by number) was assigned to one of the treatment arms. Treatment allocation was only known by the statistician and the study assistants (CM and AD) that assigned participants to interventions and generated visit schedules.

Study Design and Interventions

This study was a randomized clinical trial with four treatment arms (and one Usual Care arm) designed to assess the effects of 8 weeks of a standardized Swedish massage protocol (see *Manualization*) provided at four distinct doses (Figure 1). Group 1 received 30 minutes of massage weekly for eight weeks. Group 2 received 30 minutes of massage twice weekly for the initial four weeks, and once weekly for the remaining four weeks. Group 3 received 60 minutes of massage weekly for eight weeks. Group 4 received 60 minutes of massage twice weekly for the initial four weeks, and once weekly for the remaining four weeks. Group 4 received the same dosing regimen as was given in our pilot trial [41]. The Usual Care group continued with their current treatment without the addition of massage therapy.

The doses were chosen as practical regimens that are commonly used in massage therapy and were designed to investigate the variables of length of individual treatment (30 min vs. 60 min), frequency (weekly vs. twice weekly), and total treatment time (240 min (Group 1, 30 min weekly×8 wk), 360 min (Group 2, 30 min biweekly×4 wk+30 min weekly×4 wk), 480 min (Group 3, 60 min weekly×8 wk), or 720 min (Group 4, 60 min biweekly×4 wk+60 min weekly×4 wk)).

Manualization

Prior to enrolling subjects, a formal manualization process produced a study protocol that was tailored to subjects with OA of

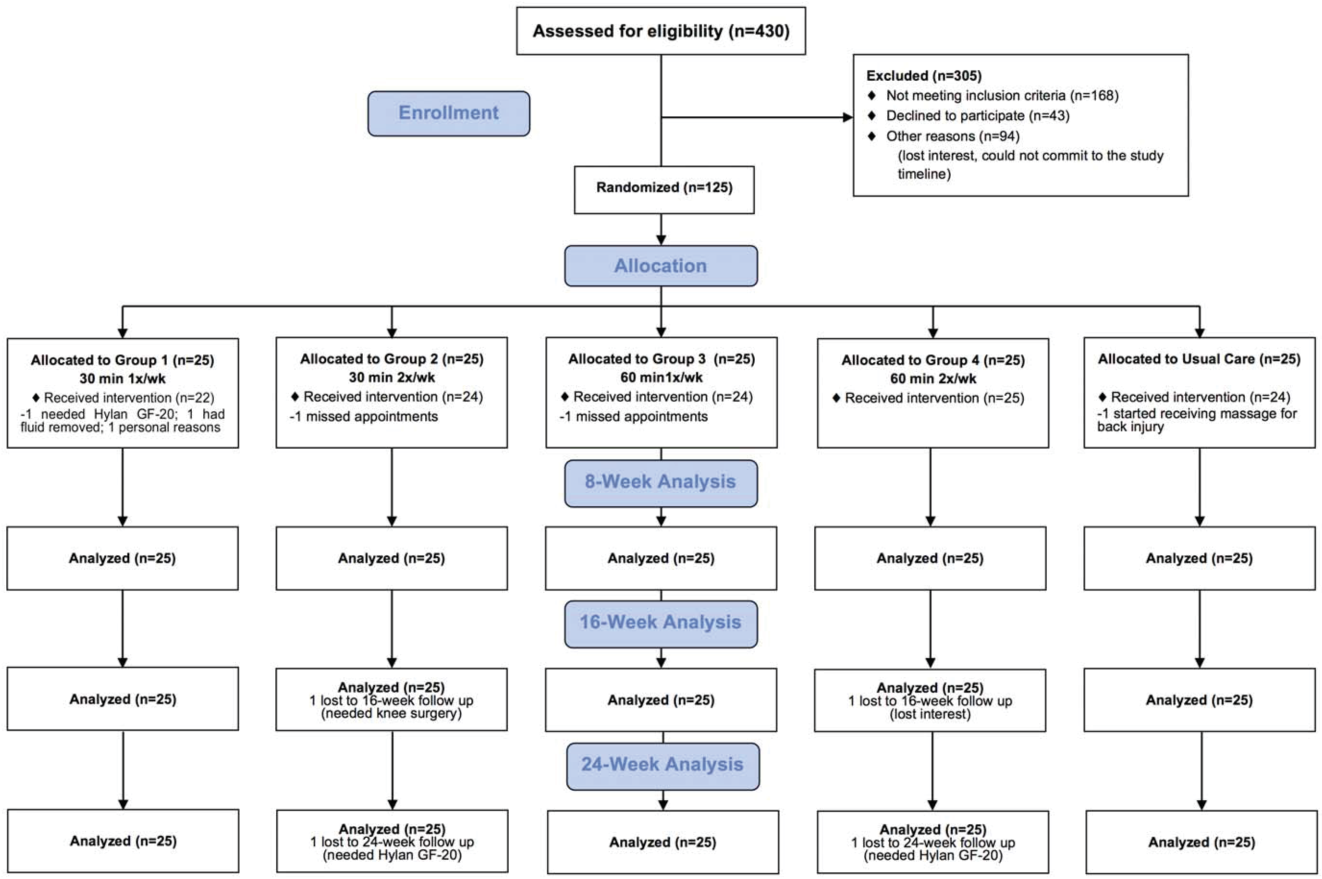

Figure 1. Participant Flow Diagram.
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the knee, while respectful of the individualized nature of massage therapy [42]. The manualization process, conducted over the course of two months, involved the input of licensed massage therapists that participated in the pilot study, massage researchers, as well as the investigative team. The resulting massage protocol was made reproducible, using standard massage techniques [18,43], as well as flexible for individual subject variability.

The manualized protocol specifies the body regions to be addressed; with distinct 30 and 60-minute protocols (Table 1), as well as the standard Swedish strokes to be used (effleurage, petrissage, tapotement, vibration, friction, and skin rolling) [18]. Each protocol specifies the time allocated to various body regions (lower/upper limbs, lower/upper back, head, neck, chest). The protocol was specifically designed to address symptoms of osteoarthritis of the knee. The order of body regions is not specified in order to account for individual practitioner preference. The manual specifies intentions/attentions for the study massage therapists. Each study therapist was taught and agreed to the protocol and signed a form attesting to adherence to the study protocol after each massage session. Study personnel reviewed adherence to the protocol at regular intervals throughout the study period. No deviations from the manualized massage protocol occurred.

Primary outcome measure

The primary outcome measure was change in the Western Ontario and McMaster Universities Arthritis Index (WOMAC–Global). The WOMAC has been used extensively in the quantitative assessment of OA of the knee, and has been proven to be effective in assessing pain in those suffering from the illness [37,38,44]. It assesses dimensions of pain, functionality and joint stiffness through 24 questions. The WOMAC has been subject to numerous validation studies to assess reliability and responsiveness to change in therapy, including physical forms of therapy [37,38,44] and was successfully utilized in the Phase 1 study [18].

Secondary outcome measures

Secondary measures included pain as measured on a visual analog scale (0 to 100 scale), a validated [39] mechanical scale used to measure pain sensation intensity evoked by nociceptive stimuli [45]. Other secondary outcomes were joint flexibility, defined as the range of motion (ROM) allowed at the knee during flexion using a double-armed goniometer, and measured time to walk 50 feet (15 m) on a level surface within the clinic facilities.

Outcomes were assessed at baseline, 8-weeks, 16-weeks, and 24-weeks post-baseline. Assessment visits were scheduled by a research assistant, though the measurements were assessed by separate personnel blinded to treatment assignments. Adherence was assessed by tracking the number of massage visits that subjects completed.

Statistical Analysis

Statistical analysis was conducted using SAS software (Version 9.1, SAS Institute, Cary, NC). Repeated measures ANOVA using linear mixed model regression was used to determine between-group changes in all outcome measures and changes in domain-

Table 1. 30- and 60-Minute Massage Protocols.

Region	Time Allotted	Distribution
30 minute protocol (25 minutes of table time)		
Region	**Time Allotted**	**Distribution**
Lower Limbs	12–15 min (45–50% of session)	From knee down including lower leg, ankle, and foot. From knee up including hips, pelvis, buttocks & thigh.
Upper Body	8–12 min (36–44% of session)	Lower and upper back. Head/Neck/Chest
Discretionary	2–5 min (6–19% of session)	Therapist to expand treatment to other affected areas; i.e. rib cage, flank, upper limbs, etc.
60 minute protocol (55 minutes of table time*)		
Lower Limbs	20–27.5 min (45–50% of session)	From knee down including lower leg, ankle, and foot. From knee up including hips, pelvis, buttocks and thigh.
Upper Body	15–24 min (36–44% of session)	Lower and upper back. Head, neck, and chest.
Discretionary	3.5–20 min (6–19% of session)	Therapist to expand treatment to other affected areas; i.e. rib cage, flank, upper limbs, etc.

*Accounting for time spent in transition including the welcome, transition to the massage room, taking off jewelry, and other preparatory activities.
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specific (i.e. pain, stiffness, and functionality) WOMAC measures, controlling for time-dependent variables. In all analyses, a two-tailed α of less than 0.05 was considered statistically significant. Duncan's multiple range test (a multiple comparison test) was used to determine whether means differ significantly across treatment groups. A dose-response curve was plotted assessing the magnitude of improvement on 8-week WOMAC Global scores plotted against the total 8-week dose of massage. A sample size of 125 individuals in five arms was based on budgetary and logistical constraints.

Results

Of the 125 enrolled subjects, 119 completed the 8-week assessment and 115 completed the entire trial (Figure 1). Subjects received the intervention between November 2009 and October 2010.

Baseline characteristics of the study participants are provided in Table 2. The randomization process with stratification by BMI was largely successful in producing equivalent groups. The only differences seen at baseline were that Group 1 was older than the other groups, and Group 3 had more perceived pain than usual care as assessed by the visual analog scale, though no differences were seen in the pain subscale of the WOMAC.

Primary Outcome

WOMAC Global scores improved significantly (24.0 points, 95% CI ranged from 15.3–32.7) in the 60-minute massage groups compared to Usual Care (6.3 points, 95% CI 0.1–12.8) at the primary endpoint of 8-weeks (Table 3). No statistically significant differences between the massage groups were detected at 8 weeks, though the magnitude of change in the groups receiving 60-minute doses (Groups 3 and 4) was greater than the magnitude of change in the groups receiving 30-minute doses (Groups 1 and 2) (Table 3).

WOMAC Pain Subscale

The 60-minute doses (Groups 3 and 4) were also significantly (27.2–27.7 points, 95% CI ranged from 18.0–36.9 points) improved compared to usual care (5.6 points, 95% CI ranged from −1.9–13.1) at 8-weeks (Table 3). Significant improvement ($p<0.05$) from baseline was achieved for all massage groups at 8 weeks, and at 16 and 24 weeks for the three highest doses of massage (Groups 2, 3 and 4), whereas no improvement ($p>0.05$) in Usual Care was seen at any time point (Tables 3 and 4).

WOMAC Stiffness Subscale

No significant between-group changes were seen in WOMAC Stiffness, though the magnitude of change was greater in all treatment groups compared to usual care.

WOMAC Functionality Subscale

The 60-minute doses (Groups 3 and 4) were significantly (21.2–22.0 points, 95% CI ranged from 12.5–31.6 points) improved compared to usual care (6.6 points, 95% CI ranged from 0.9–12.2) at 8-weeks (Table 3).

Dose Response

A dose-response curve based on changes in WOMAC Global scores at 8-weeks shows increasing effect with greater total time of massage, but with a plateau at the 480-minute dose (Group 3) (Figure 2).

Visual Analog Pain Scale

Pain perception improved significantly (31.2–39.8 points, 95% CI ranged from 22.9–48.1 points) in both 60-minute dose groups (Groups 3 and 4) compared to Usual Care at 8-weeks post baseline, with no significant differences between Groups 3 and 4. All treatment groups reported decreased pain perception compared to baseline at all time points (Tables 3 and 4).

Timed 50-foot walk

All groups showed decreased time to walk 50 feet at all time points, except group 1 at week 8 (Tables 3 and 4). However, there were no significant differences between the groups at any timepoint.

Range of Motion

No significant between-group differences were seen in range of motion at 8-weeks post-baseline, though all massage groups changed in the positive direction. Group 4, the highest total dose of massage, was significantly improved from baseline at all time points. The 30-minute protocols and Usual Care groups did not demonstrate any significant changes from baseline at any timepoint.

Table 2. Demographic Characteristics and Baseline Values.

Variable	Group 1 (n = 25)	Group 2 (n = 25)	Group 3 (n = 25)	Group 4 (n = 25)	Usual Care (n = 25)
Gender					
Female	15 (12.0%)	18 (14.4%)	19 (15.2%)	17 (13.6%)	19 (15.2%)
Male	10 (8.0%)	7 (5.6%)	6 (4.8%)	8 (6.4%)	6 (4.8%)
Race					
White	23 (18.4%)	22 (17.6%)	19 (15.2%)	20 (16.0%)	22 (17.6%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
White/Asian	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
African American	2 (1.6%)	2 (1.6%)	4 (3.2%)	4 (3.2%)	2 (1.6%)
Hispanic	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	1 (0.8)	0 (0.0%)	1 (0.8%)
Age (years)	69.9±8.6	61.9±9.5	62.6±10.6	63.6±13.0	63.6±10.2
Body Mass Index (kg/m^2)	31.0±7.5	32.1±6.8	31.8±6.7	31.3±7.1	31.7±6.5
WOMAC (mm)					
Pain	52.3±19.9	42.4±23.0	52.5±16.5	44.4±19.3	46.3±15.4
Stiffness	53.4±24.1	58.6±21.1	58.4±24.7	51.2±24.4	62.8±18.2
Functionality	52.9±17.9	49.5±19.5	49.8±19.7	48.3±20.2	50.5±17.4
Global	52.9±18.3	50.2±19.4	53.6±17.3	48.0±19.0	53.2±14.8
Pain (VAS) (mm)	61.2±16.8	64.0±12.7	66.4±11.3	59.2±13.3	57.6±9.0
50-foot walk (seconds)	18.3±6.9	16.8±7.0	15.6±3.2	15.7±5.4	15.7±2.8
Range of Motion (degrees)	108.7±14.6	114.4±10.4	115.3±10.5	112.8±12.6	115.6±9.6

Values are mean ± SD except otherwise stated.
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Adherence

Subjects completing 80% or more of assigned visits (8 or 12 visits, based on treatment assignment) were considered adherent; 119/125 subjects were adherent to all assigned massage visits with no significant differences in adherence between treatment assignments (Figure 1).

Adverse Effects

No adverse effects related to the intervention were seen during the course of the study.

Discussion

This was the first formal dose-finding study of massage therapy for any condition. This study investigated four different doses of tailored Swedish massage, varying both the time (30 vs. 60 minutes per treatment) and frequency (once a week vs. twice a week for the first month) to determine an optimal, practical dose to use in future studies. Our manualized protocol incorporated standard Swedish massage techniques focused on osteoarthritis of the knee, based on the protocol used in our Phase 1 study. We operationally defined 'optimal-practical' as 'producing the greatest

Table 3. Mean change (95% CI) in outcomes at 8-weeks post-baseline (primary endpoint).

GROUP (n)	Group 1 (n = 22)	Group 2 (n = 24)	Group 3 (n = 24)	Group 4 (n = 25)	Usual Care (n = 24)
DOSE	**30 min 1×/wk**	**30 min 2×/wk**	**60 min 1×/wk**	**60 min 2×/wk**	**(no massage)**
TOTAL MASSAGE RECEIVED	**240 min**	**360 min**	**480 min**	**720 min**	**0 min**
WOMAC (mm)					
Pain	−15.1 (−23.4, −6.8)	−14.4 (−23.8, −5.1)	−27.2 (−36.3, −18.0)†	−27.7 (−36.9, −18.6)†	−5.6 (−13.1, 1.9)
Stiffness	−19.0 (−30.4, −7.6)	−23.4 (−34.5, −12.3)	−23.7 (−34.6, −12.7)	−22.3 (−32.9, −11.6)	−6.7 (−15.7, 2.2)
Functionality	−18.0 (−25.5, −10.4)	−17.2 (−26.9, −7.6)	−21.2 (−29.3, −13.1)†	−22.0 (−31.6, −12.5)†	−6.6 (−12.2, −0.9)
Global	−17.4 (−25.3, −9.4)	−18.4 (−27.5, −9.2)	−24.0 (−32.1, −15.9)†	−24.0 (−32.7, −15.3)†	−6.3 (−12.8, 0.1)
Visual Analog Scale (mm)	−14.2 (−25.0, −3.4)	−26.1 (−36.8, −15.3)	−39.8 (−48.1, −31.4)†‡	−31.2 (−39.4, −22.9)†	−9.8 (−18.6, −1.1)
50-foot walk (seconds)	−1.3 (−3.0, 0.4)	−2.4 (−4.7, −0.1)	−1.7 (−2.7, −0.6)	−2.0 (−3.4, −0.6)	−1.3 (−2.4, −0.2)
Range of Motion (degrees)	−2.5 (−7.5, 2.6)	−4.8 (−9.9, 0.4)	−1.3 (−6.2, 3.5)	−6.6 (−11.6, −1.6)	0.2 (−4.1, 4.4)

Values are mean with 95% confidence intervals; negative values indicate improvement;
†Significant (non-overlap) compared to Usual Care;
‡Significant (non-overlap) compared to Group 1.
doi:10.1371/journal.pone.0030248.t003

Table 4. Changes in outcomes at 24-weeks post-baseline.

GROUP (n)	Group 1 (n = 22)	Group 2 (n = 24)	Group 3 (n = 24)	Group 4 (n = 25)	Usual Care (n = 24)
DOSE	**30 min 1×/wk**	**30 min 2×/wk**	**60 min 1×/wk**	**60 min 2×/wk**	**(no massage)**
WOMAC (mm)					
Pain	−12.2 (−22.4, −2.0)	−3.9 (−12.7, 4.9)	−13.7 (−23.4, −4.0)	−14.2 (−24.5, −3.8)	−7.5 (−16.0, 1.1)
Stiffness	−15.4 (−26.4, −4.5)	−9.6 (−20.6, 1.3)	−16.9 (−28.5, −5.2)	−16.8 (−29.7, −3.9)	−6.4 (−13.2, 0.4)
Functionality	−15.3 (−24.5, −6.1)	−7.4 (−14.8, 0)	−12.1 (−22.0, −2.1)	−14.4 (−23.4, −5.4)	−4.2 (−11.1, 2.7)
Global	−14.3 (−22.9, −5.7)	−7.0 (−15.6, 1.6)	−14.2 (−23.4, −5.0)	−15.1 (−25.1, −5.1)	−6.0 (−12.6, 0.5)
Visual Analog Scale (mm)	−14.4 (−25.9, −2.8)	−14.0 (−24.7, −3.3)	−18.5 (−29.0, −8.1)	−22.8 (−35.5, −10.1)	−11.5 (−21.0, −2.0)
Time to walk 50 Feet (seconds)	−2.4 (−4.4, −0.4)	−1.8 (−3.6, 0)	−1.4 (−2.8, 0)	−1.8 (−3.3, −0.3)	−1.4 (−2.6, −0.2)
Range of Motion (degrees)	−4.7±(−10.9, 1.5)	0.4 (−5.7, 4.8)	−2.7 (−7.6, 2.3)	−8.3 (−14.2, −2.5)	−0.3 (−4.7, 4.1)

Values are mean with 95% confidence intervals; negative values indicate improvement.
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ratio of desired effect compared to costs (in time, labor, and convenience).' If the most effective dose were the least labor-intensive, 'optimal' and 'optimal-practical' would be the same.

We were also interested in seeing whether the promising results of our pilot study would be repeated and extended with this now manualized protocol of Swedish massage, with a more diverse population at two sites, with a longer follow up period. The potential effectiveness of this treatment was further supported in this study, as all massage doses demonstrated significant improvement from baseline, as well as differences from usual care in WOMAC Global scores at the termination of massage (8-week timepoint). In addition, all massage groups reported significantly decreased WOMAC Pain as assessed by VAS at the 8-week timepoint compared to baseline, which was also different from usual care for the three highest doses.

Angst et. al estimated minimal clinically important differences (MCID) in WOMAC global scores (for improvement) to be 18% change from baseline [46], while Escobar et al. found that a MCID is approximately 15 points in patients following total knee replacement [47]. In our study, subjects receiving the 60-minute

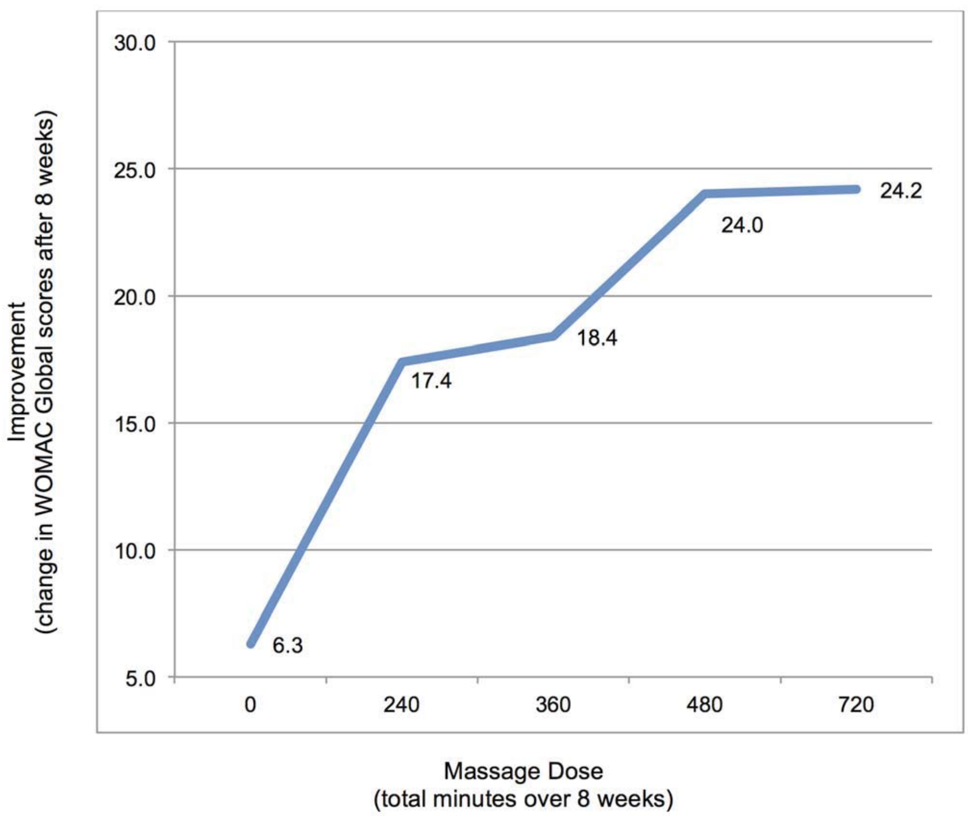

Figure 2. Dose-Response Curve. Dose-response curve plotting dose (total minutes over the course of 8-weeks of massage) (x-axis) vs. improvement (change in WOMAC Global scores after 8-weeks). Dose-response effects plateaued at 480-minutes (Group 3), with no significant improvements noted in the 720-minute (Group 4) dose.
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doses improved a mean of 24.0 points in WOMAC global scores (44%–50% change from baseline). Thus, the magnitude of change in WOMAC scores is highly clinically significant.

Our results suggest a benefit of increasing massage dose with diminishing returns at the highest level. Our dose-response curve based on WOMAC Global scores indicates increasing improvement with greater total dose (minutes) of massage, with a threshold effect at the 480-minute dose (Group 3). While it is difficult to tease out differences due to total dose and effectiveness of 30 vs. 60 minute individual treatments, due to the design of the study, there is a clear trend for greater magnitude of changes in our outcomes in both of the 60-minute doses (Groups 3 and 4), compared to baseline, usual care, and the 30-minute dose groups. There were no significant differences when comparing the 60-minute groups to each other at any time point or for any outcome. WOMAC subscales generally followed the pattern of the global scores, with strongest responses for the higher doses.

The durability of the response in improvement of OA symptoms and functionality to massage treatment was also supported by the results of this study. Our Phase 1 trial [18] demonstrated significant effects of massage therapy 16-weeks post-baseline on the WOMAC, visual analog pain scale, and the 50-foot timed walk. Anticipating similar effects, we assessed subjects at 16 weeks and extended our observations to 24-weeks post-baseline. Although the magnitude of effects was strongest after 8 weeks of treatment and generally decreased with time, the persistence of improvements at 2 months and 4 months after treatment cessation indicate that the effects of the 8 weeks of massage go beyond immediate changes to longer term shifts that may be global and/or localized to the knee, suggesting that periodic maintenance doses of massage may help sustain effects over time. The mechanisms for such persistent benefit are not fully elucidated, and clearly warrant investigation.

All massage groups demonstrated significant improvement in WOMAC Global scores at 16 and 24 week timepoints compared to baseline, whereas those in the usual care group did not (Figure 3). The three highest doses of massage improved relative to baseline in WOMAC pain at 16 and 24 weeks, in stiffness at 24 weeks, and functionality at 16 and 24 weeks.

All groups, including usual care, demonstrated decreases in the timed 50-foot walk compared to baseline, but no clear patterns of dose effect or significant differences between the groups. Larger groups and perhaps a 100-foot walk may be needed to detect between-group differences. Although almost no statistically significant differences between the massage groups and Usual Care were seen in the 16 and 24 week time points, the directionality of all changes was towards improvement, and the magnitude of changes seen was greater than changes seen in Usual Care (Table 4). Our sample size was inadequate to determine statistically significant between-group changes, as the goal for this Phase 2 trial was to determine an optimal-practical dose, rather than to determine efficacy.

Future studies should incorporate larger samples that adequately power for between group changes in longer term effects of massage therapy. The improvements in the Usual Care arm in some outcome measures, possibly due to Hawthorne [48] or other nonspecific effects [49], reduced the magnitude of between-group differences, and reaffirm the importance of control groups in this type of study.

Massage is theorized to work through a variety of mechanisms. Increased blood circulation to the muscles promoting gas exchange and delivery of nutrients and removal of waste products has long been thought to be one of the outcomes and benefits of massage, and recent studies support this effect [50,51,52,53]. There is some evidence for the promotion of a relaxation response and shift to parasympathetic nervous system activation, with reduced heart rate, blood pressure, biochemical, (including blood and salivary stress hormones, endorphins, and serotonin), and brain activation changes, associated with reduced anxiety [40,54,55,56,57,58,59]. This may be mediated through the activation of mechanoreceptors in the deep tissues innervated by alpha beta fibers with subsequent central nervous system (CNS) effects on the pituitary gland and limbic system and/or other mechanisms [60]. The need for moderate pressure to achieve many of the effects of massage therapy may support this mechanism, deserves further investigation, and supports light touch as an appropriate active control for future trials [25,51,55,58,61,62]. A recent study comparing a single session of Swedish massage to light touch showed significant neuroendocrine and immune system changes over time, with differing patterns and degree in the massage and control intervention [59]. Other potential outcomes and mechanisms of massage therapy's effectiveness include decreasing muscle strain, balancing muscle tension across the joint, positive mechanical changes in muscles, increased joint flexibility and proprioception, increased lymphatic circulation, immunologic and inflammatory changes, improved sleep, and blocking pain signals [32,53,63,64,65,66,67]. Research dedicated to exploring the mechanisms of effect is clearly warranted.

Limitations of this trial included a small sample. Further, the truly ''optimal'' dose might differ from any of the four studied. Although additional doses for the massage intervention could have been considered, the regimens that were assessed conform well to massage regimens currently in use, are advocated by massage therapists, and were practical to implement. Our trial was also limited to Swedish massage techniques. This limits generalizability to other techniques, but offers the advantage of clear standardization of the intervention. Swedish technique predominates in clinical settings [68] and is thus the logical, initial choice; other massage techniques should be compared to Swedish massage once its efficacy is established. Further, the Swedish technique has been successfully applied and demonstrated promise in our pilot study [18].

As the mechanism(s) of action of massage are not fully elucidated, it is premature to predict dose-responses for higher or lower doses than the doses utilized in this trial, or applied to clinical models besides osteoarthritis of the knee. For example, if massage enhances regional blood flow, it might be that a follow-up massage too soon (i.e. within one week) actually attenuates benefit by applying pressure to slightly engorged tissue. Thus, there might be an optimal periodicity to massage, with suboptimal effects seen with dosing outside this purported ideal. Changes in neuroendocrine and inflammatory status, pain generation and sensitivity, or musculature strain or balance, may also reach an optimal state, which persists for some time, and is not enhanced by further massage within a weeks' time. Our study, however, did not attempt to establish a dose-response gradient. Rather, the goal was to establish an optimal-practical dose for future testing, based on the combination of convenience, practicability, and therapeutic effectiveness.

Conclusion

This dose-finding trial established an optimal dose of 60-minutes of this manualized Swedish massage therapy treatment delivered once weekly in an eight week protocol for OA of the knee. This decision was based on the superiority of the 60 minute compared to 30 minute treatments, the essentially equivalent outcomes of the two 60 minute doses, the convenience of a once-

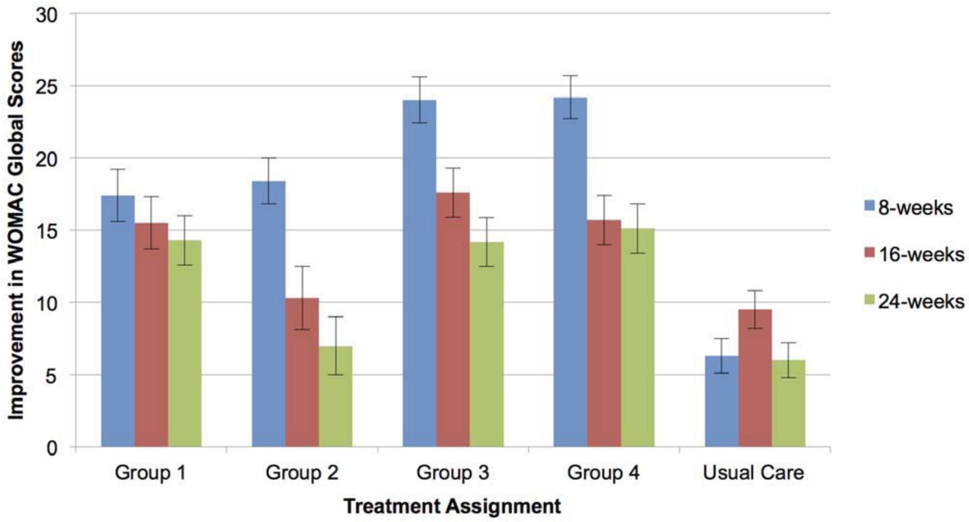

Figure 3. Improvement in WOMAC-Global Scores at Assigned Doses of Massage.
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weekly protocol (compared to biweekly), cost savings, and consistency with a typical real-world massage protocol. As there is promising [18], but not definite [69], potential for the utility of massage therapy for knee osteoarthritis, future research on this standardized approach to massage therapy should utilize this dose. In addition, future, more definitive research is needed investigating not only the efficacy, but also cost-effectiveness of massage for OA of the knee and other joints, as well as research exploring the mechanism(s) by which massage may exert its effects in this clinical application and in general.

Supporting Information

Checklist S1 CONSORT Checklist.
(DOC)

Protocol S1 Trial Protocol.
(PDF)

Acknowledgments

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Author Contributions

Conceived and designed the experiments: AP AA DH SGF DLK. Performed the experiments: AA AD CM. Analyzed the data: AP AA VYN SGF DLK. Wrote the paper: AP AA AD SGF DLK.

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Research Article

Comparative Effects of Acupressure at Local and Distal Acupuncture Points on Pain Conditions and Autonomic Function in Females with Chronic Neck Pain

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Acupressure on local and distal acupuncture points might result in sedation and relaxation, thereby reducing chronic neck pain. The aim was to investigate the effect of acupressure at local (LP) and distal acupuncture points (DP) in females with chronic neck pain. Thirty-three females were assigned to three groups: the control group did not receive any stimuli, the LP group received acupressure at local acupuncture points, GB 21, SI 14 and SI 15, and the DP group received acupressure at distal acupuncture points, LI 4, LI 10 and LI 11. Verbal rating scale (VRS), Neck Disability Index (NDI), State-Trait Anxiety Inventory (STAI), muscle hardness (MH), salivary alpha-amylase (sAA) activity, heart rate (HR), heart rate variability (HRV) values and satisfaction due to acupressure were assessed. VRS, NDI, STAI and MH values decreased after acupressure in the LP and the DP group. HR decreased and the power of high frequency (HF) component of HRV increased after acupressure in only the LP group. Although acupressure on not only the LP but also the DP significantly improved pain conditions, acupressure on only the LP affected the autonomic nervous system while acupuncture points per se have different physical effects according to location.

1. Introduction

Chronic neck pain is a very common symptom especially in females. In general, neck pain is felt as a dull pain, stiffness, or discomfort along the trapezius muscles and the muscles around the scapulae [1]. Common treatment for chronic neck pain consists of medication, trigger point injection, massage, and other physical therapies and patient education [2]. Massage therapy applied on the tender points is popular in patients with chronic neck pain and provides the patients not only with comfort during and immediately after it but also with various side effects such as discomfort/soreness, tiredness/fatigue, and headache afterwards [3]. Recently, alternative therapies such as acupuncture and acupressure have been increasingly sought. Acupressure is a noninvasive and safe technique, which is manipulated with the fingers instead of needles on the traditional acupuncture points, and has been shown to be effective in pain relief, sedation, and relaxation [4, 5]. Tender points located on the trapezius muscles are consistent with local acupuncture points such as "*Jianjing*" (GB 21), "*Jianwaishu*" (SI 14), and "*Jianzhongshu*" (SI 15) and are applied to massage therapy in patients with chronic neck pain. On the other hand, distal traditional acupuncture points, "*Hegu*" (LI 4), "*Shousanli*" (LI 10), and "*Quchi*" (LI 11), are contained in the Large Intestine Meridian of Hand-Yangming and are suggested to be the points for improving neck-shoulder-arm disorders in the Chinese/Japanese traditional medicine.

Chronic pain influences the autonomic nervous system. For example, sympathetic hyperactivation was shown in

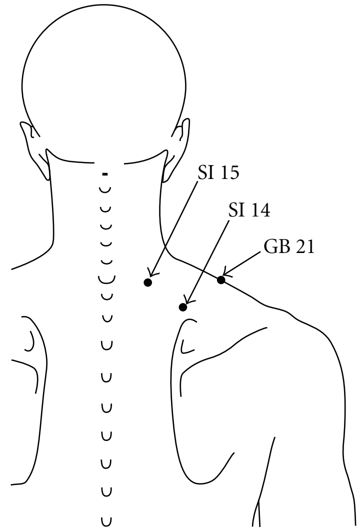

Figure 1: Local acupuncture points/tender points. "*Jianjing*" (GB 21) is located at the highest point on the shoulder and at the midpoint of the line which connects the prominent vertebra and the acromion. "*Jianwaishu*" (SI 14) is located directly above the superior angle of scapula, at 5-6 cm lateral from the posterior midline and below the spinous process of the first thoracic vertebra. "*Jianzhongshu*" (SI 15) is located on the back, at 3-4 cm lateral from the posterior midline and below the spinous process of the seventh cervical vertebra.

fibromyalgia (FM) [6], low back pain [7], whiplash associated disorders [8], and migraine [9]. Furthermore, a study showed functional change of the sympathetic nervous system in workers with chronic neck pain [10]. This abnormality in the sympathetic nervous system might generate and sustain chronic pain [11]. Several reports showed that acupuncture and acupressure on the traditional acupuncture points influence the autonomic nervous system [4, 5, 11, 12]. That is, these procedures could modulate the activities of the sympathetic and parasympathetic nerves.

Autonomic nervous function is known to be reflected in heart rate variability. Rhythmic components of HRV can be quantitatively assessed by means of power spectral analysis. HRV is a reliable and noninvasive tool, used to assess autonomic nervous system regulation of the heart [4, 5]. Frequency fluctuations in low frequency of 0.04–0.15 Hz (LF) component of HRV are considered markers of sympathetic and parasympathetic nerve activities, and high frequencies of 0.15–0.4 Hz (HF) component fluctuation of HRV are considered as a marker of parasympathetic nerve activity. Thus, the LF/HF ratio is considered to be an index of sympathetic nerve activity.

We hypothesized that acupressure not only on the tender points/local acupuncture points, "*Jianjing*" (GB 21), "*Jianwaishu*" (SI 14), and "*Jianzhongshu*" (SI 15), but also on the distal acupuncture points, "*Hegu*" (LI 4), "*Shousanli*" (LI 10), and "*Quchi*" (LI 11), could induce sedation, thereby reducing pain, muscle tone, and disability and changing autonomic nervous activity in subjects with chronic neck pain. In the present study, we therefore investigated what effect pressure applied on the local and distal acupuncture points had on the pain conditions and HRV in females with chronic neck pain.

2. Methods

2.1. Subjects. After obtaining approval from the ethics committee of Nihon Fukushi University and written informed consent, 33 female subjects who complained of chronic neck pain participated in the present study. The subjects were randomly allocated to three groups. The exclusion criteria were menstruation, cardiovascular or neurological disease, or administration of sedatives, analgesic, or other medication.

2.2. Group, Administration, and Measurements. Subjects in the local acupuncture point (LP) group received acupressure at three tender points on the neck/shoulder muscles, which were consistent with local acupuncture points, "*Jianjing*" (GB 21), "*Jianwaishu*" (SI 14), and "Jianzhongshu" (SI 15) (Figure 1), subjects in the distal acupuncture point (DP) group received acupressure at three distal acupuncture points, "*Hegu*" (LI 4), "*Shousanli*" (LI 10), and "*Quchi*" (LI 11) (Figure 2), and subjects in the control group did not receive any stimuli.

All measurements were performed during the afternoon hours. Subjects were assessed regarding pain intensity using verbal rating scale (VRS), pain-related disability using Neck Disability Index (NDI), pain-related anxiety using State-Trait Anxiety Inventory-I (STAI-I), muscle hardness (MH) on bilateral trapezius muscles, pain-associated stress using salivary alpha-amylase (sAA) activity, heart rate variability (HRV), and satisfaction using VRS due to acupressure. For the VRS, the intensity of neck pain or stiffness was evaluated on a numerical scale from 0 to 3 (0: no pain, 1: mild pain, 2: moderate pain, and 3: severe pain). NDI, which was published by Vernon in 1991, is the most commonly used and validated scale designed to assess self-rated disability in patients with neck pain and disorder [13]. MH was evaluated using a tissue hardness meter (PEK-1, Imoto Machinery Co. Ltd., Kyoto, Japan) bilaterally on the midpoint between the spinous process of seventh cervical vertebra and the acromion. This point is located on the trapezius muscles, and the tender point of neck pain often lies on this point, which is just the acupuncture point, "*Jianjing*" (GB 21) [1]. sAA was evaluated using a hand-held sAA monitor (CM-2.1, Nipro, Osaka, Japan) [14]. Satisfaction due to acupressure was evaluated on a numerical scale from 0 to 3 (0: no satisfaction, 1: mild satisfaction, 2: moderate satisfaction, and 3: sufficient satisfaction). VRS and STAI-I before, immediately following, and 1 day after receiving the treatment, MH and sAA before and immediately after the treatment, NDI before and 1 day after the treatment, satisfaction immediately following and 1 day after the treatment were sampled.

After the initial assessment, the subjects were allowed to lie comfortably on the bed in a quiet environment for 5 min. Then, the record of the electrocardiogram (ECG) signals for HRV analysis started.

Table 1: Age, weight, VRS, NDI, STAI, MH, sAA, HR, and HRV values at pretreatment for each group.

	C group ($n = 11$)	LP group ($n = 11$)	DP group ($n = 11$)	P value
Age (yr)	34.8 (4.0)	35.5 (6.4)	37.2 (7.0)	.637
Weight (kg)	50.4 (6.8)	52.3 (10.1)	52.2 (4.8)	.643
VRS	1.8 (0.6)	2.1 (0.5)	1.7 (0.8)	.413
NDI	7.9 (3.8)	9.4 (4.4)	7.6 (4.6)	.430
STAI	39.2 (9.5)	44.5 (8.0)	43.2 (6.8)	.772
MH (N)	56.9 (5.0)	57.4 (4.5)	56.2 (5.3)	.507
sAA (kU/l)	38.2 (20.1)	20.0 (9.0)	36.8 (27.9)	.079
HR (bpm)	65.4 (8.7)	65.8 (6.7)	62.3 (14.1)	.941
LF (ms^2)	490.7(409.2)	274.2 (253.3)	494.1 (1050.7)	.084
HF (ms^2)	381.8(338.3)	212.8 (186.7)	764.8 (1045.2)	.587
LF/HF	1.7(1.4)	1.4 (0.8)	1.0 (0.6)	.399

Values expressed as mean (SD).VRS: verbal rating scale. NDI: Neck Disability Index. STAI: State-Trait Anxiety Inventory-I. MH: muscle hardness. sAA: salivary alpha-amylase. HR: heart rate. LF: the power of low-frequency (0.04–0.15 Hz, LF) component of heart rate variability (HRV). HF: the power of high-frequency (0.15–0.4 Hz, HF) component of HRV. LF/HF: LF/HF ratio of HRV.

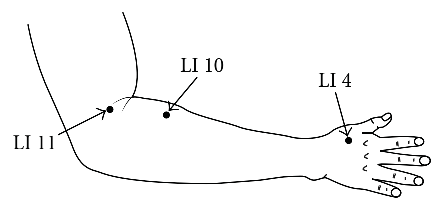

Figure 2: Distal acupuncture point. "*Hegu*" (LI 4) is the most important analgesic point in the body and is intensively stimulated in all painful conditions and is located on the highest point of the adductor pollicis muscle with the thumb and index finger adducted. "*Shousanli*" (LI 10) is located on the radial side of the dorsal surface of the forearm at about 3 cm below the lateral transverse elbow crease and between the extensor carpi radialis longus and brevis. "*Quchi*" (LI 11) is located on the end of the lateral transverse elbow crease at the middle of the connection between the biceps tendon and the lateral epicondylus of the humerus.

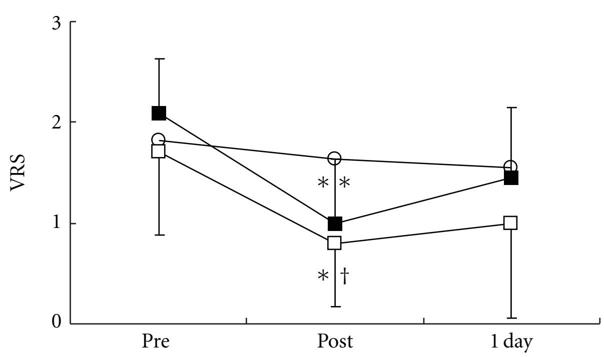

Figure 3: Changes in pain intensity (VRS: verbal rating scale). ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups. * significantly different from pre-treatment in the DP group ($P < .05$). ** significantly different from pretreatment in the LP group ($P < .01$). † significantly different from control group in the DP group ($P < .05$).

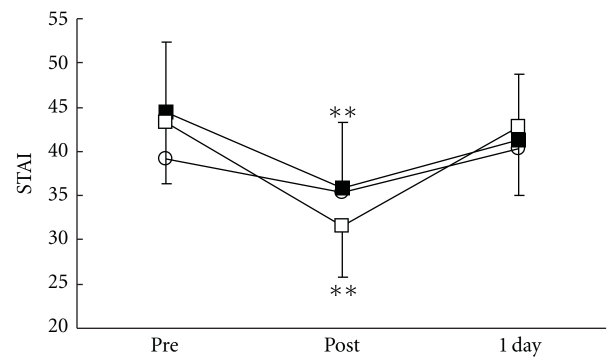

Figure 4: Changes in pain-associated anxiety (STAI-I: State-Trait Anxiety Inventory-I). ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups. ** significantly different from pre-treatment in the LP and the DP groups ($P < .01$).

Ten minutes later, three sets of acupressure by the pulp of the right thumb in a rotary fashion at 20–25 cycles per minute for 30 seconds on each point were administered at the right side of GB 21, SI 14, and SI 15 consecutively and afterwards at the left side of these three points in the LP group. On the other hand, three sets of procedures conducted in the same way as shown in the LP group were administered at the right side of LI 4, LI 10, and LI 11 consecutively and afterwards on the left side of these three points in the DP group. These procedures were applied by the same investigator. Following release of acupressure, the subjects were observed for another 10 minutes. The ECG signals were obtained from a portable ECG (AC301A, GMS, Tokyo, Japan) and transferred to a computer loaded with HRV analysis software (TARAWA/WIN; Suwa Trust, Tokyo, Japan). The R-R intervals (RRIs) were obtained every 10 seconds. The two components of power of the RRI (ms.ms), LF (0.04–0.15 Hz) and HF (0.15–0.5 Hz), were calculated.

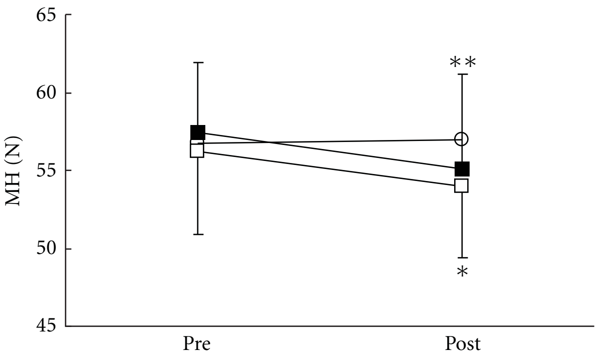

Figure 5: Changes in muscle hardness (MH). ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups. * significantly different from pre-treatment in the DP group ($P < .05$). ** significantly different from pre-treatment in the LP group ($P < .01$).

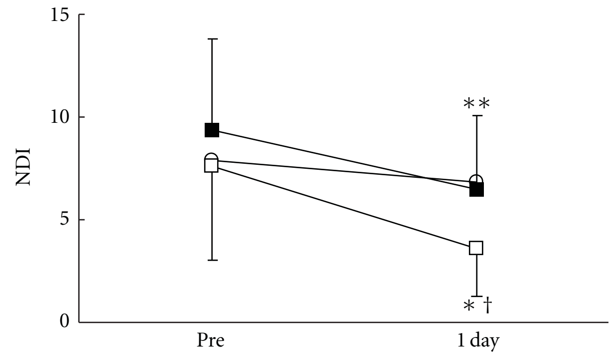

Figure 6: Changes in pain-associated disability (NDI:Neck Disability Index). ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups. * significantly different from pre-treatment in the DP group ($P < .05$). ** significantly different from pre-treatment in the LP group ($p < .01$). † significantly different from control group in the DP group ($P < .05$).

Heart rate (HR) and the LF and the HF values and the LF/HF ratio of HRV were analyzed. The data of HR and HRV values for 30 seconds at 5 minutes before the beginning of the pressure (pre-treatment) and for 30 seconds at 5 minutes after pressure release (post-treatment) were sampled for subsequent analysis.

2.3. Data Analysis. Data was presented as mean (SD). VRS, STAI-I, MH, NDI, HR, and HRV values were analyzed with Kruskal-Wallis test for intergroup comparison followed by Dunn's Multiple Comparison Test. Satisfaction due to acupressure was analyzed with Mann-Whitney's U test for intergroup comparison on the LP and the DP groups. VRS and STAI-I were analyzed using Friedman test for intragroup comparison followed by Dunn's Multiple Comparison Test. Wilcoxon signed-rank test was used to analyze MH, NDI, HR, and HRV values for intragroup comparison. $P < .05$ was considered as statistically significant.

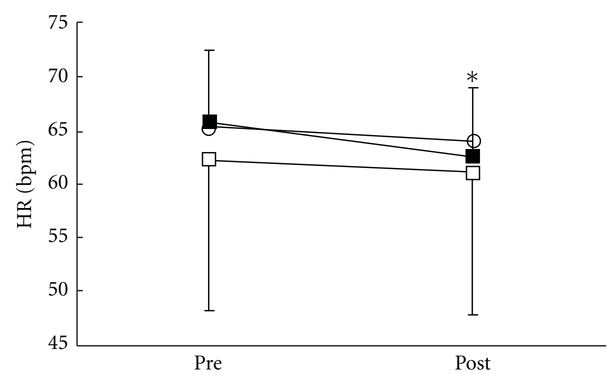

Figure 7: Changes in heart rate (HR). ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups. * significantly different from pre-treatment in the LP group ($P < .05$).

3. Results

Table 1 shows the demographic data of the three groups. There were no significant differences in age, weight, and pre-treatment values regarding pain conditions among the three groups (Table 1).

There were no significant differences in all parameters in the control group. VRS (Figure 3), STAI-I (Figure 4), and MH (Figure 5) values significantly decreased immediately after treatment, and NDI (Figure 6) was lower at 1 day following treatment compared with pre-treatment in the LP and the DP groups. HR (Figure 7) significantly decreased and the HF component of HRV (Figure 9) significantly increased after treatment in the LP group only. There were no differences on the sAA and the LF components (Figure 8) and the LF/HF ratio (Figure 10) of HRV among the three groups. Satisfaction due to acupressure continued to 1 day after the treatment in the LP and the DP groups (Figure 11).

4. Discussion

Our results demonstrated that acupressure on the local and the distal acupuncture points significantly reduced various parameters of the pain-associated conditions, that is, VRS, STAI-I, MH, and NDI whereas there were no significant differences in all parameters in the control group. Although acupressure did not change the LF and the LF/HF ratio of HRV, acupressure on the local acupuncture points significantly reduced HR and increased the HF of HRV. Satisfaction due to acupressure continued until 1 day after treatment on the distal points as well as the local points. These results show that acupressure on not only the local points but also the distal acupuncture points improved pain-related condition, and furthermore acupressure could influence the autonomic nervous system.

Mechanical pressure such as massage and acupressure has been known to decrease tissue adhesion, promote relaxation,

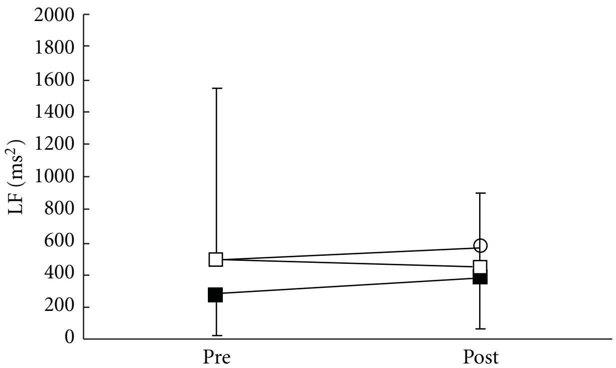

Figure 8: Changes in the low-frequency (LF) component of heart rate variability. ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups.

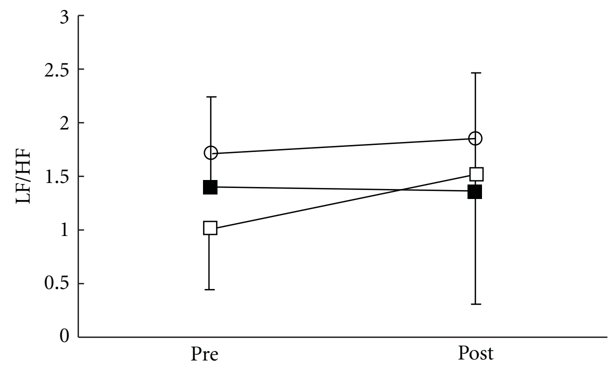

Figure 10: Changes in the LF/HF ratio (LF/HF) of heart rate variability. ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups.

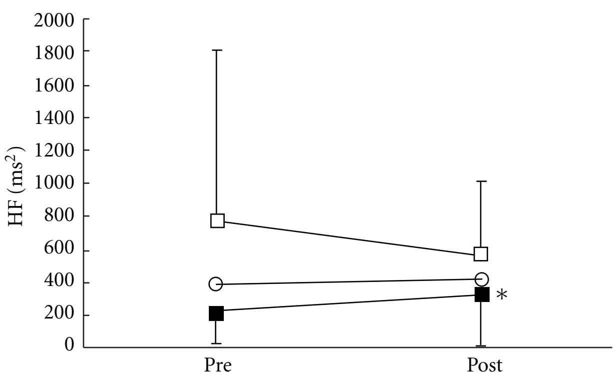

Figure 9: Changes in the high-frequency (HF) component of heart rate variability. ○: control group. ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups. * significantly different from pre-treatment in the LP group ($P < .05$).

increase regional blood circulation, increase parasympathetic nervous activity, increase intramuscular temperature, and decrease neuromuscular excitability [15]. Also, many researchers have demonstrated the effect of acupressure and acupuncture for sedation [4, 5, 16, 17].

Acupuncture on the tender points has been commonly used as a treatment for chronic neck pain and appears to alleviate pain and stiffness [1, 18]. The tender points are known to be located at traditional acupuncture points, "*ah si*" point, and also to conform with trigger points and criterion sites for fibromyalgia [1, 18, 19]. Tender points are supposed to be the site where there are nociceptors and polymodal receptors, which have been sensitized by various factors. Thus, stimulation such as acupuncture and acupressure on the tender points may activate sensitized polymodal receptors more powerfully, resulting in stronger effects on pain relief [1]. In traditional acupuncture medicine, tender points eliciting tenderness or pain could be selected when treating chronic neck pain [1].

Acupuncture treatment typically applies to not only the tender points but also the distal acupuncture points for the treatment of chronic pain. Acupuncture at the distal acupuncture points could improve pain conditions in chronic neck pain patients, indicating that nonsegmental antinociceptive systems may play a major role in acupuncture analgesia [2]. Also, electroacupuncture at the acupuncture point "*Hegu*" (LI 4) decreases the activity on anterior cingulated cortex (ACC) and cingulum, thereby inhibiting nociceptive processing in the brain. Acupuncture point stimulation at a rich nerve junction such as "*Hegu*" may reduce pain-induced cingulation processing, thereby resulting in pain relief/analgesia [20]. A study showed that acupuncture improved pain-related disability assessed by NDI [21], as observed in the present study. Furthermore, acupuncture may improve activities at work, the quality of sleep and consequently tiredness, pain-related quality of life, and psychological variables for women with chronic neck pain [22].

Acupuncture has been reported to affect the autonomic nervous system [11, 23]. However, acupuncture/acupressure might have different physiological effects between local and distal acupuncture points, since we showed that acupressure at LI-4, LI-10, and LI-11 did not, but at GB-21, SI-14, and SI-15 significantly influenced autonomic nervous activity.

There are several limitations to the present study. One of them is that we did not perform longer term followup after acupressure. We need further evaluation of the longer effects of acupressure on chronic neck pain and autonomic nervous system. Another limitation is that we showed only the effect of acupressure on either local or distal points. Most acupuncturists and acupressurists use both local and distal points together in clinical practice. Therefore, further study is required in order to assess combinational effects.

In conclusion, acupressure significantly improved pain conditions on not only the local points but also the distal acupuncture points in females with chronic neck pain but affected the autonomic nervous system on only local acupuncture points, as acupuncture points *per se* have different physical effects depending on location.

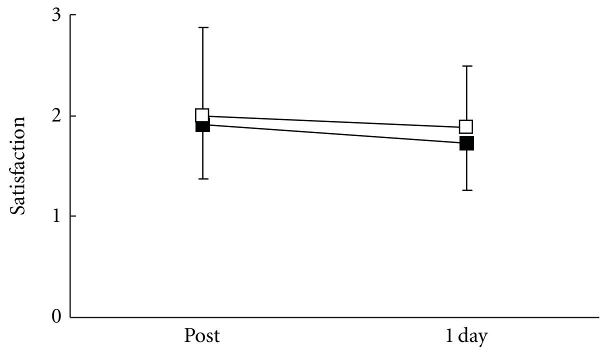

Figure 11: Changes in satisfaction due to treatment (VRS: verbal rating scale). ■: local acupuncture point (LP) group. □: distal acupuncture point (DP) group. Values are presented as mean. SD represented with error bars in the LP and the DP groups.

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