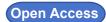
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ORIGINAL RESEARCH



From the Perspective of Myofascial Theory: Warm Acupuncture Combined with Kinesio Taping–A Novel Exploration in the Treatment of Early-Middle Stage Knee Osteoarthritis

Hui Liu 1,*

Department of Rehabilitation, Hangzhou Xiaoshan District Hospital of Traditional Chinese Medicine, 311201 Zhejiang, China

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* Correspondence

Hui Liu

Department of Rehabilitation, Hangzhou Xiaoshan District Hospital of Traditional Chinese Medicine, 311201 Zhejiang, China

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E-mail: xsbsmt121401@163.com

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Abstract

Objective: One frequent degenerative joint condition is osteoarthritis of the knee. The conservative treatment effect for patients in the early and middle stages is often limited. This study investigates the effectiveness of kinesio taping in conjunction with warm acupuncture and myofascial theory-based moxibustion in treating early and middle-stage knee osteoarthritis. Methods: A total of 60 patients with early-middle stage knee osteoarthritis were randomly assigned to the treatment group and control group, with 30 patients in each group. The treatment group received warm acupuncture at myofascial trigger sites along with kinesio taping, while the control group received traditional warm acupuncture and kinesio taping. Both groups were treated for 2 weeks. The clinical efficacy, visual analog scale (VAS) score, joint range of motion (active range of motion (AROM), passive range of motion (PROM)), Lysholm score and isokinetic muscle strength parameters were compared between the two groups. Results: The total effective rate of the treatment group (90.00%) was higher than that of the control group (66.67%, p = 0.028). After 2 weeks of treatment and 3-month follow-up, the VAS score of the treatment group was lower and the Lysholm score was higher (ρ < 0.05). After treatment, the AROM, PROM and isokinetic muscle strength parameters of the treatment group were significantly better (ρ < 0.05). Conclusion: The combination of warm acupuncture at myofascial trigger points and kinesio taping can effectively relieve pain in patients with early to mid-stage knee osteoarthritis, improve joint function and muscle strength, and is worthy of clinical promotion.



1 Introduction

As the population ages, the prevalence of knee osteoarthritis (KOA), one of the most prevalent degenerative joint disorders in the elderly, rises annually [1,2]. According to statistics, over 300 million people worldwide suffer from limited mobility due to osteoarthritis, and 75% of them are caused by KOA [3]. The main pathological features of this disease include degeneration of joint cartilage, bone hyperplasia, and dysfunction of surrounding muscles [4]. The clinical manifestations include knee joint pain, stiffness, and limited mobility. In severe cases, patients may lose the ability to walk independently, which significantly affects their quality of life and imposes a heavy medical burden on families and society [5,6].

Currently, the treatment for early and middle-stage KOA mainly relies on conservative interventions. Physical therapy, traditional acupuncture, and oral non-steroidal anti-inflammatory medications are common treatment strategies [7-9]. However, long-term use of oral medications can lead to adverse reactions such as gastrointestinal damage and cardiovascular risks [8]; conventional acupuncture can temporarily relieve pain, but as it targets multiple local acupoints around the joints, it lacks sufficient intervention on the key pathological process of muscle dysfunction, resulting in limited therapeutic effects [9]. Therefore, exploring more precise, safe, and long-lasting treatment plans has become an important direction in clinical research.

The myofascial theory posits that the activation of myofascial trigger points (MTrPs) in the muscles surrounding the knee joint of patients with KOA is a significant cause of pain and functional impairment [10,11]. These trigger points, by forming local spastic bands and releasing pain-inducing substances, not only directly cause pain but also lead to decreased muscle strength and reduced joint stability [11].

Therefore, precise intervention targeting MTrPs may break this cycle and achieve deep regulation of the pathological mechanism of KOA. Warm acupuncture, as an innovative application of traditional Chinese medicine therapy, can improve local blood circulation and relieve muscle spasms by stimulating acupoints [12]. The kinesio taping technique, through special mechanical stimulation to regulate proprioception, enhances muscle recruitment ability and assists in maintaining joint stability [13]. The combination of these two methods has shown a synergistic effect in patients with KOA. However, current clinical studies mostly focus on the combination of conventional acupoint warm acupuncture and kinesio taping [14]. There are no reports on targeted intervention studies for MTrPs, and the efficacy and mechanism of action still need to be verified.

Guided by myofascial theory, this study designed a randomized controlled trial. It compared the efficacy of two approaches in treating early and middle-stage KOA: warm acupuncture at MTrPs combined with kinesio taping, versus conventional acupoint acupuncture combined with kinesio taping. By evaluating indicators such as pain degree, joint range of motion, and muscle function, the clinical value of this treatment plan was explored, providing new evidence-based basis for the precise treatment of early and middle-stage KOA.

2 Materials and methods

2.1 Study design and ethical declaration

This was a prospective randomized controlled study involving 60 patients with early-middle stage KOA admitted to our hospital, who were randomized into the treatment group and control group (30 cases each). The therapeutic efficacy of different interventions was evaluated by comparing relevant indicators at different time points. Written informed consent was obtained from all patients. This study was approved by the Medical Ethics Committee of Xiaoshan

District, Hangzhou.

2.2 Study population

A total of 60 patients meeting the criteria were included. They were randomly divided into the control group and the treatment group using a random number table, with 30 patients in each group. The inclusion criteria are as follows: (1) conform to the diagnostic criteria for knee osteoarthritis established by the American College of Rheumatology (ACR) [15]; (2) confirmed as Kellgren-Lawrence grade I - Ⅲ via X-ray examination; (3) aged between 40 and 70 years; (4) having knee pain lasting for over 3 months, with a visual analog scale (VAS) score of no less than 7 points; (5) the informed permission form has been signed by the patient or members of their family. The exclusion criteria are: (1) presence of severe joint deformity or joint space stenosis (Kellgren-Lawrence grade IV); (2) secondary knee osteoarthritis induced by trauma, rheumatoid arthritis, gout, etc.; (3) history of knee surgery or injection therapy within the past 3 months; (4) skin lesions at the treatment site; (5) suffering from severe systemic diseases like heart failure, liver or kidney dysfunction; (6) having contraindications to acupuncture or moxibustion, such as hemorrhagic diseases; (7) being pregnant or lactating.

2.3 Treatment method

Both groups were treated once daily, 5 times a week, for 2 weeks. The control group received warm acupuncture at conventional knee acupoints, such as Sanyinjiao (SP6), Liangqiu (ST34), Dubi (ST35), Neixiyan (EX-LE4), and Xuehai (SP10). Sterile needles that are disposable (0.30 mm × 40 mm) were inserted perpendicularly 15-25 mm to achieve "deqi". 2 cm-long moxa cones were placed on needle handles, ignited, and needles were retained for 30 minutes after moxibustion. They also received kinesio taping [16]: 5 cm-wide elastic tape was applied along the quadriceps and hamstrings, with the base and end fixed without tension, the middle stretched 10-15% Exploration and Verfication Publishing

over the muscle belly, and replaced every 3 days.

The treatment group underwent warm acupuncture at MTrPs, identified by palpation (local tender points with taut bands or twitch responses) in the quadriceps, hamstrings, and gastrocnemius [17]. Warm acupuncture was administered at these acupoints. Kinesio taping was performed the same way as the control group.

2.4 Observation index

2.4.1 General information

Demographic and clinical baseline information of the two groups of patients was collected at baseline, including gender, age, disease duration, body mass index (BMI), affected joint (left knee, right knee) and Kellgren-Lawrence grade, to assess the comparability of the two groups at baseline.

2.4.2 Clinical efficacy

Clinical efficacy was evaluated in both groups of patients after 2 weeks of treatment. The evaluation criteria were divided into four grades: complete recovery indicated that knee pain was completely relieved and joint function returned to normal; marked improvement indicated that knee pain was significantly alleviated and joint function was basically restored; improvement indicated that knee pain was somewhat relieved and joint function was partially improved; no effect indicated that clinical symptoms did not show significant improvement or even worsened. The formula for calculating the total effective rate was: (number of cases of complete recovery + number of cases of marked improvement + number of cases of improvement) / total number of cases $\times 100\%$ [18].

2.4.3 VAS scale

The VAS scale was used to measure the patients' knee pain levels before treatment (baseline), two weeks following treatment, and at the three-month mark. Higher ratings on the scale, which goes from 0 to 10, indicate more acute pain. This was utilized to measure how much pain had changed in both patient groups before and after therapy, as well as during the follow-up period [19,20].

2.4.4 Joint range of motion

At baseline and 2 weeks after treatment, the active range of motion (AROM) and passive range of motion (PROM) of the knee joints of the two groups of patients were measured and recorded using a measuring instrument to evaluate the improvement effect of the treatment on the functional movement of the knee joints [21].

2.4.5 Lysholm score

At the baseline, 2 weeks after treatment, and 3 months during follow-up, the Lysholm score scale was used to evaluate the overall knee joint function of the patients. The scale has a maximum score of 100, and the higher the score, the better the knee joint function. By comparing the scores at different time points, the dynamic changes in knee joint function of the two groups of patients were analyzed [22].

2.4.6 Isokinetic muscle strength parameters

In order to objectively assess the impact of the treatment on the muscle strength and coordination surrounding the knee joint, the extensor and flexor muscle strength parameters of the two patient groups' knee joints were measured using an isokinetic dynamometer at angular velocities of 60°/s and 180°/s. These parameters included peak torque (PT), peak torque/body weight ratio (PT/BW), average power (AP), and hamstring/quadriceps (H/Q).

2.5 Statistical methods

SPSS 20.0 was used for the statistical analysis [23]. The Shapiro-Wilk test was used to check for normality.

The χ^2 test was used to compare count data. The measurement data was normally distributed and presented as mean ± standard deviation. The independent sample t-test was used for intergroup comparisons, the paired sample *t*-test for intragroup comparisons between two time points, and the repeated measures analysis of variance followed by the Bonferroni test for comparisons across multiple time points. Non-normally distributed variables were presented by the quinterle method [M (P₂₅, P₇₅)], with inter-group comparisons using the Mann-Whitney U test and multiple time point comparisons via generalized estimating equations with Bonferroni test. Rank sum tests were applied to categorical data. Statistical significance was indicated by a p-value < 0.05.

3 Results

3.1 Comparison of general data

Gender, age, disease duration, BMI, lesion site, and Kellgren-Lawrence grading did not differ statistically significantly between the two groups at baseline (Table 1, $\rho > 0.05$).

3.2 Comparison of clinical efficacy

The clinical effectiveness of the two patient groups was assessed following two weeks of treatment. According to the results, the therapy group's overall effective rate was 90.00%, with 12 cases (40.00%) being cured, 10 cases (33.33%) exhibiting notable improvement, 5 cases (16.67%) being effective, and 3 cases (10.00%) being ineffective (Table 2). 9 (30.00%) of the cases in the control group were cured, 8 (26.67%) exhibited significant improvement, 3 (10.00%) were effective, and 10 (33.33%) were unsuccessful (Table 2). The treatment group's overall effective rate was statistically significant (Table 2, ρ = 0.028) and much higher than the control group's (90.00% vs. 66.67%).

Table 1 General data comparison.

Index		Control group (n = 30)	Treatment group (n = 30)	x²/t/Z	P
Gender [case (%)]	Male	12 (40.00)	14 (46.67)	0.271	0.602
Gender [case (%)]	Female	18 (60.00)	16 (53.33)	0.271	
Age (years)		58.47 ± 6.21	60.07 ± 5.11	-1.090	0.280
Disease duration(years)		7 (6-7)	6 (6-7)	-0.968	0.333
BMI (kg/m²)		23.24 ± 2.09	23.18 ± 2.07	0.127	0.899
Locion location [case (0/)]	Left knee	17 (56.67)	15 (50.00)	0,268	0.605
Lesion location [case (%)]	Right knee	13 (43.33)	15 (50.00)	0.200	
	0 grade	2 (6.67)	3 (10.00)		
Kellgren-Lawrence	I grade	5 (16.67)	7 (23.33)	0.606	0.406
grading [case (%)]	II grade	6 (20.00)	5 (16.67)	-0.696	0.486
	Ⅲ grade	17 (56.67)	15 (50.00)		

Note: BMI, body mass index.

Table 2 Comparison of clinical efficacy between the two groups [case (%)].

Clinical efficacy	Control group (n = 30)	Treatment group $(n = 30)$	X²	P
Recovery	9 (30.00)	12 (40.00)		
Improvement	8 (26.67)	10 (33.33)		
Effective	3 (10.00)	5 (16.67)		
Ineffective	10 (33.33)	3 (10.00)		
Overall effectiveness situation	20 (66.67)	27 (90.00)	4.812	0.028

3.3 Comparison of VAS scores

Prior to treatment, the two groups' VAS scores did not differ statistically significantly, according to the comparison of VAS ratings at various time periods (Table 3, ρ = 0.372). At the 3-month follow-up and two weeks after treatment, both groups' VAS scores were significantly lower than their pre-treatment

levels (Table 3, ρ < 0.05), and the treatment group's scores were significantly lower than the control group's (5 (5-6) vs. 6 (6-7), 3 (3-4) vs. 5 (4-6)) (Table 3, ρ < 0.01). In addition, compared with the VAS scores two weeks after treatment in the same group, the VAS scores at the 3-month follow-up were also decreased in both groups (Table 3, ρ < 0.05).

Table 3 Comparison of VAS scores between the two groups.

VAS	Control group $(n = 30)$	Treatment group $(n = 30)$	Wald χ^2	P
Before the treatment	8 (7-9)	8 (7-9)	0.798	0.372
Two weeks after the treatment	6 (6-7) *	5 (5-6) *	8.985	0.003
Follow up for 3 months	5 (4-6) *,+	3 (3-4) *,+	70.579	0.000

Note: VAS, Visual Analogue Scale. Compared with that before treatment in the same group, * ρ < 0.05; compared with the same group after 2 weeks of treatment, * ρ < 0.05.

3.4 Comparison of joint range of motion

The measurement results of joint range of motion showed that there was no statistically significant Exploration and Verfication Publishing difference in AROM and PROM between the two groups before treatment (Table 4, $\rho > 0.05$). Two weeks after treatment, both groups showed significant

improvement in AROM and PROM compared to their respective pre-treatment levels (Table 4, ρ < 0.05). Additionally, two weeks following treatment, the treatment group's AROM (115.73 \pm 4.86°) and PROM

(129.70 \pm 5.19°) were noticeably higher than the control group's (AROM: 107.70 \pm 4.35°, PROM: 113.43 \pm 3.81°), and the differences were statistically significant (Table 4, ρ < 0.001).

Table 4 Comparison of joint range of motion between the two groups.

Index	Time	Control group (n = 30)	Treatment group $(n = 30)$	t	P
AROM	Before the treatment	98.43 ± 2.51	98.07 ± 2.24	0.596	0.553
ARUM	Two weeks after the treatment	107.70 ± 4.35 *	115.73 ± 4.86 *	-6.745	0.000
DDOM	Before the treatment	105.40 ± 2.76	106.20 ± 3.03	-1.068	0.290
PROM	Two weeks after the treatment	113.43 ± 3.81 *	129.70 ± 5.19 *	-13.829	0.000

Note: AROM, active range of motion; PROM, passive range of motion. Compared with that before treatment in the same group, * ρ < 0.05.

3.5 Lysholm score comparison

The comparison of Lysholm scores at different time points showed that there was no statistically significant difference in the scores between the two groups at the baseline (Table 5, ρ = 0.655). Two weeks after treatment and at the 3-month follow-up, the scores of both groups were significantly higher

than those before treatment in their respective groups (Table 5, ρ < 0.05), and the scores of the treatment group were significantly higher than those of the control group (two weeks after the treatment: 70.47 \pm 9.46 vs. 45.13 \pm 5.34; follow up for 3 months: 86.50 \pm 5.90 vs. 56.47 \pm 6.93), and the differences were all statistically significant (Table 5, ρ < 0.001).

Table 5 Comparison of Lysholm scores between the two groups.

Lysholm	Control group (n = 30)	Treatment group (n = 30)	F	P
Before the treatment	24.50 ± 5.48	23.80 ± 6.55	0.201	0.655
Two weeks after the treatment	45.13 ± 5.34 *	70.47 ± 9.46 *	163.024	0.000
Follow up for 3 months	56.47 ± 6.93 * ^{,+}	$86.50 \pm 5.90 *, +$	326.844	0.000

Note: Compared with that before treatment in the same group, * ρ < 0.05; compared with the same group after 2 weeks of treatment, $^+\rho$ < 0.05.

3.6 Comparison of isokinetic muscle strength training parameters

Following two weeks of treatment, the results of the isokinetic muscle strength test revealed that, at baseline, the PT, PT/BW, AP, and H/Q parameters of the extensor and flexor muscles in both groups at 60°/s and 180°/s rotational velocities did not differ statistically significantly (Table 6, ρ > 0.05). The parameters in the treatment group were significantly better than those in the control group, including 60°/s

extensor/flexor muscle PT, $180\,^{\circ}$ /s extensor/flexor muscle PT, 60° /s extensor/flexor muscle PT/BW, 180° /s extensor/flexor muscle PT/BW, 60° /s extensor/flexor muscle AP, $180\,^{\circ}$ /s extensor/flexor muscle AP, $180\,^{\circ}$ /s extensor/flexor muscle AP, $60\,^{\circ}$ /s extensor H/Q, $180\,^{\circ}$ /s extensor H/Q, and the differences were all statistically significant (Table 6, ρ < 0.05). And all of the aforementioned parameters in both groups showed significant improvements after two weeks of therapy when compared to those in the same group before to treatment (Table 6, ρ < 0.05).

Table 6 Comparison of two groups of isokinetic muscle strength training parameters.

Indov	Angular velocity		Time	Control group			
Index	Angula	r velocity	rime	(n = 30)	(n = 30)	E	p
			Before the treatment	46.80 ± 15.34	52.43 ± 20.16	-1.218	0.228
	C00/-	Extensor	Two weeks after the treatment	64.70 ± 21.32 *	91.20 ± 30.90 *	-3.810	0.000
	60°/s	Flexor	Before the treatment	32.53 ± 10.74	36.41 ± 12.03	-1.317	0.193
PT		muscle	Two weeks after the treatment	40.40 ± 8.30 *	66.81 ± 17.01 *	-7.664	0.000
(N/m)			Before the treatment	43.11 ± 12.28	38.46 ± 15.65	1.282	0.205
	1000/	Extensor	Two weeks after the treatment	55.20 ± 18.96 *	72.15 ± 24.98 *	-2.962	0.004
	180°/s	Flexor	Before the treatment	16.88 ± 6.58	17.76 ± 7.79	-0.473	0.638
		muscle	Two weeks after the treatment	23.31 ± 7.13 *	36.54 ± 10.42 *	-5.736	0.000
			Before the treatment	92.67 ± 28.46	96.74 ± 21.59	-0.624	0.535
		Extensor	Two weeks after the treatment	106.21 ± 27.43 *	124.47 ± 25.17*	-2.686	0.000 0.624
	60°/s	Floren	Before the treatment	40.29 ± 8.39	38.49 ± 9.63	0.772	0.443
PT/BW		Flexor muscle	Two weeks after the treatment	58.42 ± 14.89 *	72.90 ± 17.04 *	-3.504	2 0.443 04 0.001 4 0.278 66 0.017
(%)			Before the treatment	45.18 ± 13.69	41.76 ± 10.28	1.094	0.278
		Extensor	Two weeks after the treatment	63.29 ± 15.85 *	75.61 ± 22.45 *	-2.456	0.017
	180°/s	Flexor	Before the treatment	32.46 ± 10.27	34.82 ± 10.77	-0.869	0.389
		muscle	Two weeks after the treatment	53.47 ± 17.16 *	65.13 ± 21.46 *	-2.324	0.024
			Before the treatment	29.50 ± 12.42	31.47 ± 11.90	-0.626	0.524
		Extensor	Two weeks after the treatment	44.40 ± 16.59 *	56.07 ± 18.04 *	-2.608	0.012
	60°/s	Flexor	Before the treatment	15.50 ± 7.26	12.87 ± 4.42	1.697	0.096
AD (M/)		muscle	Two weeks after the treatment	32.23 ± 12.10 *	43.43 ± 10.54 *	-0.626 0.5 -2.608 0.0 1.697 0.0 -3.823 0.0	0.000
AP (W)			Before the treatment	38.27 ± 14.24	34.83 ± 11.96	1.011	0.316
	1909/c	Extensor	Two weeks after the treatment	51.60 ± 17.67 *	61.40 ± 14.45 *	-2.351	0.022
	180°/s	Flexor	Before the treatment	17.43 ± 6.81	16.87 ± 6.66	0.326	0.746
		muscle	Two weeks after the treatment	35.20 ± 12.87 *	46.90 ± 14.98 *	-1.218	0.002
H/Q (%)			Before the treatment	53.50 ± 7.92	51.81 ± 13.67	0.586	0.560
	60°/s	Extensor	Two weeks after the treatment	70.12 ± 7.36 *	74.69 ± 9.25 *) ± 9.25 * -2.113	0.039
			Before the treatment	52.46 ± 10.57	57.48 ± 9.98	-1.891	0.064
	180°/s	180°/s Extensor	Two weeks after the treatment	69.41 ± 6.25 *	76.72 ± 7.56 *	-4.084	0.000

Note: PT, peak torque; PT/BW, peak torque/body weight ratio; AP, average power; H/Q, hamstring/quadriceps. Compared with that before treatment in the same group, * ρ < 0.05.

4 Discussion

KOA is a degenerative disease centered on the degeneration of joint cartilage, involving multiple aspects such as cartilage damage, synovial inflammation, and muscle dysfunction, with pain and functional limitation being its main clinical manifestations [24-26]. MTrPs are contracture nodules with high sensitivity in the muscle fascia [27]. A study involving 70 KOA patients showed that acupuncture on MTrPs can treat knee osteoarthritis, and the morphological changes of trigger points are correlated with the patient's pain symptoms [28]. Although the combined treatment of warm acupuncture and kinesio taping has been proven to improve knee joint function and reduce knee joint effusion in KOA patients [14], there is still a lack of research on the combined application of MTrPs in KOA, and the specific efficacy and advantages need to be clarified.

The benefits of focused intervention were confirmed in this study when the treatment group's overall effective rate (90.00%) was much greater than the control group's (66.67%). This is in line with Wang et al.'s findings [29], which demonstrated that MTrPs acupuncture can effectively alleviate myogenic pain. In this study, the combined effect of moxibustion and kinesio taping further enhanced the therapeutic effect. The control group had relatively limited therapeutic effect as it did not precisely intervene in the abnormal muscle fascia. The VAS score is an important indicator for reflecting knee joint function. The VAS scores of the treatment group were significantly lower than those of the control group after treatment and during follow-up, and continued to decline, suggesting that this therapy has both rapid and long-lasting analgesic effects. This may be related to the disruption of the "pain - muscle spasm" cycle after MTrPs inactivation,

and the combined effect of warm acupuncture and kinesio taping prolonged the analgesic duration [30]. The improvement in joint range of motion (AROM, PROM) indicates an enhancement in joint function. The treatment group showed significantly better AROM and PROM compared to the control group after treatment. Since the MTrPs intervention relieved muscle adhesions and spasms, warm acupuncture relaxed tense muscle fascia, and kinesio taping reduced the muscle tension and increased the range of motion. This aligns with the findings of Lv et al. [28], who found that acupuncture at MTrPs can increase the ROM of patients with KOA. This study further expanded the improvement range through a combined therapy.

The continuous increase in the Lysholm score indicates that the treatment group was more effective in improving the patients' daily activity ability, and this advantage was maintained for 3 months during the follow-up. This is similar to the study by Chen et al. [31], which stated that myofascial release therapy may help increase the strength of the hamstring muscles and alleviate the swelling and pain in the patients' knee joints. The control group, due to the failure to correct the abnormality of the muscle fascia, experienced frequent recurrence of symptoms due to insufficient muscle coordination, and the score improvement was limited. The isokinetic muscle strength parameters showed that the treatment group had better muscle strength indicators at different angular velocities, suggesting that this therapy can enhance muscle strength and coordination. Patients with KOA often experience muscle atrophy due to pain, and MTrPs inactivation restored muscle contraction function. Warm acupuncture promoted muscle fiber repair, and muscle efficacy patches enhanced muscle recruitment. In contrast, in studies using only kinesio

taping, the improvement in muscle strength was weaker [32], indicating that the repair effect of warm acupuncture is indispensable.

This study does, however, have certain drawbacks. The study's single-center design and limited sample size restrict how broadly the findings may be applied; the follow-up period is only 3 months, and the long-term efficacy needs to be verified; the impact on indicators such as inflammatory factors was not explored, and the mechanism of action requires further investigation.

5 Conclusion

In conclusion, the combined treatment of MTrPs warm acupuncture and kinesio taping for early and middle-stage KOA can significantly relieve pain, improve joint function and muscle strength, with long-lasting effects. This provides a better clinical option. In the future, large-sample, multi-center studies should be conducted, combined with molecular methods to explore the mechanism, and further verify its value.

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Not applicable.

Conflicts of Interest

The author(s) declare(s) no conflicts of interest.

Author Contributions

Substantial contributions to conception and design: H.L. Data acquisition, data analysis and interpretation: H.L. Drafting the article or critically revising it for important intellectual content: H.L. Final approval of the version to be published: All authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved: All authors.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Supplementary

Not applicable.

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