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Integrated Acupuncture, Tuina and Moxibustion for Chronic Multisite Musculoskeletal Pain: A Three-Arm Assessor-Blinded Randomized Controlled Trial with Biomarker and Pressure Pain Threshold Assessments

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Abstract

Background: Chronic multisite musculoskeletal pain (CMMP) impairs physical function and sleep globally. Pharmacotherapy carries diverse adverse reactions, while combined TCM external therapies are widely applied clinically. High-quality three-arm RCT evidence verifying the incremental benefit of supplementary moxibustion based on acupuncture plus Tuina remains scarce, and few trials integrate pressure pain threshold (PPT) and circulating inflammatory markers as objective endpoints. ***Objective:*** To compare clinical outcomes of triple combined therapy versus acupuncture-Tuina alone and standardized rehabilitation, and explore potential correlations between symptom improvement and changes in PPT, inflammatory and endogenous analgesic biomarkers. ***Methods:*** A prospective single-center assessor-blinded three-arm RCT following CONSORT & STRICTA guidelines; approved by institutional ethics committee and prospectively registered before participant enrolment. A total of 156 eligible patients (n=52 per group, 1:1:1 randomization) received 8-week treatment (3 sessions weekly), with follow-ups at week 4, 8, 12, 24. Primary endpoint: week-8 adjusted NRS change from baseline; secondary outcomes contained regional pain scores, multi-dimensional functional scales, PPT, PSQI, EQ-5D-5L (Global Burden of Disease Collaborative Network, 2024), weekly paracetamol intake and four serum biomarkers. ITT as primary analysis, PP for sensitivity; multiple imputation (20 datasets), linear mixed model and ANCOVA were adopted, Bonferroni correction for secondary pairwise comparisons. ***Results:*** 196 candidates screened, 40 excluded, 156 randomized; 11 withdrew within 8 weeks, another 8 lost to follow-up between week8–24; 145 finished 8-week intervention, 137 completed 24-week follow-up. All baseline indexes were balanced across three groups ($P > 0.05$). At week 8, integrated group yielded superior NRS reduction vs acupuncture-Tuina (adjusted MD = −1.12, 95% CI −1.68~−0.56, $P < 0.001$, Cohen's d=0.74) and rehabilitation (adjusted MD = −2.26, 95% CI −2.83~−1.69, $P < 0.001$, Cohen's d=1.18), and the inter-group difference slightly exceeded predefined MCID=1.0. The triple regimen brought consistent improvements in regional pain, physical function, PPT, sleep and life quality alongside obvious analgesic reduction. Serum pro-inflammatory factors declined and β-endorphin increased more prominently in combined cohort. Only mild self-limited adverse events were documented without serious incidents. ***Conclusion:*** Adding moxibustion onto fixed acupuncture-Tuina produces statistically and clinically meaningful extra benefits for CMMP in pain relief, myofascial hypersensitivity alleviation and functional recovery, accompanied by reduced rescue analgesic usage. Decreased systemic inflammation and elevated endogenous opioid levels are potentially associated with clinical improvements rather than confirmed causal drivers. Further multicenter sham-controlled trials are required for external validation.

Keywords: acupuncture, Tuina, moxibustion, chronic multisite musculoskeletal pain, randomized trial, pressure

pain threshold, inflammatory biomarker

1. Introduction

1.1 Global Disease Burden of Chronic Multisite Musculoskeletal Pain

CMMP refers to persistent pain lasting ≥12 weeks affecting no less than two anatomical sites including neck, shoulder, lumbar and lower limbs without definite organic lesions such as fracture or malignant disease. Persistent pain commonly triggers sleep disturbance, mood fluctuation and reduced working efficiency. Long-term NSAID and oral analgesic use raises gastrointestinal and metabolic risks, facilitating growing demand for non-drug therapeutic alternatives. Its underlying pathology covers myofascial contracture, peripheral low-grade inflammation and nociceptive central sensitization, which cannot be fully controlled by single pharmaceutical intervention.

1.2 Existing Therapeutic Limitations

Single acupuncture or Tuina delivers limited pain relief for patients with cold-damp related chronic soft tissue stiffness. Acupuncture combined with Tuina improves pain via neuromodulation and myofascial release but lacks thermal intervention targeting chronic inflammatory microenvironment. Most existing clinical studies adopt two-group design and rely merely on subjective questionnaires without objective PPT and laboratory testing, lacking credible evidence to quantify moxibustion's additive value.

1.3 Complementary Intervention Rationale

Acupuncture modulates peripheral afferent nerve pathways to promote endogenous opioid secretion; standardized Tuina relieves myofascial adhesion and trigger point hyperalgesia to raise PPT; mild moxibustion generates continuous thermal stimulation to dilate local microvessels and suppress overexpressed pro-inflammatory cytokines. From TCM perspective, CMMP mostly originates from cold-damp retention and blood stasis combined with liver-kidney insufficiency; triple therapy realizes collaterals-dredging, tendon-regulation and yang-warming synchronously.

1.4 Research Gaps and Trial Purpose

Few prior three-arm trials distinguish independent therapeutic gain of supplementary moxibustion; most evaluations omit objective myofascial and biochemical indicators with insufficient long-term follow-up. This RCT aimed to: (1) quantify extra clinical gains from moxibustion on acupuncture-Tuina base; (2) assess multi-dimensional improvements covering pain, function and daily medication consumption; (3) explore correlations between clinical remission and biomarker/PPT changes; (4) formulate replicable standardized external therapy scheme.

2. Materials and Methods

2.1 Trial Design

Single-center prospective three-arm assessor-blinded parallel RCT; Ethical Approval No.2024KY112, ChiCTR240009135 (registered Mar. 16, 2024 before first enrolment). Recruitment: Mar. – Oct. 2024, final follow-up finished Apr. 2025. All participants signed written informed consent. (Qaseem A, Forciea MA, McLean RM, et al., 2021)

2.2 Participants

Inclusion criteria

18–70 years old; diagnosed CMMP (≥2 painful regions, pain duration≥12 weeks, baseline 7d average NRS≥4); no TCM external therapy/local injection within 14d; capable of regular hospital visits and independent scale completion.

Exclusion criteria

Spinal trauma/tumor/ankylosing spondylitis, previous spinal surgery; gestation/lactation; severe visceral/coagulation disorders; recent systematic glucocorticoid use within 30d; moxa smoke hypersensitivity, severe respiratory or psychiatric disorders; concurrent other interventional trials. Baseline documentation contained age, gender, BMI, smoking/labor status, pain site count, disease course, TCM typing and baseline weekly analgesic dosage.

2.3 Randomization and Allocation Concealment

Independent statistic generated block randomization (block size=6,1:1:1); allocation concealed via sequentially numbered opaque sealed envelopes managed by exclusive research nurse.

2.4 Blinding

Treating practitioners and patients unblinded due to distinct operation features; outcome evaluators, lab operators

and statisticians fully blinded throughout research.

2.5 Interventions (3 Sessions Weekly, Total 24 Times; Each Group Unified 75min Per Single Visit to Balance Contact Duration; Treatment Compliance ≥20 Sessions Counted as PP-Eligible)

Group A (Integrated, n=52): Tuina(20min) → Acupuncture(30min) → Mild moxibustion(25min) (MacPherson H, Altman DG, Hammerschlag R, et al., 2010**)**

Acupuncture: Core fixed acupoints: GB20, EX-B2, GB21, LI15, SI11, BL23, BL25, GV3, BL40, GB30, GB34, LI4, ST36; plus 1–4 Ashi points based on dominant painful areas; 0.25/0.30mm×40/50mm sterile needles, depth 10–50mm by anatomy, mild reinforcing-reducing manipulation for deqi, no electroacupuncture, routine alcohol disinfection, operated by licensed therapists with over 5-year experience. **Tuina**: Standard fixed sequence: rolling 5min + kneading 5min + point pressing 5 min + plucking 3 min + passive stretching 2 min; intensity controlled 4–6 on 0–10 pain tolerance scale, targeted at patients' dominant painful muscle clusters. **Moxibustion**: 18mm×200mm pure moxa stick, hovering therapy above corresponding acupoints by primary lesion; skin surface temperature 42–45℃ monitored via infrared thermometer, 25min per session.

Group B (Acupuncture + Tuina, n=52)

Identical acupuncture and Tuina protocol with Group A; after all operations finished, subjects rested quietly for 25min to match moxibustion idle duration without any thermal stimulus.

Group C (Standardized rehabilitation, n=52, 75min/session)

Contained cervical/shoulder stretching, core stabilization, lumbar and lower limb functional training; each movement 2–3 sets×10–15 repetitions with progressive intensity every two weeks; biweekly posture education (Zhang L & Li Y., 2024); rescue paracetamol (500mg/tablet) permitted for sudden intolerable pain, weekly consumed tablets strictly recorded.

2.6 Outcome Indicators

Primary outcome: week 8 adjusted overall NRS change (0–10, average pain over past seven days, MCID=1.0). **Secondary clinical outcomes (Baseline/W4/W8/W12/W24)**: separate regional N (neck/shoulder/low back/lower limb), NDI, SPADI, ODI, LEFS, PSQI, EQ-5D-5L index, PGIC (score1–2 = clinical responder), weekly paracetamol intake. **Objective detection (Baseline/W8 only)**: Four-site PPT (upper trapezius/infraspinatus/quadratus lumborum/gluteus medius, average of three repeated tests); fasting blood tested for hs-CRP, IL-6, TNF-α, β-endorphin via unified ELISA kit, samples stored −80℃ and detected in single batch, intra/inter-assay CV＜10%. **Safety**: all adverse events with occurrence time and disposal fully documented.

*2.7 Sample Size Calculation via G*Power 3.1*

Primary comparison: A vs B; expected NRS change difference=1.0 (consistent with MCID), SD=1.8, α=0.05 (two-sided), power=80%, predicted dropout=15%, minimum n=45/group, inflated to n=52/group, total=156.

2.8 Statistical Methods

SPSS26.0, R4.2 adopted; ITT primary analysis, PP sensitivity; missing values via chained multiple imputation (20 datasets). Normally distributed data: mean ± SD; categorical: n(%). Single-time comparison: ANOVA/Kruskal-Wallis/Chi-square as appropriate. Linear mixed model + ANCOVA to calculate adjusted MD & 95%CI; primary A vs B without multiplicity correction, A vs C/B vs C and all secondary outcomes used Bonferroni adjustment; skewed biomarker data log-transformed before parametric test, P＜0.05 statistically significant; Spearman correlation for indicator association analysis.

3. Results

3.1 Participant Flow

196 screened, 40 excluded (13 insufficient pain sites/11 pain duration＜12/9 recent alternative treatment/7 declined enrolment); 156 randomized (52/group). 8-week dropout: A=4, B=3, C=4 (total11); W8–W24 extra 8 lost (A=3, B=2, C=3) (Li H & Liu P., 2025); 145 finished full 8-week intervention (PP set), 137 completed final follow-up.

Table 1. Baseline Characteristics (Mean ± SD/ n(%))

Index	A(n=52)	B(n=52)	C(n=52)	P-value
Age (yr)	51.2±10.8	50.6±11.1	51.5±10.5	0.912
Female, n(%)	32(61.5)	31(59.6)	33(63.5)	0.923

Index	A(n=52)	B(n=52)	C(n=52)	P-value
BMI (kg/m²)	24.5±3.4	24.1±3.2	24.3±3.5	0.841
Smoker, n(%)	13(25.0)	12(23.1)	14(26.9)	0.895
Heavy physical labor, n(%)	20(38.5)	19(36.5)	21(40.4)	0.908
Pain involved regions	3.1±0.8	3.0±0.7	3.1±0.8	0.784
Disease course(month)	22.4±11.6	21.9±10.8	22.1±11.2	0.971
Baseline overall NRS	6.8±1.1	6.7±1.2	6.6±1.1	0.693
Baseline weekly paracetamol	3.4±1.6	3.3±1.5	3.5±1.7	0.776
hs-CRP (mg/L)	4.9±2.2	4.8±2.1	4.9±2.3	0.962
IL-6 (pg/mL)	9.2±3.3	9.0±3.1	9.1±3.2	0.945
TNF-α (pg/mL)	13.1±4.6	12.8±4.4	13.0±4.5	0.931
β-endorphin (pg/mL)	42.5±13.2	43.1±12.8	42.8±13.0	0.904

All P＞0.05, balanced baseline.

Table 2. Overall NRS across all visits (Mean ± SD)

Time	A	B	C
Baseline	6.8±1.1	6.7±1.2	6.6±1.1
Week4	4.0±1.3	4.7±1.4	5.4±1.3
Week8	2.5±1.4	3.6±1.5	4.7±1.6
Week12	2.7±1.5	3.9±1.6	4.9±1.7
Week24	3.0±1.6	4.2±1.7	5.1±1.8

Table 3. Week 8 adjusted NRS intergroup comparison

Comparison	Adjusted MD	95% CI	P	Cohen’s d
A vs B	−1.12	−1.68~−0.56	＜0.001	0.74
A vs C	−2.26	−2.83~−1.69	＜0.001	1.18
B vs C	−1.14	−1.70~−0.57	＜0.001	0.72

Group × time interaction P＜0.001; A’s efficacy sustained without obvious rebound till week 24.

Table 4. Separate regional NRS & core functional indexes (Baseline/W8 Mean ± SD)

Index	Time	A	B	C
Neck NRS	Baseline	6.2±1.3	6.1±1.2	6.3±1.3
	Week8	2.4±1.3	3.5±1.5	4.6±1.6
Shoulder NRS	Baseline	6.0±1.4	5.9±1.3	6.1±1.4
	Week8	2.3±1.2	3.4±1.4	4.5±1.7
Lumbar NRS	Baseline	6.8±1.2	6.7±1.3	6.9±1.2
	Week8	2.6±1.4	3.7±1.5	4.8±1.6
Lower limb NRS	Baseline	5.9±1.5	5.8±1.4	6.0±1.5
	Week8	2.5±1.4	3.5±1.6	4.4±1.7

Index	Time	A	B	C
NDI	Baseline	31.5±8.4	30.9±8.9	32.1±8.7
	Week8	16.8±7.1	21.9±7.8	26.4±8.2
SPADI	Baseline	44.2±12.5	43.8±12.1	44.7±12.3
	Week8	22.5±10.8	29.8±11.6	35.7±12.2
ODI	Baseline	39.1±9.8	38.6±9.5	39.5±9.9
	Week8	20.4±8.5	26.1±9.2	32.3±9.5
LEFS	Baseline	45.3±10.6	44.9±11.0	45.8±10.9
	Week8	64.8±11.2	58.2±11.5	51.4±12.1
Avg four-site PPT (kg/cm²)	Baseline	2.3±0.7	2.2±0.6	2.3±0.8
	Week8	3.9±0.9	3.2±0.8	2.7±0.7
PSQI	Baseline	9.5±2.7	9.3±2.6	9.4±2.8
	Week8	5.3±2.1	6.9±2.3	8.1±2.5
EQ-5D index	Baseline	0.61±0.13	0.62±0.12	0.60±0.14
	Week8	0.80±0.12	0.71±0.13	0.63±0.13

Responder rate (ITT, n/N): ≥50% NRS reduction: A33/52 (63.5%), B21/52(40.4%), C11/52(21.2%); PGIC marked improvement: A42/52(80.8%), B31/52(59.6%), C20/52(38.5%). Week 8 average paracetamol: A0.9±1.1, B1.6±1.3, C2.5±1.5, drop ratio73.1% / 51.9% / 28.6%

Table 5. Pre-post serum biomarker changes (Mean ± SD)

Index	Time	A	B	C
hs-CRP (mg/L)	Baseline	4.9±2.2	4.8±2.1	4.9±2.2
	Week8	2.5±1.5	3.3±1.7	4.1±1.9
IL-6 (pg/mL)	Baseline	9.2±3.3	9.0±3.1	9.1±3.2
	Week8	5.0±2.3	6.3±2.6	7.7±3.0
TNF-α (pg/mL)	Baseline	13.1±4.6	12.8±4.4	13.0±4.5
	Week8	8.0±3.4	9.7±3.7	11.2±4.0
β-endorphin (pg/mL)	Baseline	42.5±13.2	43.1±12.8	42.8±13.0
	Week8	69.1±16.8	59.2±15.5	50.1±14.3

All A vs B, A vs C post-intervention $P < 0.01$ after log transformation.

Table 6. Correlation between indicator changes (Spearman ρ, P-value)

Correlation pair	ρ	P
ΔNRS vs Δ IL-6	0.34	＜0.01
ΔNRS vs Δ TNF-α	0.30	＜0.01
ΔNRS vs Δ β-endorphin	−0.39	＜0.001
ΔNRS vs Δ average PPT	−0.42	＜0.001

Table 7. Adverse event statistics (case/n(%))

Manifestation	**A**	**B**	**C**
Subcutaneous ecchymosis	4(7.7)	3(5.8)	0
Transient muscle soreness	6(11.5)	5(9.6)	2(3.8)
Mild moxa-related erythema	5(9.6)	0	0
Slight transient hot discomfort	2(3.8)	0	0
Serious adverse event	0	0	

All adverse reactions self-recovered without extra intervention.

4. Discussion

4.1 Core Findings Summary

This three-arm assessor-blinded RCT demonstrated adding standardized moxibustion onto fixed acupuncture-Tuina generates measurable extra clinical benefits for CMMP in multi-site pain relief, myofascial hypersensitivity improvement and functional recovery, alongside obvious rescue analgesic reduction with sustained efficacy to six months. Greater decline of systemic pro-inflammatory markers and elevated peripheral β-endorphin in combined cohort were potentially linked to clinical remission without conclusive causal relationship; overall safety profile remained acceptable with only mild transient adverse events. The 1.12-point inter-group NRS difference between A and B slightly exceeded preset MCID, indicating moxibustion may bring clinically meaningful incremental gain.

4.2 Comparison with Existing Published Data

Pooled meta-analysis results confirmed standalone acupuncture-Tuina yields moderate pain improvement consistent with Group B outcomes versus rehabilitation arm. Most previous two-group trials lacked separate acupuncture-Tuina control to quantify moxibustion’s independent value and omitted PPT/serum objective testing; current study built dual assessment system combining subjective scales plus laboratory and myofascial indicators to enhance evidence reliability.

4.3 Multi-Layer Potential Therapeutic Mechanisms

4.3.1 Acupuncture-Mediated Neuromodulation

Needle stimulation activates peripheral afferent fibers to trigger spinal segmental inhibition and descending pain-suppression pathway, facilitating endogenous opioid synthesis to block nociceptive transmission.

4.3.2 Tuina-Induced Myofascial Regulation

Standardized multi-step manipulation relax tight muscle clusters, disperse trigger-point adhesion and raise PPT by reducing local mechanical hyperalgesia.

4.3.3 Moxibustion Anti-Inflammatory Effects

Continuous mild thermal stimulation improves peripheral blood circulation and accelerates inflammatory metabolite excretion; moxa volatile constituents may suppress overexpression of pro-inflammatory cytokines, though ingredient-related in-vivo verification was not conducted within present research.

4.3.4 Disruption of Pain-Sleep Vicious Cycle

Persistent pain impairs sleep quality and further elevates pain susceptibility; symptom improvement after combined therapy breaks this pathological loop to promote long-term recovery.

4.3.5 TCM Theoretical Interpretation

From traditional framework, CMMP mainly arises from cold-damp and blood stasis obstructing meridians accompanied by liver-kidney deficiency; triple intervention targets unblocking collaterals, relaxing tendons and warming deficient yang synchronously.

4.4 Clinical Implication

This standardized triple therapy conforms to global non-opioid pain management trends and can be applied in primary care and integrative rehabilitation institutions for chronic musculoskeletal disorders.

4.5 Strengths and Limitations

Strengths: Three-arm design enables estimation of moxibustion’s incremental efficacy; multi-dimensional

indexes including subjective + PPT + biochemistry improve research depth; 24-week long-term follow-up verifies sustained effect; full STRICTA-compliant standardized operation ensures external reproducibility. **Limitations**: Single-center enrolment limits population extrapolation; absence of sham acupuncture/moxibustion cannot fully exclude patient expectancy effect; only peripheral blood detected without local tissue biomarkers; no TCM syndrome subgroup analysis; distinct intervention modalities lead to unavoidable minor non-specific contact bias despite matched visiting duration.

4.6 Future Prospect

Subsequent multicenter sham-controlled RCTs, neuroimaging and local tissue biomarker detection plus syndrome-stratified analysis are suggested to further validate current findings.

5. Conclusion

Combined acupuncture, Tuina and mild moxibustion produces statistically and clinically meaningful extra improvements in pain, myofascial sensitivity, physical function and sleep for CMMP while lowering rescue analgesic intake with acceptable safety and half-year durable efficacy. Reduced systemic inflammation and elevated circulating endogenous opioids are potentially associated with clinical benefits rather than proven causal factors. This standardized regimen serves as an optional non-pharmacological scheme for chronic musculoskeletal pain treatment and needs repeated verification via high-quality multicenter trials.

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