

Clinical efficacy and safety of a novel acupuncture point combination for knee osteoarthritis: A Randomized Controlled Trial

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Research Article

Keywords: Knee osteoarthritis, Pain, Acupuncture, Acupuncture point combination, Randomized controlled trial

Posted Date: July 2nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9863569/v1>

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Additional Declarations: No competing interests reported.

Abstract

Introduction: Chronic pain in knee osteoarthritis (KOA) is bidirectionally linked with emotional disorders. This randomized controlled trial evaluated the efficacy and safety of a novel acupuncture point combination for KOA.

Methods: Between March 2025 and December 2025, a total of 80 patients were randomized 1:1 to the Novel Acupuncture Point Combination (NAPC) group or the Standard Peri-Knee Acupuncture (PKA) group. Both groups received conventional peri-knee acupuncture treatment, while the NAPC group additionally received acupuncture at the "Three Shen" head points. Treatment was administered 3 times per week for 4 weeks. The primary outcome was the Numerical Rating Scale (NRS). Additional outcomes included the Self-Rating Anxiety Scale (SAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the response rate assessed at weeks 4, 8, and 12, as well as serum 5-hydroxytryptamine (5-HT) levels measured before and after treatment. Outcome assessors and statisticians remained blinded to treatment assignment. All main analyses were by Per-Protocol.

Results: Of the 80 participants recruited in the trial, 75 were evaluated for efficacy. Both groups showed significant reductions in NRS, SAS and WOMAC over time (all $P < 0.001$), with greater pain and anxiety improvement in the NAPC group and a significant group-by-time interaction ($P < 0.05$). Serum 5-HT levels increased in both groups, with a larger post-treatment rise in the NAPC group ($P < 0.05$). Response rates were consistently higher with NAPC group, although between-group differences were not statistically significant. No serious adverse events were observed.

Conclusion: Compared to the peri-knee acupuncture, the novel acupuncture point combination conferred additional benefits in alleviating pain and anxiety, which may be associated with elevated serum 5-HT levels.

1. Introduction

Knee osteoarthritis (KOA) is a chronic degenerative joint disease with high prevalence and disability rates, predominantly affecting middle-aged and older adults[1]. Epidemiological data indicate that the overall prevalence of symptomatic KOA in China is 14.6%, increasing almost linearly after the age of 40, and imposing a substantial social and economic burden[2]. Pain is the primary reason for most patients with KOA to seek medical care, with more than 75% reporting daily pain-related distress[3]. The mechanisms underlying KOA pain are complex and involve multiple interacting factors, including imbalance of the local inflammatory microenvironment, abnormal biomechanical loading, and changes in neural plasticity[4]. Beyond these biological factors, a growing body of evidence suggests that the onset and progression of KOA are also closely associated with psychosocial factors such as emotional disturbances and cognitive impairments.

The comorbidity of KOA and emotional disorders has attracted increasing clinical and public health attention. A cohort study reported a bidirectional association between KOA pain and

anxiety/depression[5]. Approximately 91% of older adults with KOA experience at least mild depressive symptoms, and about 15% suffer from moderate to severe depression[6]. Adverse emotional states can further exacerbate pain perception via mechanisms including impaired pain regulation, inflammatory responses, and neural remodeling. This not only increases healthcare utilisation, medication use, and medical costs[7], but also reduces treatment adherence and impairs long-term rehabilitation outcomes, thereby complicating disease management. Therefore, exploring an integrated mind-body intervention that addresses both pain control and emotional regulation is critical to breaking the vicious cycle between pain and emotional disturbances and improving long-term therapeutic outcomes.

Acupuncture is a non-pharmacological treatment for KOA explicitly recommended by international osteoarthritis guidelines. Many high-quality clinical studies[8] have confirmed that it effectively relieves pain, improves joint function, and has a favorable safety profile in patients with KOA. However, most mainstream intervention protocols in published studies on acupuncture for KOA focus on local joint pathology. They have not yet addressed the critical impact of emotional status on pain perception and treatment response. Acupuncture interventions targeting the pain-emotion interaction remain scarce. This failure to leverage acupuncture's core advantages of bidirectional regulation, multi-target effects, and holistic therapy may explain the suboptimal response observed in some patients. Therefore, adding an acupoint combination with mood-regulating properties to conventional acupuncture is expected to provide additional analgesic benefits for patients with KOA.

The mood-regulating acupoint used in this study (Three Shen head points: Shenting [GV24], Benshen [GB13], Sishencong [EX-HN1]) is derived from the academic thought of Professor Yang Jiasan, a renowned Chinese acupuncturist. Many clinical studies have confirmed that this acupoint combination can significantly improve anxiety and depressive symptoms, with a solid clinical application foundation. However, no high-quality international clinical studies have yet verified whether adding this combination to guidelines-recommended conventional local acupuncture for KOA can provide additional analgesic benefits or explored its underlying mechanisms. Although a small number of exploratory studies have been conducted in China, most are limited to preliminary efficacy observations. They generally suffer from methodological limitations including small sample sizes and high heterogeneity in intervention protocols. We therefore designed a randomized controlled trial to evaluate the clinical efficacy and safety of a novel acupuncture point combination for KOA on pain, knee function, mood, and serum 5-hydroxytryptamine (5-HT), with the aim of providing novel acupoint selection strategies for clinical practice.

2. Materials and methods

2.1 Study design

This single-center randomized controlled trial was conducted in the acupuncture outpatient clinic of Dongfang Hospital, Beijing University of Chinese Medicine. The study protocol was approved by the Clinical Research Ethics Committee of Dongfang Hospital (JDF-IRB-2023055803), and the trial was

registered in the Chinese Clinical Trial Registry (ChiCTR2400080288). The reporting for the trial followed the Consolidated Standards of Reporting Trials (CONSORT) guideline [9].

2.2 Participants

Participants were recruited through posters and WeChat (a social media networking platform) between March 2025 and December 2025. A total of 96 patients were screened, of whom 80 were enrolled according to the predefined eligibility criteria. All enrolled participants provided written informed consent prior to participation (Fig. 1).

Patients were eligible if they met the American College of Rheumatology clinical criteria[10] for KOA, were 45–75 years of age, had experienced knee pain for more than 6 months, had radiographic evidence of KOA with a Kellgren–Lawrence grade[11] of 1, 2, or 3, and reported a pain score of ≥ 4 on the 0–10 numeric rating scale (NRS), with higher scores indicating more severe pain.

Exclusion criteria were as follows: a history of serious adverse reactions to acupuncture (e.g., syncope or needle allergy); long-term use of medications that could confound treatment efficacy (including non-steroidal anti-inflammatory drugs, glucocorticoids, or other analgesics); a history of or scheduled knee surgery; knee pain attributable to other conditions (such as rheumatoid arthritis, gout, or traumatic injury); receipt of acupuncture for KOA within 1 month prior to enrollment; severe cardiac, hepatic, renal, or coagulation dysfunction; pregnancy or lactation; or psychiatric conditions that could compromise compliance with the treatment protocol. All participants were required to abstain from analgesic medications for at least 48 h before each treatment session.

2.3 Randomization and masking

Participants were randomly assigned in a 1:1 ratio to the Novel Acupuncture Point Combination (NAPC) group or the peri-knee acupuncture (PKA) group using a computer-generated simple random sequence. The randomization sequence was prepared by an independent research assistant who was not involved in any other part of the study. Allocation was concealed using sequentially numbered, opaque, sealed envelopes that were opened in order after patient enrollment.

To maintain blinding, each participant received treatment in a private room and was not informed which acupuncture protocol was considered the “test” or “control” intervention. Acupuncturists were allowed to treat both knees if bilateral KOA was present; however, only the most symptomatic knee was selected for outcome assessment throughout the trial. Due to the nature of acupuncture manipulation, acupuncturists could not be blinded to group allocation. Outcome assessors and statisticians remained blinded to treatment assignment.

2.4 Intervention

The acupuncture protocol was developed from clinical experience and expert consensus. Six obligatory acupoints and three adjunct acupoints were used in both the NAPC and PKA groups. The obligatory acupoints were Dubi (ST35), Neixiyan (EX-LE4), Liangqiu (ST34), Xuehai (SP10), Yanglingquan (GB34),

and Zusanli (ST36). In addition, three adjunct acupoints were selected by the acupuncturists from a pool of 18 candidate acupoints according to meridian differentiation (Table 1). On this basis, patients in the NAPC group received additional needling at four mind-regulating points: Shenting (GV24), bilateral Benshen (GB13), and Sishencong (EX-HN1). Deqi sensation was required in all treatment sessions.

Table 1
Selection of adjunct acupoints

Affected meridian	Alternative adjunct acupoints
Stomach meridian of Foot-yangming	ST32, ST40, EX-LE2
Gallbladder meridian of Foot-shaoyang	GB33, GB39, GB41
Bladder meridian of Foot-taiyang	BL40, BL57, BL60
spleen meridian of Foot-taiyin	SP9, SP4, SP6
kidney meridian of Foot-shaoyin	KI10, KI3, KI7
liver meridian of Foot-jueyin	LR7, LR3, LR8

Treatment sessions lasted 30 minutes each and were administered three times per week on alternate days over a 4-week period, for a total of 12 sessions in each group. Disposable, sterile stainless-steel needles (0.25 mm*40 mm) were used for all procedures. All acupuncturists held valid clinical licences and received standardised training on the study protocol before the trial commenced.

2.5 Outcomes

Efficacy outcomes were assessed at baseline and at weeks 4, 8, and 12 after randomization. Week 4 corresponded to the end of treatment, whereas weeks 8 and 12 were follow-up assessments without further acupuncture.

2.5.1 Primary outcome

The primary outcome was pain intensity assessed by the 11-point numeric rating scale (NRS; range 0–10)[12], where 0 indicates no pain and 10 indicates the worst imaginable pain. Patients were asked to rate their average knee pain over the previous week, and the corresponding numerical score was recorded.

2.5.2 Secondary outcomes

Secondary outcomes included anxiety status, assessed using the Self-Rating Anxiety Scale (SAS)[13]; knee function over the previous week, measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function subscale (range 0–96)[14], and changes in serum 5-hydroxytryptamine (5-HT) levels, measured from fasting venous blood samples collected at baseline and at week 4. In addition, we calculated a response rate, defined as the proportion of participants who

simultaneously achieved the minimal clinically important improvement (MCII) in both the NRS (≥ 2 -point reduction from baseline) and the WOMAC function subscale (≥ 6 -point reduction from baseline)[15].

2.6 Adverse events

After each treatment session, potential adverse events (AEs) were actively screened by directly questioning participants and were also recorded if spontaneously reported. All AEs were classified according to their relevance to acupuncture treatment.

2.7 Statistical analysis

Sample size was calculated using SPSS 11 software. The estimation was based on changes in NRS scores reported in previous studies[16], in which the PKA group showed a mean NRS score of 6.0 ± 0.44 . We assumed that, by the end of treatment, the NAPC group would show a 2.0-point greater reduction in mean NRS score from baseline compared with the PKA group, with similar standard deviations between groups. With a two-sided α of 0.05 and 90% power, the required sample size was 32 participants per group. Allowing for a 20% dropout rate, we planned to enroll 80 participants in total.

For descriptive analyses, continuous variables are presented as means (standard deviations, SD) or medians (interquartile ranges, IQR) according to their distribution, and categorical variables are summarised as counts (percentages). Between-group comparisons for categorical variables were performed using Pearson's chi-square test. For repeated-measures continuous outcomes, repeated-measures analysis of variance (ANOVA) was used when the assumptions of normality and sphericity were satisfied; otherwise, a generalized estimating equations (GEE) model was applied, with Bonferroni correction for multiple comparisons. Other continuous variables that followed a normal distribution were analysed using the independent-samples t-test, whereas non-normally distributed data were compared using appropriate non-parametric tests. The per-protocol analysis set, including all participants who completed treatment and follow-up without major protocol violations, was used for the primary analysis. All statistical analyses were conducted using SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). A two-sided P value < 0.05 was considered statistically significant.

3. Result

3.1 Study participants

Ninety-six participants were screened for eligibility, and 80 were recruited and randomly assigned to the two treatment groups (40 to the NAPC group and 40 to the PKA group). No statistically significant differences were observed in baseline demographic or clinical characteristics between the two groups. All participants received at least one treatment session. Five patients (6.25%) discontinued the trial (2 in the NAPC group and 3 in the PKA group), resulting in 75 participants (93.75%) who completed the 8- and 12-week follow-up assessments (38 in the NAPC group and 37 in the PKA group). (Table 2)

Table 2
Demographics and Baseline Characteristics of Participants

Characteristics		NAPC group (n = 38)	PKA group (n = 37)	All participants (n = 75)	P value
Age, mean (SD) years		62.21(8.30)	62.86(9.32)	62.52(8.82)	0.626
Gender, no. (%)	Male	8 (21.1%)	13(35.1%)	21(28%)	0.174
	Female	30(78.9%)	24(64.9%)	54(72%)	
BMI, mean (SD) kg/m ²		24.07(2.54)	25.36(3.12)	24.71(2.89)	0.053
Occupation	Mental	19(50%)	20(54.1%)	39(52%)	0.725
	Manual	19(50%)	17(45.9%)	36(48%)	
Knee OA duration, mean (SD) years		7.11(5.96)	6.81(7.86)	6.96(6.92)	0.308
Disease Stag, no. (%)	Acute Phase	17(44.7%)	13(35.1%)	30(40%)	0.447
	Remission Phase	21(55.3%)	24(64.9%)	60(45%)	
	Recovery Phase	0(0%)	0(0%)	0(0%)	
Radiologic grade, no. (%)	Grade 1	4(10.5%)	3(8.1%)	7(9.3%)	0.828
	Grade 2	20(52.7%)	22(59.5%)	42(56%)	
	Grade 3	14(36.8%)	12(32.4%)	26(34.7%)	
Affected Joints, no. (%)	Left	7(18.5%)	8(21.6%)	15(20%)	0.454
	Right	11(28.9%)	7(18.9%)	18(24%)	
	Bilateral	20(52.6%)	22(59.5%)	42(56%)	
Joint Deformity, no. (%)	Absent	24(63.2%)	26(70.2%)	50(66.7%)	0.514
	Present	14(36.8%)	11(29.8%)	25(33.3%)	
NRS score, mean (SD)		6.18(1.35)	6.14(1.78)	6.15(1.56)	0.597
Abbreviation: BMI, body mass index; NRS, numerical rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SAS, Self-Rating Anxiety Scale; 5-HT, 5-hydroxytryptamine.					

Characteristics		NAPC group (n = 38)	PKA group (n = 37)	All participants (n = 75)	P value
WOMAC score, mean (SD)	Total	33.83 ± 16.42	36.44 ± 17.79	35.12 ± 16.88	0.865
	Pain	7.76(3.57)	8.89(5.14)	8.32(4.38)	0.587
	Stiffness	2.52(1.74)	3.07(2.18)	2.79(1.95)	0.979
	Function	23.55(12.30)	24.49(12.03)	24.01(12.01)	0.842
SAS score, mean (SD)		51.02(5.84)	49.79(4.18)	50.53(5.16)	0.647
Serum 5-HT, mean (SD) ng·L ⁻¹		427.85(27.06)	423.04(23.06)	425.58(22.88)	0.377
Abbreviation: BMI, body mass index; NRS, numerical rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SAS, Self-Rating Anxiety Scale; 5-HT, 5-hydroxytryptamine.					

3.2 NRS

NRS scores demonstrated significant reductions from baseline at all post-treatment time points in both groups (main effect of time: Wald $\chi^2 = 371.79$, $P < 0.001$). At the 12-week follow-up, the NAPC group showed significantly lower NRS scores than the PKA group ($P = 0.003$). A significant group-by-time interaction was observed (interaction effect: Wald $\chi^2 = 15.96$, $P = 0.001$), indicating distinct trajectories of pain reduction between the two groups. The median NRS score in the NAPC group decreased from 6 (IQR: 5, 7) at baseline to 3 (IQR: 1, 4) at week 12, whereas in the PKA group it decreased from 6 (IQR: 5, 8) to 4 (IQR: 3, 4), demonstrating superior and sustained pain improvement in the NAPC group over time.

3.3 SAS

SAS scores demonstrated significant reductions from baseline at all post-treatment assessments in both groups (main effect of time: Wald $\chi^2 = 189.60$, $P < 0.001$). A significant main effect of group was observed (Wald $\chi^2 = 24.91$, $P < 0.001$), with the NAPC group consistently showing lower SAS scores than the PKA group at all time points (all $P < 0.001$). Furthermore, a significant group-by-time interaction was identified (Wald $\chi^2 = 103.62$, $P < 0.001$), indicating divergent temporal patterns between the two groups. The NAPC group exhibited a steeper decline in SAS scores over time and maintained this superior reduction through the 12-week follow-up. (Table 3).

Table 3
Outcomes and differences between groups [Median (IQR)]

Variable	NAPC group (n = 38)	PKA group (n = 37)	U	P value
NRS				
Baseline	6(5,7)	6(5,8)	654	0.597
Week 4	3(2,4) ^{a,d}	3(2,4) ^a	649.5	0.562
Week 8	3(1.75,4) ^a	3(2,4) ^{a,d}	611.5	0.323
Week 12	3(1,4) ^{a,b}	4(3,4) ^{a,c}	425.5	0.003
SAS				
Baseline	50(45.9375,53.75)	50(46.25,51.25)	660	0.647
Week 4	42.5(38.75,45) ^a	45(43.75,49.6875) ^{a,c,d}	318	0.001
Week 8	41.875(38.75,45) ^a	50(45.3125,51.25) ^{a,b}	150	0.001
Week 12	41.25(37.5,45.3125) ^a	50(45,51.25) ^{a,b}	157.5	0.001
WOMAC				
Baseline	34.5(22.5,48.5)	36.5(19,49.5)	694	0.924
Week 4	17(6,26) ^{a,c,d}	18.5(10.25,26.75) ^a	596.5	0.259
Week 8	12(5,24.25) ^{a,b}	17(11,28.5) ^a	554.5	0.115
Week 12	13.5(4,25.25) ^{a,b}	18(10.75,29.5) ^a	533.5	0.072
Significant within-group differences ($P < 0.05$) are indicated as: ^a vs. Week 0; ^b vs. Week 4; ^c vs. Week 8; ^d vs. Week 12.				

Abbreviation: NRS, numerical rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SAS, Self-Rating Anxiety Scale

3.4 WOMAC

Analysis of total WOMAC scores revealed significant improvements from baseline at all post-treatment time points in both groups (main effect of time: Wald $\chi^2 = 232.82$, $P < 0.001$). However, no significant between-group differences were observed in total WOMAC scores (main effect of group: Wald $\chi^2 = 0.82$, $P = 0.365$), and the trajectories of improvement were parallel (interaction effect: Wald $\chi^2 = 4.49$, $P = 0.213$).

Subscale analysis (Table 6) showed significant pain relief over time (main effect of time: Wald $\chi^2 = 144.96$, $P < 0.001$), with better outcomes in the NAPC group (main effect of group: Wald $\chi^2 = 4.25$, $P = 0.039$). Stiffness scores also improved significantly in both groups (main effect of time: Wald $\chi^2 = 108.17$, $P < 0.001$), with greater reductions in the NAPC group (main effect of group: Wald $\chi^2 = 2.61$, $P < 0.001$). Although the overall interaction was non-significant (interaction effect: Wald $\chi^2 = 6.17$, $P = 0.104$), the NAPC group demonstrated additional reductions in stiffness of 0.63 points at week 8 ($P = 0.027$) and 0.78 points at week 12 ($P = 0.018$) compared with the PKA group. Function scores significantly improved over time in both groups (main effect of time: Wald $\chi^2 = 192.39$, $P < 0.001$), with no significant between-group differences (main effect of group: Wald $\chi^2 = 0.18$, $P = 0.672$; interaction effect: Wald $\chi^2 = 4.21$, $P = 0.239$)(Table 3).

Table 6
WOMAC Subscale Scores in the Two Groups Across Study Time Points [Median (IQR)]

Group	Time	WOMAC		
		Pain	Stiffness	Function
NAPC (n = 38)	Baseline	7(5,12.75)	2(2,4)	23.5(15,33.5)
	Week 4	3(2,5) ^{a,b}	1(0,2) ^a	10.5(5,20.25) ^a
	Week 8	2(1,4) ^{a,b}	0.5(0,2) ^{a,b}	9(4,20) ^a
	Week 12	2(1,4) ^{a,b}	0(0,1) ^{a,b}	10.5(3,20) ^a
PKA (n = 37)	Baseline	7(5,10)	3(1,4)	24(12.25,35.5) ^a
	Week 4	3.5(3,5.75) ^a	1(1,2) ^a	14(7.25,19) ^a
	Week 8	3(2,4.75) ^a	1(1,2) ^a	13(6.75,17.75) ^a
	Week 12	4(2,5) ^a	2(1,2) ^a	14(7.5,22) ^a
Significant within-group differences ($P < 0.05$) are indicated as: ^a vs. Week 0; ^b vs. Week 4; ^c vs. Week 8; ^d vs. Week 12.				

3.5 Serum 5-HT

Serum 5-HT levels significantly increased from baseline in both groups after treatment ($P < 0.05$). A statistically significant between-group difference in post-treatment 5-HT levels was observed, with the NAPC group showing greater increases than the PKA group ($P < 0.05$). (Table 4)

Table 4
Comparison of Serum 5-HT levels change from baseline($\bar{x} \pm s$, ng/L)

Group	n	Baseline	Week 4	t	P value
NAPC group	38	427.85 $\pm$ 27.06	444.89 $\pm$ 22.78	5.997	<0.001
PKA group	37	423.04 $\pm$ 23.06	431.51 $\pm$ 23.07	2.086	0.045
t		0.890	2.337		
P value		0.377	0.022		

3.6 Response rate

At week 4, the composite response rate was 63.1% (24/38) in the NAPC group and 48.6% (18/37) in the PKA group, with a between-group difference of 14.5 percentage points that was not statistically significant ($P > 0.05$). At weeks 8 and 12, the NAPC group consistently demonstrated higher composite response rates than the PKA group, although the between-group differences remained statistically non-significant (all $P > 0.05$). (Table 5)

Table 5
Response rates during the entire study

Week 4	NAPC group (n = 38)	PKA group(n = 37)	χ^2	P value
	24(63.1)	18(48.6)	1.60	0.206
Week 8	28(73.7)	21(56.8)	2.37	0.124
Week 12	27(71.1)	19(51.3)	3.07	0.08

3.7 AEs

Three patients in the NAPC group experienced adverse events (AEs), all of which presented as subcutaneous haemorrhage at the needling site. In the PKA group, two AEs were recorded: one case of subcutaneous haemorrhage and one case of local bruising at the acupoint site. Subcutaneous haemorrhage is a common acupuncture-related reaction, and symptoms resolved promptly after compression with cotton swabs. The local bruising resolved spontaneously within 7 days. No serious AEs, such as needle breakage, syncope, or skin infection, were observed during the treatment period, indicating that both acupuncture protocols were well tolerated and safe.

4. Discussion

This randomized controlled trial showed that both NAPC and PKA significantly improved pain intensity (NRS), anxiety (SAS), and knee symptoms (WOMAC) over 12 weeks in patients with KOA. At week 4, the two interventions produced comparable improvements in pain, emotional status, and some aspects of

joint function, although NACP group had already begun to show an advantage in anxiety reduction. By week 8, this advantage in alleviating anxiety became more pronounced and was accompanied by a tendency toward greater improvement in joint stiffness. By week 12, NACP group not only sustained its superior anxiolytic effect but also produced significantly greater pain relief than PKA group. These findings suggest that NACP group can effectively improve both pain and mood in KOA, and that its mood-regulating effect may in turn contribute to sustained pain relief at later time points.

With respect to pain, the NACP group exhibited a larger decrease in NRS scores than the PKA group across the 12-week treatment period. The significant time-by-group interaction indicated a progressively widening difference in pain improvement between the two groups, implying that NACP group may exert cumulative or delayed-onset analgesic effects. This pattern is consistent with previous work[17] showing that inclusion of GV20 and EX-HN1 can enhance the cumulative analgesic effect of acupuncture. In addition, earlier studies[18] have reported that, relative to conventional local acupuncture, mind-regulating acupuncture more effectively reduces inflammatory mediators and improves pain and joint function in KOA, possibly by modulating the local inflammatory microenvironment and attenuating excessive inflammatory responses.

The advantages of NACP group were more prominent in emotional outcomes. SAS scores declined significantly over time in both groups, with NACP group producing a larger and more rapid reduction. Significant between-group differences and time-by-group interactions confirmed the superior efficacy of NACP group in alleviating negative affect in KOA. For patients with chronic pain, emotional disturbances are known to substantially influence disease progression and prognosis. In the present trial, the addition of mind-regulating acupoints markedly ameliorated anxiety, helping to interrupt the vicious cycle of “pain–anxiety–pain”. Moreover, sustained improvement in SAS may partially explain the long-term advantage in pain scores observed in the NACP group, suggesting that emotional regulation can enhance patients’ pain tolerance and endogenous pain modulation capacity[19].

In terms of functional outcomes, both groups demonstrated significant reductions in total WOMAC scores from baseline, indicating that acupuncture can alleviate overall KOA symptoms. However, no significant between-group differences were observed. This may be related to the relatively gradual improvement in the WOMAC function subscale: although both groups showed marked functional gains over time, intergroup comparisons did not reach statistical significance, suggesting comparable efficacy of the two acupuncture protocols in enhancing knee function within 12 weeks. Given that functional recovery of the knee joint is influenced by multiple factors—including structural damage, muscle strength, and physical activity—functional improvements often lag behind pain relief, potentially explaining why significant differences in pain reduction were not paralleled by divergent functional outcomes.

Analysis of responder rates further supports the potential long-term benefits of NACP group. In our study, the week-4 response rate in the PKA group was 48.6%, similar to the 41.4% reported for manual acupuncture in previous research[20]. The week-4 response rate in the NACP group was 63.1%, which

was 14.5% higher than that of the PKA group, although this difference did not reach statistical significance ($P = 0.206$). This may reflect the predominance of local anti-inflammatory mechanisms during the early treatment phase, when both protocols can effectively reduce inflammatory mediators. At weeks 8 and 12, however, response rates in the NACP group rose to 73.7% and 71.1%, respectively, exceeding the corresponding rates in the PKA group (56.8% and 51.3%). Although between-group differences remained statistically non-significant at each time point ($P > 0.05$), the consistent numerical advantage suggests that the clinical efficacy of NACP group may be superior to that of peri-knee acupuncture over time. At week 12, the between-group difference approached statistical significance ($P = 0.08$), indicating a possible advantage of NACP group in long-term efficacy. This pattern echoes findings from a 3-year randomized controlled trial[21], in which chronic pain patients receiving adjunctive cognitive-behavioural therapy maintained better outcomes than those receiving conventional rehabilitation alone.

To preliminarily explore potential mechanisms, we examined changes in serum 5-hydroxytryptamine (5-HT) levels. Post-treatment 5-HT increased in both groups, with a significantly greater rise in the NACP group. This suggests that NACP group, particularly through stimulation of the head acupoint combination sometimes referred to as “Tou Sanshen”, may more strongly activate central serotonergic pathways and thereby enhance endogenous pain inhibition compared with PKA group. These results are consistent with studies of liver-soothing and mind-regulating acupuncture in migraine, which have shown that its therapeutic effects in chronic migraine models are associated with upregulation of 5-HT levels[22].

From the perspective of acupoint prescription, this study integrated local analgesia with systemic mood regulation. For local pain relief, EX-LE4 and ST35 were selected to alleviating joint pain and functional limitation. ST34 and SP10 were used to promoting blood circulation and reduce inflammatory responses, while also contributing to better limb nutritional status and enhanced knee joint stability. ST36 was included to regulate systemic immune function and enhance host resistance. GB34 was also included, modern acupoint-sensitisation studies[23] have shown that GB34 is among the most frequently sensitised acupoints in KOA, supporting its pivotal role in the management of knee joint disease.

For mood regulation, GV24, GB13, and EX-HN1 were combined to calm the mind, stabilize mental state, and relieve pain. Among them, GV24 has a well-documented mood-regulating effect. As it belongs to the Governor Vessel, which traverses the hip and knee joints along with the Foot-Taiyang and Foot-Yangming meridians, it is also commonly used in the combined treatment of lower extremity joint disorders[24]. GB13 further augments the mood-regulating effect, and EX-HN1, located at the vertex of the head, can synergistically regulate central nervous system function, exerting sedative and mood-improving effects[25].

Modern studies further suggest that this acupoint combination can increase local cerebral blood flow. On the one hand, it directly modulates signal transmission between subcortical nuclei and the cerebral cortex, participating in emotional processing and cognitive appraisal to achieve multidimensional

regulation of pain perception. On the other hand, it enhances neuronal electrical activity and may improve the control of spinal ventral horn motor neurons over limb skeletal muscles, thereby facilitating both central and peripheral aspects of pain modulation.

Our findings are therefore in line with contemporary management strategies that address the coexistence of pain and emotional disorders. A number of prospective studies have underscored the predictive role of psychological factors in KOA. A 5-year cohort study, for example, demonstrated that anxiety, pain-related cognitions, and other psychological variables predict long-term symptoms, with lower baseline anxiety associated with better pain and functional outcomes[26]. Another study identified anxiety symptoms as important predictors of pain severity and functional limitation in knee osteoarthritis[27]. Moreover, cognitive dysfunction has been closely linked to the transition from acute to chronic pain, with evidence showing that patients with cognitive impairment are at increased risk of developing chronic pain after acute episodes[28].

Against this background, the present trial provides a comprehensive intervention strategy grounded in traditional Chinese medicine theory, and demonstrates clinically meaningful improvements in both anxiety and pain. These results suggest that early intervention targeting emotional disorders and maladaptive pain cognition may help slow the deterioration of pain and joint function in KOA.

5. Limitations

This study has several limitations. First, blinding of acupuncturists was not feasible because of the characteristics of acupuncture manipulation. To minimise potential performance bias, all acupuncturists received unified training, including standardised operating procedures and patient-communication protocols. Second, the follow-up period was relatively short, which precluded assessment of long-term efficacy and durability of response. Third, we did not perform subgroup analyses based on baseline characteristics such as age, disease duration, or psychological status. Future trials should consider larger sample sizes, multicentre designs, longer follow-up, inclusion of sham-acupuncture controls, and in-depth exploration of differential treatment responses across patient subgroups.

6. Conclusion

In conclusion, compared with standard peri-knee acupuncture alone, adding the "Three Shen" head points to peri-knee acupuncture provides superior relief of joint pain and stiffness in patients with knee osteoarthritis and more effectively alleviates anxiety symptoms. These therapeutic benefits may be mediated, at least in part, by enhancement of serotonergic neurotransmission, as reflected by increased serum 5-HT levels.

Declarations

Acknowledgements

The authors thank the following people for their support in data collection and storage: Xiao Li, Yanyan Hao, Keqin Wei, Yi Tang, Mengyun Yu.

Authors' contributions

All authors revised the manuscript critically and gave final approval of the submitted version. Hua Li had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Hua Li conceived and designed the study. Yuexin Li collected the data. Zhiyuan Fang supervised patient diagnosis and inclusion criteria. Xiao Guo, Zou Yi, and Jian Huang performed the acupuncture treatments. Yuan Li analyzed and interpreted the data and drafted the manuscript. Hui Hu and Hua Li critically revised the manuscript for important intellectual content.

Funding

This work was supported by the Beijing Administration of Traditional Chinese Medicine's "3+3" Inheritance and Development Rolling Construction Project -Yang Jiasan Master's Studio (Grant No. 2007-SZ-A-12). There was no financial support from any commercial sources. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability

The deidentified participant data supporting the analyses in the manuscript will be made available upon reasonable written request from researchers whose proposed use of the data for a specific purpose has been approved with publication.

Ethics approval and consent to participate

The study protocol was approved by the Clinical Research Ethics Committee of Dongfang Hospital (JDF-IRB-2023055803). The written informed consent was obtained from all individual participants included in this study.

Clinical trial registration

The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2400080288) on January 25, 2024.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References

1. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578–89. 10.1136/bmjebm-2023-112626.
2. Li D, Li S, Chen Q, et al. The prevalence of symptomatic knee osteoarthritis in relation to age, sex, area, region, and body mass index in China: a systematic review and meta-analysis[J]. *Front Med*. 2020;7:304. 10.3389/fmed.2020.00304.
3. Conaghan PG, Cook AD, Hamilton JA, et al. Therapeutic options for targeting inflammatory osteoarthritis pain[J]. *Nat Rev Rheumatol*. 2019;15(6):355–63. 10.1038/s41584-019-0221-y.
4. Du X, Liu Z, Tao X, et al. Research progress on the pathogenesis of knee osteoarthritis[J]. *Orthop Surg*. 2023;15(9):2213–24. 10.1111/os.13809.
5. Lu H, Wang L, Zhou W, et al. Bidirectional association between knee osteoarthritis and depressive symptoms: evidence from a nationwide population-based cohort[J]. *BMC Musculoskelet Disord*. 2022;23(1):213. 10.1186/s12891-022-05137-8.
6. Yang W, Ma G, Li J, et al. Anxiety and depression as potential risk factors for limited pain management in patients with elderly knee osteoarthritis: a cross-lagged study[J]. *BMC Musculoskelet Disord*. 2024;25(1):1–8. 10.1186/s12891-024-08127-0.
7. Sharma A, Kudesia P, Shi Q, et al. Anxiety and depression in patients with osteoarthritis: impact and management challenges[J]. *Open access Rheumatol*. 2016;103–13. 10.2147/OARRR.S93516.
8. Liu CY, Duan YS, Zhou H, et al. Clinical effect and contributing factors of acupuncture for knee osteoarthritis: a systematic review and pairwise and exploratory network meta-analysis. *BMJ Evid Based Med*. 2024;29(6):374–84. 10.1136/bmjebm-2023-112626.
9. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869. 10.1016/j.ijisu.2011.10.001.
10. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. *American College of Rheumatology*[J]. *Arthritis Rheum*. 1995;38(11):1541–6. 10.1002/art.1780381104.
11. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis[J]. *Ann Rheum Dis*. 1957;16(4):494. 10.1136/ard.16.4.494.
12. Robinson CL, Phung A, Dominguez M, et al. Pain Scales: What Are They and What Do They Mean. *Curr Pain Headache Rep*. 2024;28(1):11–25. 10.1007/s11916-023-01195-2.
13. Zung WW. A rating instrument for anxiety disorders. *Psychosomatics*. 1971;12(6):371–9. 10.1016/S0033-3182(71)71479-0.
14. Roos M, Klässbo LS, Lohmander EMWOMAC, Osteoarthritis Index. Reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis[J]. *Scand J Rheumatol*. 1999;28(4):210–5. 10.1080/03009749950155562.
15. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement[J]. *Ann*

- Rheum Dis. 2005;64(1):29–33. 10.1136/ard.2004.022905.
16. Hao XW, Tu JF, Wang LQ, et al. Influence of sex on the therapeutic effect of acupuncture on knee osteoarthritis: a secondary analysis of data from a multi-center randomized controlled study[J]. J Beijing Univ TCM. 2023;46(01):125–31. 10.3969/j.issn.1006-2157.2023.01.021.
 17. Xu QL, Xu T. Therapeutic Evaluation of the Accumulative Analgesic Effect of Electroacupuncture[J]. Shanghai J Acupunct Moxibustion. 2013;32(04):289–90. 10.3969/j.issn.1005-0957.2013.04.289.
 18. Cao SH, Zeng HW, Liang JL, et al. Therapeutic effect of acupuncture for regulating spirit and relieving pain on knee osteoarthritis patients and its effect on IL-1 and hs-CRP [J]. Mod J Integr Traditional Chin Western Med. 2019;28(07):688–91. 10.3969 / j.issn.1008- 8849.2019.07.002.
 19. Norman-Nott N, Hesam-Shariati N, Wewege MA, et al. Emotion regulation skills-focused interventions for chronic pain: A systematic review and meta-analysis. Eur J Pain. 2024;28(8):1276–93. 10.1002/ejp.2268.
 20. Tu JF, Yang JW, Shi GX, et al. Efficacy of intensive acupuncture versus sham acupuncture in knee osteoarthritis: a randomized controlled trial[J]. Arthritis Rheumatol. 2021;73(3):448–58. 10.1002/art.41584.
 21. Ólason M, Andrason RH, Jónsdóttir IH, et al. Cognitive behavioral therapy for depression and anxiety in an interdisciplinary rehabilitation program for chronic pain: a randomized controlled trial with a 3-year follow-up[J]. Int J Behav Med. 2018;25:55–66. 10.1007/s12529-017-9690-z.
 22. Huang LX, Luo Q, Zhang JP, et al. Effects of Soothing Liver,Regulating Mind and Harmonizing Stomach Acupuncture on Plasma 5-HT,CGRP and VIP in Rats with Chronic Migraine [J]. Liaoning J TCM. 2023;50(11):230–3. 10.13192/j.issn.1000-1719.2023.11.061.
 23. Ye J, Yang H, Xiao QW, et al. Phenomenon and regularity of acupoints sensitization for knee osteoarthritis [J]. China J Traditional Chin Med Pharm. 2019;34(11):5127–30.
 24. Chen ZQ, Chen S, Wang H, et al. An Exploration of the Therapeutic Use of Shenting Acupoint (GV24) [J]. Chin J Basic Med Traditional Chin Med. 2021;27(07):1153–5. 10.19945/j.cnki.issn.1006-3250.2021.07.029.
 25. Xu K, Chen XL, Luo RH. Effects of Electroacupuncture at Sishencong(Ex-HN1) on 5-Hydroxytryptamine and Dopamine in Serum of Depression Patients [J]. J New Chin Med. 2011;43(04):87–9.
 26. Helminen EE, Arokoski JPA, Selander TA, et al. Multiple psychological factors predict pain and disability among community-dwelling knee osteoarthritis patients: a five-year prospective study[J]. Clin Rehabil. 2020;34(3):404–15. 10.1177/0269215519900533.
 27. Helminen EE, Sinikallio SH, Valjakka AL, et al. Determinants of pain and functioning in knee osteoarthritis: a one-year prospective study[J]. Clin Rehabil. 2016;30(9):890–900. 10.1177/0269215515619660.
 28. Attal N, Masselin-Dubois A, Martinez V, et al. Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort[J]. Brain. 2014;137(3):904–17. 10.1093/brain/awt35.

Figures

Image not available with this version

Figure 1

Legend not included with this version