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CLINICAL TRIAL REPORT

The Efficacy of Acupuncture, Exercise Rehabilitation, and Their Combination in the Treatment of Knee Osteoarthritis: A Randomized Controlled Trial

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Video abstract

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Objective: To assess the effectiveness of acupuncture, exercise rehabilitation, and their combination in treating knee osteoarthritis (KOA).

Methods: This randomized controlled trial was done on patients with KOA, who were randomly allocated to three groups: acupuncture (AP), exercise rehabilitation (ER), or a combination of acupuncture and exercise rehabilitation (AE). The study lasted 12 weeks with 4 weeks of treatment and 8 weeks of follow-up. The primary outcome was the response rate, which was determined by the percentage of participants who experienced a significant improvement in pain and function by the fourth week. The primary analysis utilized a Z test for proportions in the modified intent-to-treat population, consisting of all randomized participants with at least one post-baseline measurement.

Results: Out of the 120 patients initially enrolled in the study, 110 completed the trial and were included in the intention-to-treat analysis. Response rates at week 4 were 65.7% (23 out of 35), 58.3% (21 out of 36), and 83.3% (32 out of 39) in the AP, ER, and AE groups, respectively. The response rate in the AE group was found to be significantly higher than that in the ER group at week 4. No significant differences were observed in the overall response rates between the AP and ER groups, as well as between the AP and AE groups.

Conclusion: Our research indicates that both acupuncture and exercise rehabilitation can effectively enhance pain relief, functional improvement, and joint mobility in individuals aged 45 to 70 with moderate to severe chronic KOA. Furthermore, the AE group demonstrated the highest response rate. These beneficial outcomes were sustained for a minimum of 8 weeks post-treatment. The combination of acupuncture and exercise rehabilitation appears to enhance the overall therapeutic efficacy for KOA patients, suggesting a synergistic effect that may be particularly advantageous for those with moderate to severe symptoms.

Keywords: knee osteoarthritis, acupuncture, exercise rehabilitation

Introduction

Knee osteoarthritis (KOA) is a prevalent chronic degenerative joint disease necessitating considerable medical resources. Given China's notable aging population, the estimated prevalence of KOA stands at 8.1%, implying a minimum of 100 million KOA patients in the country.[1] KOA manifests through pain, stiffness, and restricted range of motion, thereby precipitating a substantial decline in quality of life and potential disability.[2,3] Presently, treatment modalities for KOA encompass weight loss, cognitive behavioral therapy, exercise therapy, medication, and knee injections.[4–6] However, the efficacy of symptomatic and intra-articular injection treatments is limited to providing temporary relief of symptoms, and prolonged utilization may result in notable adverse effects.[7] Consequently, there exists a necessity to explore non-invasive, secure, and efficacious therapeutic approaches. Contemporary guidelines underscore the significance of non-pharmacological interventions for KOA, including exercise rehabilitation, acupuncture, and massage.[1,8,9]

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Acupuncture and exercise rehabilitation have demonstrated efficacy as non-pharmacological interventions for mitigating pain, enhancing range of motion, and improving joint function in individuals diagnosed with KOA.[10–20] In China, acupuncture enjoys widespread utilization for KOA treatment, exhibiting favorable curative outcomes and patient acceptance. These interventions possess distinctive characteristics. The main objective of this study is to assess and compare the effectiveness of acupuncture and exercise rehabilitation in the management of KOA, while also investigating their immediate and long-term impacts. Acupuncture is associated with rapid alleviation of symptoms, whereas exercise rehabilitation is known to provide more enduring relief. This trial seeks to provide initial evidence supporting the combined utilization of acupuncture and exercise rehabilitation as a treatment approach for KOA.

Patients and Methods

Study Design

This single-center, three-arm, open-label, randomized controlled trial, approved by the Ethics Committee of the People's Liberation Army General Hospital (ethics number: S2020-496-02), was conducted in adherence to the ethical principles set forth in the Declaration of Helsinki. The study followed the guidelines set forth by the Consolidated Standards of Reporting Trials (CONSORT) and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) for the conduct and documentation of its research.[21–23] Prior to their enrollment in the study, all participants received a thorough briefing on the study's objectives, methodologies, potential risks, and benefits, and provided their written informed consent. To ensure the utmost protection of personal privacy, designated researchers will securely store all participants' personal data. No interim analysis was performed prior to the implementation of these modifications. Participants did not receive any financial compensation throughout the duration of the trial, and all acupuncture interventions were provided free of charge. Please refer to Supplementary Table 1 for the process of subject inclusion, treatment, and evaluation.

Trial Population

Patients will be recruited utilizing a multimodal approach, which encompasses extensive promotion on the official website of the PLA General Hospital, social software (WeChat), and the distribution of posters. In order to be considered eligible for participation, individuals must meet the following criteria:[7,24,25] 1) A diagnosis of KOA in accordance with the clinical criteria established by the American College of Rheumatology in 1995; 2) An age range between 45 and 70 years; 3) A Kellgren-Lawrence grade II or III observed on knee joint imaging; 4) Sustained knee pain for a minimum duration of 3 months; 5) Knee pain intensity exceeding 4 mm on a visual analogue scale (VAS) that ranges from 0 to 10 mm; 6) Ability to provide informed consent. The primary criteria for exclusion encompassed the following: 1) Prior history of knee replacement surgery or awaiting knee replacement surgery; 2) Knee pain attributed to conditions such as rheumatic joints or gout; 3) Recent arthroscopic examination within the past year or intra-articular injection within the past 6 months; 4) Previous acupuncture treatment within the past 3 months; 5) Presence of severe acute or chronic organic disease, serious mental illness, coagulation dysfunction, metal allergy, fear of needles, pregnancy, or breastfeeding; 6) Involvement in other clinical trials within the preceding 3 months; 7) Unsuitability for participation due to factors such as frequent changes of residence or mental disorders.

Randomization and Blinding

Participants who met the criteria were randomly assigned to three groups in a 1:1:1 ratio. The randomization sequence was generated by an independent statistician using Excel. The specific allocation was determined based on the enrollment order. Acupuncturists and patients were not blinded as they needed to be aware of the group assignment for treatment purposes. However, the assessors of the outcomes and the statistician were unaware of the group assignment for each patient.

Treatments

Acupuncture

Each participant received treatment in a designated consultation room, with patients diagnosed with bilateral KOA receiving treatment on both lower limbs, while patients with unilateral KOA received treatment exclusively on the affected side. Acupuncture sessions were administered twice weekly for a duration of 4 weeks. All participating acupuncturists possessed a minimum of 3 years of clinical experience in acupuncture and underwent training in standardized operating procedures, including acupuncture point localization and needling techniques, prior to the initiation of the study. The needling procedure employed sterile acupuncture needles (0.25 mm × 25–40 mm; Hwato) in adherence to clinical practice and classical literature. The primary emphasis was on targeting Ashi points located on the quadriceps muscle (Figure 1). The needling procedure encompassed multiple stages. Initially, the acupuncturist conducted a physical examination to identify pathological muscle bundles displaying evident pain and coarseness along the longitudinal axis of the affected side's quadriceps muscle. These identified regions were subsequently designated as Ashi points. A total of 5–10 Ashi points were selected on the affected lower limb. Following this, both the patient's Ashi points and the acupuncturist's hands underwent regular disinfection using a 75% ethanol solution. Subsequently, a needle was inserted into the designated points at a depth ranging from 10–35 mm. Additionally, patients may experience sensations such as soreness, numbness, distension, and pain, as well as muscle twitching reactions, throughout the needling process. However, the main focus was not on inducing Deqi or twitching responses, but rather on evaluating the relaxation of muscle groups following needle insertion. The needle was promptly removed after being inserted into the acupoint, without being left in place, and a cotton swab was delicately applied for a short period to minimize any potential bleeding.

Exercise Rehabilitation

The exercise rehabilitation (ER) program encompassed various elements, including strength training, joint range of motion training, proprioceptive training, and core strengthening. For a comprehensive overview of the ER program, please refer to Supplementary Material 1 and Supplementary Table 2. To optimize the teaching process and enable patients to review the program, an instructional video was created, resulting in notable improvements in patient learning efficiency and adherence to treatment. The ER program consisted of nine exercises, with a suggested frequency of a minimum of five sessions per week (approximately ten minutes per session) over a span of four weeks. Throughout the

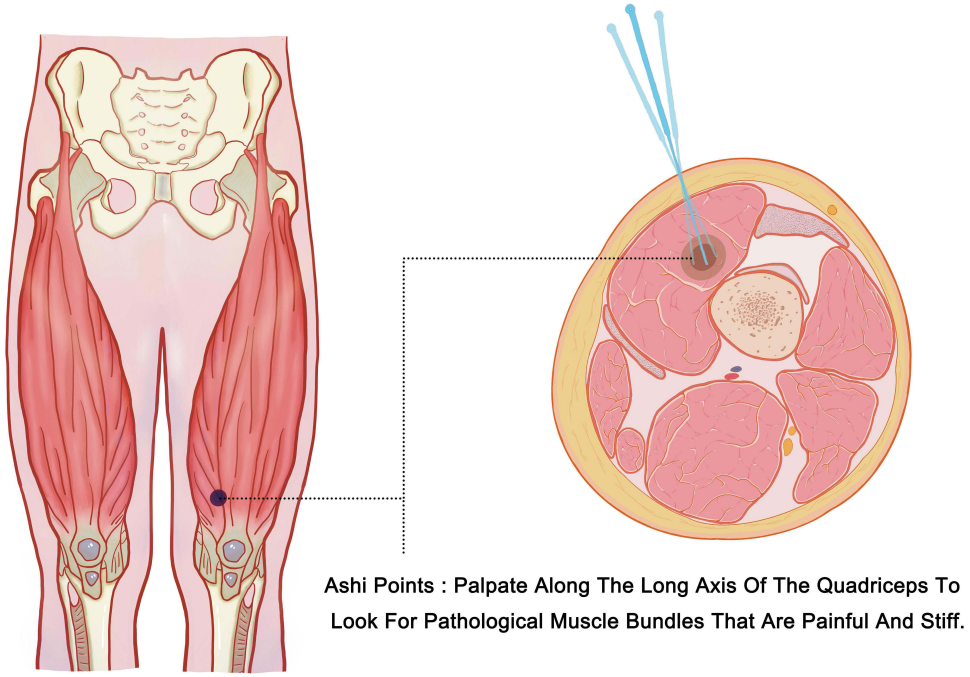

Figure 1 Acupuncture needle insertion at many angles at the quadriceps femoris pathological damage point (Ashi point).

treatment period, patients were obligated to maintain an ER diary (the details of ER diary are shown in Supplementary Material 2) on a daily basis to track their adherence to the treatment. Furthermore, patients in the ER group were assigned weekly follow-up appointments at the hospital.

Outcome Measurements

The treatment effect will be assessed by examining the more severe limb symptoms. Participants will be required to fill out questionnaires at the commencement of the study and during weeks.[1,2,4,8,12] The primary measure of outcome is the response rate observed at week 4. The determination of the response rate is based on the proportion of participants who attain the Minimal Clinically Important Improvement (MCII) on both the Visual Analogue Scale for pain (VAS) and the functional subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[20] The MCII on the 11-point VAS is established at 2 points, which is derived from a documented MCII of 19.9mm on the 100mm VAS. In a similar vein, the Minimum Clinically Important Improvement (MCII) for the 68-point WOMAC functional subscale (Likert version 3.1) has been established at 6 points, based on a reported MCII of 9.1 points on the standardized 100-point WOMAC functional subscale. The secondary outcome measures encompass the Visual Analog Scale (VAS) ranging from 0 to 10, the pain subscale of the WOMAC ranging from 0 to 20, the functional subscale of the WOMAC ranging from 0 to 68, the stiffness subscale of the WOMAC ranging from 0 to 8, the 12-item Short-Form Health Survey(SF-12), the five times sit to stand test (FTSST), and knee range of motion (ROM). To ensure proper management, all adverse events (AEs) will be diligently monitored and documented throughout the entirety of the trial.

Statistical Analysis

The null hypothesis (H0) posits that there exists no statistically significant disparity in response rates between the AP, ER, and AE groups. This study is a pilot randomized controlled trial, with the sample size determined based on the minimum sample size required for clinical trials. Consequently, the minimum sample size for each of the three groups has been established at 30 individuals, resulting in a total of 90 participants. The analysis will be conducted in accordance with the modified intention-to-treat principle, encompassing all patients who were randomized and received a minimum of 1 week of treatment. In instances where there is a lack of primary outcome data, the mean values from the respective patient group during the same time frame will be utilized for data imputation. The chi-square test will be employed to compare the response rates among the AP, ER, and AE groups. Furthermore, a mixed-effects model for repeated measures (MMRM) analysis will be conducted to compare the VAS scores across the three groups. The dependent variable for this study was the VAS scores at all time points, with baseline values serving as covariates. Treatment, time, and the interaction between treatment and time were considered fixed effects, while individuals were treated as random effects. The same methodology was applied to analyze the measurement data for the WOMAC subscales, SF-12, FTSST, and ROM. To compare the incidence rates of acupuncture-related adverse events, the chi-square test was employed. The safety analysis encompassed all patients who received at least one treatment. Statistical analysis will be conducted utilizing SPSS 25.0 for Windows, while GraphPad Prism 9 will be employed for the graphical depiction of the data. To account for multiple comparisons between the AP group, ER group, and AE group, Bonferroni correction will be applied for the primary outcome measures.

Results

Patients

A cohort of 356 qualified individuals underwent screening between August 1, 2022, and August 1, 2023. From this cohort, 120 participants were chosen for the research study and were randomly divided into three separate groups, as illustrated in Figure 2. Specifically, 37 individuals were categorized in the AP group, 39 in the ER group, and 39 in the AE group. Each of these subjects received a minimum of one treatment and were included in the safety assessment. Moreover, a total of 35 patients from the AP group, 36 patients from the ER group, and 39 patients from the AE group underwent subsequent measurements following the baseline and were included in the primary analysis. By the conclusion of the twelfth week, a total of 98 patients, representing 81.7% of the sample, successfully completed their participation in the study. The essential characteristics of the participants are detailed in Table 1.

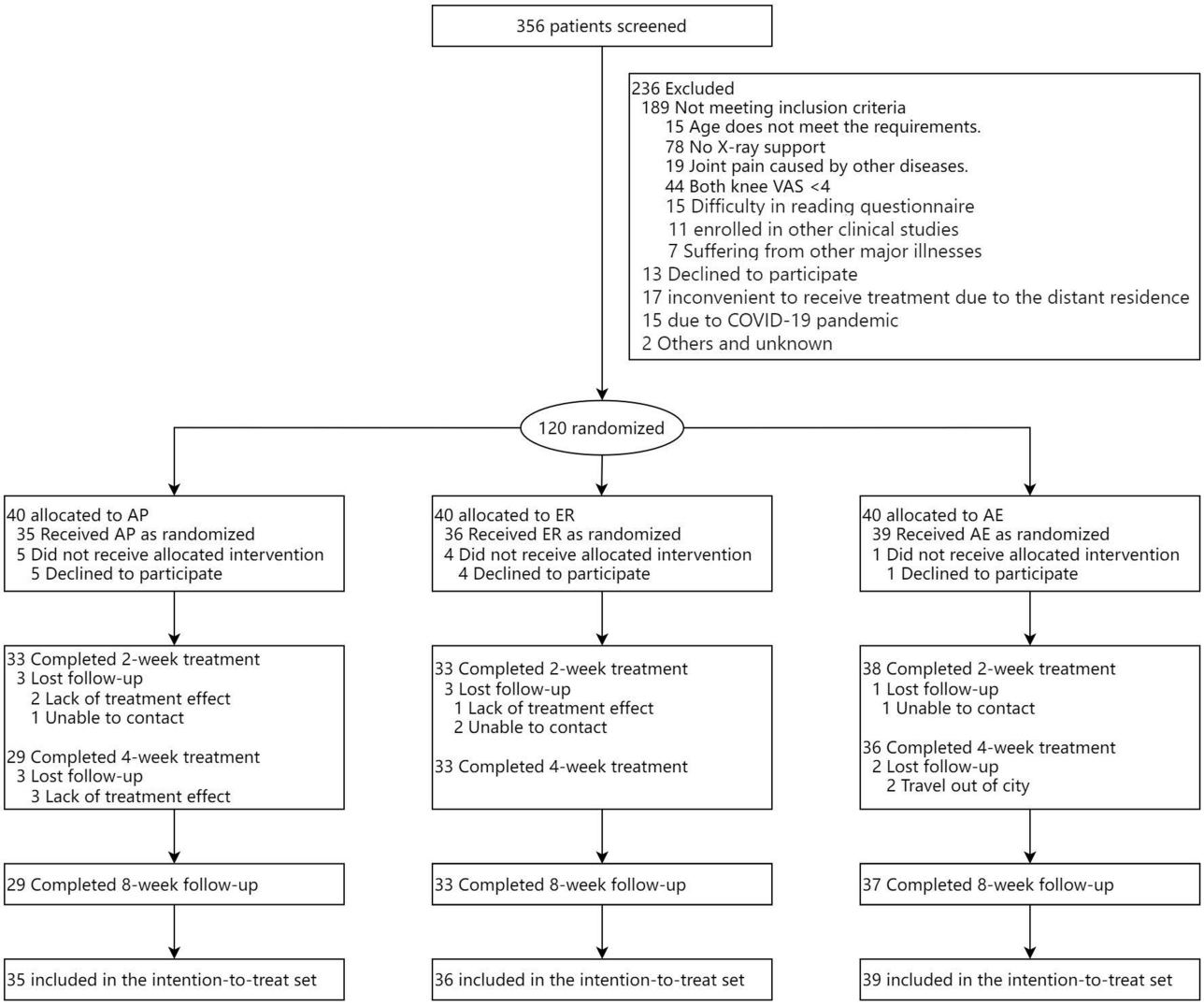

Figure 2 Flow diagram of patient enrollment.

Primary Outcome

The response rates at week 4 varied among the treatment groups, with 65.7% (23 out of 35 patients) in the AP group, 58.3% (21 out of 36 patients) in the ER group, and 83.3% (32 out of 39 patients) in the AE group (Table 2). A comparative analysis of response rates among the AP, ER, and AE groups revealed statistically significant differences. Specifically, the ER group exhibited a response rate difference of 7.38% (95% CI: −16.5% to 30.1%; P = 0.522) compared to the AP group, while the ER group demonstrated a difference of 16.34% (95% CI: −5.4% to 36.8%; P = 0.108) compared to the AP group. The AE group exhibited the highest response rate, with a statistically significant difference of 23.72% (95% CI: 1.1% to 3.75%; P = 0.024) compared to the ER group. Furthermore, the response rates in the AE group were significantly higher than those in the AP group at both week 2 and week 12 ($p < 0.05$). Moreover, by week 8, the response rates in the AE group exhibited a statistically significant increase compared to the ER group ($p < 0.05$). Over the course of the treatment, there were no notable disparities in response rates between the AP and ER groups. The temporal progression of response rates is graphically represented in Figure 3.

Secondary Outcomes

Figure 4 illustrates the changing trend of all secondary outcome indicators in the whole research process through line charts. In the fourth week, there were significant improvements in VAS scores for the AP group (Mean Difference [MD]: −3.01; 95% CI: −3.83

Table 1 Baseline Characteristics*

Characteristic†	AP (n=35)	ER (n=36)	AE (n=39)
Gender			
Male	5(14)	5(14)	11(28)
Female	30(86)	31(86)	28(72)
Age, mean (SD), yr	60.9(7.1)	61.3(6.7)	59.9(6.9)
BMI, mean (SD)	25.8(4.8)	24.2(3.4)	24.5(2.5)
Symptom duration, mean (SD)	11.3(9.9)	13.8(10.5)	12.2(8.1)
Radiologic grade			
II	19(54)	23(64)	24(62)
III	15(43)	13(36)	15(38)
IV	1(3)	0(0)	0(0)
Previous treatment for KOA			
Sports Rehabilitation	7(20)	6(17)	4(10)
Massage	7(20)	11(31)	8(21)
Acupuncture	17(49)	15(42)	15(38)
Physiotherapy	19(54)	24(67)	23(59)
Topical medication	34(97)	31(86)	36(92)
Traditional Chinese medicine	11(31)	17(47)	17(44)
Joint cavity injection	12(34)	11(31)	16(41)
Painkillers	19(54)	12(33)	17(44)
Cartilage protectant	23(66)	31(86)	32(82)
Five Times Sit-to-Stand Test	12.6(3.6)	12.8(4)	13.6(6.1)
WOMAC Index	32.4(15.7)	34.2(12.6)	32.9(14)
Pain, mean (SD)	7.6(4.3)	7.5(3.1)	7.3(2.8)
Stiffness, mean (SD)	2.5(2)	2.9(2)	2.6(1.6)
Physical function, mean (SD)	22.3(11.1)	23.8(9.6)	23.1(10.7)
VAS, mean (SD)	6.2(1.5)	6.2(1.3)	6.2(1.5)
SF-12			
Physical health, mean (SD)	34.1(21)	30.6(17.6)	26.4(15.7)
Mental health, mean (SD)	76.6(17.1)	65.5(18)	67.4(21.2)
Knee joint mobility			
Active (L), mean (SD)	98.5(30.6)	128.1(30.8)	120.8(27.9)
Active (R), mean (SD)	95.5(31.9)	128.7(31.4)	120.1(28.3)
Passive (L), mean (SD)	132.5(20.2)	142.6(11.9)	135.5(14.7)
Passive (R), mean (SD)	132.5(16.9)	140.3(14)	135.4(14.1)

Notes Data are number (%) or mean (SD). * Based on modified ITT population. † Values are reported as no. () unless otherwise indicated.

Abbreviations: AP, acupuncture; ER, exercise rehabilitation; AE, acupuncture and exercise rehabilitation; BMI, body mass index; KOA, Knee Osteoarthritis; WOMAC, Western Ontario and McMasters Universities Osteoarthritis Index; VAS, visual analogue scale; SF-12, 12-item Short Form; L, left knee; R, right knee.

to −2.19), ER group (MD: −2.02; 95% CI: −2.77 to −1.26), and AE group (MD: −3.55; 95% CI: −4.28 to −2.81) compared to baseline ($p<0.001$). These improvements continued to decrease in the eighth and twelfth weeks. In the fourth week, there was no statistically significant difference in VAS scores between the AP group and the AE group (MD: 0.51; 95% CI: −0.31 to 1.33; $p=0.23$), while VAS scores in the ER group were significantly higher than those in the AP group (MD: −0.98; 95% CI: −1.81 to −0.16; $p<0.05$) and the AE group (MD: −1.49; 95% CI: −2.25 to −0.73; $p<0.001$). These differences persisted in the eighth and twelfth weeks. Furthermore, compared to baseline ($p<0.001$) in the fourth week, there were notable improvements in WOMAC pain scores in the AE group (MD, −3.71; 95% CI, −5.03 to −2.4), AP group (MD, −3.18; 95% CI, −4.64 to −1.72), and ER group

Table 2 Primary and Secondary Outcomes in the Modified Intention-to-Treat Analysis

Variable	AP Group (n=35)	ER Group (n=36)	AE Group (n=39)	*p* value
Primary Outcome				
Response rate, no.(%)				
Week 2	10(28.6)[i]	12(33.3)	22(56.4)[a]	*0.031*
Week 4	23(65.7)	21(58.3)	32(83.3)	*0.074*
Week 8	21(60)	20(56.7) [i]	32(82.1) [e]	*0.033*
Week 12	19(54.3) [i]	18(50) [i]	32(82.1) [a, e]	*0.019*
VAS (mean,95% CI)				
Baseline	6.2(5.67,6.73)	6.19(5.67,6.72)	6.23(5.72,6.74)	0.994
Week 2	3.73(3.16,4.31) [++,f]	4.83(4.29,5.36) [++,b,k]	3.68(3.17,4.2) [++,g]	0.004
Week 4	3.19(2.57,3.81) [++,e]	4.18(3.63,4.72) [++,a,l]	2.69(2.15,3.22) [++,h]	0.001
Week 8	2.74(2.01,3.46) [++,f]	3.97(3.42,4.52) [++,b,l]	2.08(1.46,2.7) [++,h]	0.000
Week 12	2.73(2.05,3.4) [++,f]	3.94(3.38,4.5) [++,b,l]	2.28(1.69,2.86) [++,h]	0.000
WOMAC Function Subscale (mean,95% CI)				
Baseline	22.29(19.05,25.52)	23.78(20.59,26.97)	23.08(20.01,26.14)	0.813
Week 2	18.1(14.61,21.59)	17.4(14.17,20.63)**	13.97(10.87,17.08) [++]	0.164
Week 4	15.85(12.09,19.6)*	12.59(9.31,15.87)[++]	11.91(8.68,15.15) [++]	0.266
Week 8	15.79(11.4,20.18)**,[k]	12.12(8.79,15.45)[++,i]	6.42(2.67,10.18) [++,c,e]	0.005
Week 12	15.05(10.97,19.13)**,[j]	12.41(9.02,15.79)[++]	7.66(4.1,11.21) [++,b]	0.022
WOMAC Pain Subscale (mean,95% CI)				
Baseline	7.6(6.65,8.55)	7.5(6.56,8.44)	7.26(6.35,8.16)	0.868
Week 2	4.73(3.7,5.76) [++]	4.86(3.9,5.81) *	4.47(3.56,5.39)**	0.844
Week 4	4.42(3.32,5.53) [++]	3.56(2.59,4.53) [++]	3.54(2.59,4.5) [++]	0.419
Week 8	5(3.71,6.29) [+,k]	3.91(2.93,4.89) [++,i]	2.04(0.93,3.14) [++,c,e]	0.002
Week 12	4.77(3.57,5.97) [++,j]	3.88(2.88,4.87) [++]	2.66(1.61,3.7) [++,b]	0.030
WOMAC Stiffness Subscale (mean,95% CI)				
Baseline	2.54(2.06,3.03)	2.94(2.47,3.42)	2.59(2.13,3.05)	0.441
Week 2	2.1(1.58,2.62)	2.11(1.63,2.6)*	1.92(1.46,2.38)*	0.821
Week 4	2.04(1.48,2.6)	1.59(1.1,2.08)[++]	1.57(1.09,2.05) [+]	0.392
Week 8	2.32(1.66,2.97)[e,k]	1.48(0.99,1.98) [++,a]	0.88(0.32,1.44) [++,c]	0.005
Week 12	2.05(1.44,2.65)[j]	1.56(1.06,2.07) [++]	1.07(0.54,1.6) [++,a]	0.059
SF-12 Physical health (mean,95% CI)				
Baseline	34.08(27.98,40.19)	30.56(24.54,36.57)	26.37(20.59,32.16)	0.197
Week 4	45.6(38.52,52.69)*	49.58(43.39,55.77)[++]	50.82(44.71,56.92) [++]	0.534
Week 8	45.49(37.2,53.77)*,[k]	51.08(44.8,57.37) [++,j]	63.19(56.1,70.27) [++,c,f]	0.003
Week 12	44.48(36.78,52.18)*,[j]	51.12(44.73,57.5) [++]	59.11(52.41,65.82) [++,b]	0.018
SF-12 Mental health (mean,95% CI)				
Baseline	76.6(70.68,82.52)[e,j]	65.48(59.64,71.31)[a]	67.4(61.79,73.01)[b]	0.019
Week 4	82.23(75.37,89.1)	77.45(71.45,83.46)**	78.91(72.99,84.83)**	0.582
Week 8	80.2(72.17,88.23)	76.48(70.38,82.57)*	82.23(75.37,89.1)[+]	0.456
Week 12	84.42(76.95,91.88)	76.79(70.6,82.98)**	83.74(77.24,90.25)[++]	0.197

(*Continued*)

Table 2 (Continued).

Variable	AP Group (n=35)	ER Group (n=36)	AE Group (n=39)	*p* value
Five Times Sit-to-Stand Test (mean,95% CI)				
Baseline	12.57(11.53,13.6)	12.76(11.74,13.78)	13.62(12.64,14.6)	0.301
Week 2	10.04(8.91,11.16)$^{+}$	10.72(9.68,11.76)**	10.18(9.18,11.17) $^{++}$	0.640
Week 4	9.25(8.04,10.45)$^{++}$	9.84(8.78,10.89) $^{++}$	9.67(8.63,10.71) $^{++}$	0.764
Week 8	9.5(8.09,10.91) $^{+}$	9.49(8.42,10.56) $^{++}$	9.37(8.16,10.57) $^{++}$	0.986
Week 12	9.58(8.27,10.89) $^{++}$	9.5(8.42,10.59) $^{++}$	9.53(8.39,10.67) $^{++}$	0.996
Active range of motion of knee joint(mean,95% CI)				
Baseline	101.54(91.97,111.12)^{g,k}	124.88(115.44,134.33)^{c}	123.22(114.15,132.29)^{c}	0.001
Week 2	120.46(110.88,130.04) $^{+,i}$	129.27(119.83,138.71)	136.25(127.18,145.33) ^{*,a}	0.063
Week 4	133.28(123.7,142.86) $^{++}$	135.37(125.93,144.81)	142.68(133.61,151.75)$^{+}$	0.335
Week 8	139.81(130.24,149.39) $^{++}$	137.51(128.06,146.95)	147.57(138.5,156.65) $^{++}$	0.284
Week 12	143.32(133.74,152.9) $^{++}$	136.52(127.08,145.97)	146.95(137.99,155.91) $^{++}$	0.285
Passive range of motion of knee joint(mean,95% CI)				
Baseline	131.26(125.88,136.63)^{e,i}	140.84(135.54,146.14)^{a}	139.84(134.75,144.93)^{a}	0.023
Week 2	142.22(136.85,147.6)$^{+}$	142.75(137.45,148.05)	147(141.91,152.09)	0.375
Week 4	146.72(141.34,152.1) $^{++}$	145.91(140.61,151.21)	149.09(144,154.18) *	0.675
Week 8	153.82(148.44,159.19) $^{++}$	146.81(141.51,152.11)	153.32(148.22,158.41)$^{++}$	0.123
Week 12	152.29(146.91,157.66) $^{++}$	145.45(140.15,150.75)	151.9(146.88,156.93)$^{+}$	0.130

Notes: Pairwise comparisons were performed of each treatment group: * $P < 0.05$; ** $P < 0.01$; + $P < 0.005$; + + $P < 0.001$, for comparison within groups with its baseline. Compared with group A, a $P < 0.05$; b $P < 0.01$; c $P < 0.005$; d $P < 0.001$, Compared with group B, e $P < 0.05$; f $P < 0.01$; g $P < 0.005$; h $P < 0.001$, Compared with group C, i $P < 0.05$; j $P < 0.01$; k $P < 0.005$; l $P < 0.001$, for comparison between groups.

Abbreviations: CI, confidence interval; SF-12, Short Form-12; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

(MD, −3.94; 95% CI, −5.29 to −2.59). These improvements persisted until the twelfth week. In the fourth week, there were no statistically significant differences in the WOMAC pain scores between the AE, AP, and ER groups (p>0.05). On the other hand, in comparison to the AP group and ER group, the AE group showed significantly decreased WOMAC pain scores in the eighth week (p<0.005, 0.05, respectively).

Compared to the baseline, there was a significant improvement in WOMAC function scores for all three groups by the fourth week. The mean difference in scores was −6.44 (95% CI, −11.39 to −1.49; p=0.01) for the AP group, −11.19 (95% CI, −15.77 to −6.61; p<0.001) for the ER group, and −11.16 (95% CI, −15.62 to −6.71; p<0.001) for the AE group. By

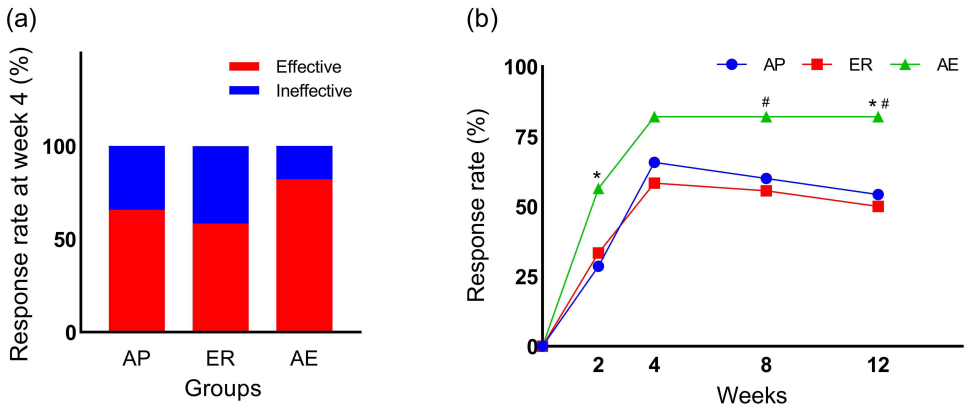

Figure 3 (**a**, **b**) Response rates were measured for each treatment group during the 1-month treatment period and the 2-month follow-up period.

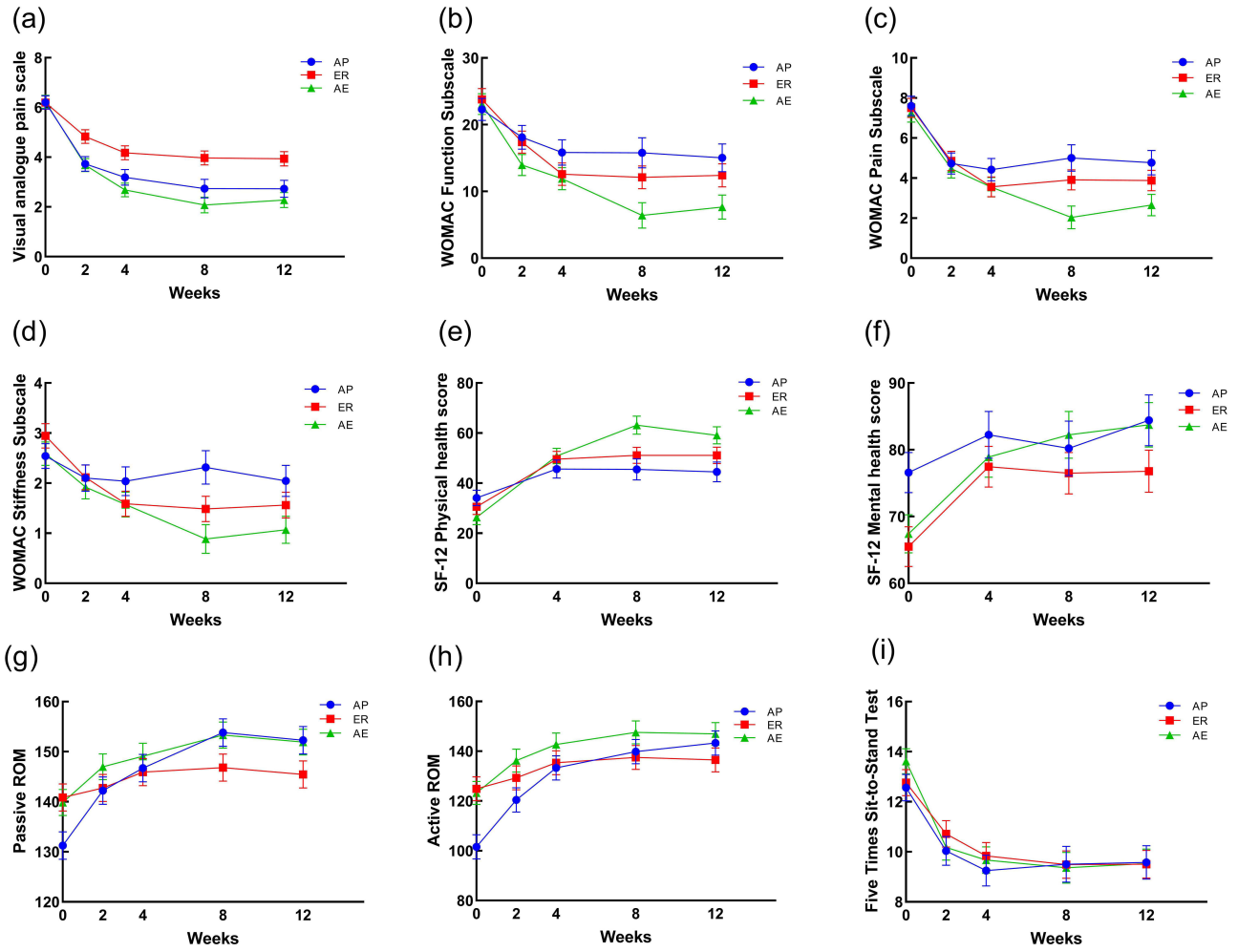

Figure 4 Trends in secondary outcome measures during the treatment period and the follow-up period. (**a**) Change in the curve of VAS within 12 weeks. (**b**) Change in the curve of WOMAC Function Subscale within 12 weeks. (**c**) Change in the curve of WOMAC Pain Subscale within 12 weeks. (**d**) Change in the curve of WOMAC Stiffness Subscale within 12 weeks. (**e**) Change in the curve of SF-12 Physical health score within 12 weeks. (**f**) Change in the curve of SF-12 Mental health score within 12 weeks. (**f**) Change in the curve of Passive ROM within 12 weeks. (**h**) Change in the curve of Active ROM within 12 weeks. (**i**) Change in the curve of Five Times Sit-to-stand test within 12 weeks.

week 12, there was no change in function scores for the AP and ER groups, while the AE group's scores continued to decline. By the fourth week, there was no statistically significant difference in WOMAC function scores among the AP, ER, and AE groups ($p>0.05$). However, by the eighth week, the function scores of the AE group were significantly lower compared to those of the AP and ER groups.

The AP group did not significantly increase their WOMAC Stiffness score from the baseline in the fourth week (MD, −0.5; 95% CI, −1.24 to 0.24; $p=0.18$). But as compared to the baseline, the stiffness scores of the AE group (MD, −1.02; 95% CI, −1.68 to −0.35) and the ER group (MD, −1.36; 95% CI, −2.04 to −0.67) were significantly improved ($p<0.001$). This improvement persisted at week 12. In the fourth week, there was no discernible variation in the stiffness scores of the AP, ER, and AE groups ($p>0.05$). Notably, in week 8, the Stiffness scores of the AE and ER groups were considerably lower than those of the AP group ($p<0.05$ and 0.005, respectively).

In the fourth week, the SF-12 Physical Health scores (PHS) significantly improved compared to the baseline in all three groups: AP (MD, 11.52; 95% CI, 2.17 to 20.87; $p=0.02$), ER (MD, 19.02; 95% CI, 10.39 to 27.66; $p<0.001$), and AE (MD, 24.44; 95% CI, 16.03 to 32.85; $p<0.001$). These improvements remained unchanged at the twelfth week. There was no statistically significant difference in PHS between the AP, ER, and AE groups in the fourth week ($p>0.05$). However, by the eighth week, the AE group had significantly higher PHS compared to the AP and ER groups ($p<0.005$,

0.001, respectively). Additionally, the SF-12 Mental Health scores (MHS) in the AP group did not show significant improvement compared to the baseline in the fourth week (MD, 5.64; 95% CI, −3.43 to 14.7; p=0.22). However, the ER group (MD, 11.97; 95% CI, 3.6 to 20.35; p<0.05) and AE group (MD, 11.51; 95% CI, 3.36 to 19.66; p<0.05) demonstrated significant improvement in MHS compared to the baseline (p<0.001), and these improvements also remained unchanged at the twelfth week.

In the fourth week, the AP, ER, and ER groups demonstrated significant improvements in their FTSST compared to baseline measurements (p<0.001). The AP group exhibited a mean difference (MD) of −3.32 (95% CI, −4.91 to −1.73), the ER group showed a MD of −2.93 (95% CI, −4.39 to −1.46), and the ER group revealed a MD of −3.95 (95% CI, −5.38 to −2.52). These improvements were sustained through the twelfth week. Additionally, there were no statistically significant differences in FTSST scores among the AP, ER, and AE groups in the fourth week (p>0.05).

We only compared differences between intervention groups and their baseline ROM values due to significant variations in the baseline ROM among the three groups. By week 4, the active ROM of the AP group (MD, 31.74; 95% CI, 18.19 to 45.28; p<0.001) and AE group (MD, 19.46; 95% CI, 6.62 to 32.3; p=0.003) demonstrated significant improvement compared to baseline. However, no significant improvement was observed in the ER group (MD, 10.49; 95% CI, −2.87 to 23.84; p=0.12).Similarly, the passive ROM in the AP group (MD, 15.46; 95% CI, 7.87 to 23.07; p<0.001) and AE group (MD, 9.25; 95% CI, 2.05 to 16.45; p=0.012) showed significant improvement compared to baseline (p<0.05), while the ER group (MD, 5.07; 95% CI, −2.42 to 12.56; p=0.19) did not demonstrate significant improvement.

Adverse Events

Adverse events associated with acupuncture encompass subcutaneous hematoma, post-needle pain, and shock, among others. Conversely, adverse events associated with sports rehabilitation primarily involve muscle pain. Within the AP group, 31.4% (11/35) of patients encountered adverse events, whereas in the ER group, the occurrence rate was 13.9% (5/36), and in the AE group, it was 30.8% (12/39). The prevailing occurrences were pain experienced during needle insertion (15 instances), soreness and pain following needle insertion (18 instances), and subcutaneous bruising (5 instances). These discomforts promptly subsided upon needle removal or within a span of 3 days. Notably, no severe adverse events, such as needle fainting, allergy, hypotension, or shock, were observed.

Discussion

According to our research, manual acupuncture combined with exercise rehabilitation is highly effective at reducing pain and symptoms associated with KOA. The positive effects of this treatment approach were observed both during the treatment period and in the subsequent eight weeks. Notably, our results indicate that acupuncture is more efficacious in alleviating pain compared to exercise rehabilitation. Among the three groups studied, the group receiving both acupuncture and exercise rehabilitation exhibited the highest response rate, surpassing the other groups significantly. Specifically, the response rate in the AE group was notably higher than the AP group at both the second and twelfth weeks. Additionally, the AE group demonstrated a significantly higher response rate compared to the ER group in the fourth and eighth weeks.

Researchers have demonstrated a lack of discernible differences between manual acupuncture and sham acupuncture in previous studies, which indicates a placebo effect in acupuncture.[26] This study utilized manual acupuncture exclusively, without the use of additional stimuli such as moxibustion or electric pulse stimulation, and the needles were not left in place to extend the duration of stimulation. Additionally, he frequency of therapy was lower compared to other similar trials,[18,20,27] with sessions occurring only twice a week for a total of eight sessions. Still, the results of manual acupuncture are fascinating. What is the cause of this phenomenon? The efficacy of KOA treatment is significantly impacted by the choice of acupuncture points and stimulation techniques. The selection of acupoints in this study deviates from previous semi-quantitative methods, we stimulate the quadriceps femoris Ashi point. With a focus on stimulating the quadriceps femoris Ashi point similar to dry acupuncture at the Myofascial Trigger Point.[28,29] Given the quadriceps muscle's substantial size and role in knee joint biomechanical stability, alterations in its size and mass have been associated with KOA development.[30,31] The straining of the quadriceps muscle can lead

to knee joint instability, misalignment of the lower extremities, and the development of symptoms such as joint effusion, bone hyperplasia, and cartilage degeneration. Therefore, improving the condition of the quadriceps is crucial in the management of knee osteoarthritis. Utilizing acupuncture at the Ashi point has been identified as an effective method for alleviating muscle strain. In contrast to the conventional technique involving "lifting, inserting, and twisting", our manual acupuncture procedure does not prioritize the attainment of "deqi" or "muscle twitches". Rather, we employ specific acupuncture techniques to target the Ashi point from various angles, resulting in a more pronounced therapeutic outcome.

This study employed a combination of subjective and objective measures to thoroughly evaluate the efficacy of the intervention. The principal manifestation of KOA and its influence on quality of life is the restriction of joint mobility, particularly in activities such as squatting. Our analysis of alterations in joint mobility (both active and passive) pre- and post-treatment revealed that the combination of acupuncture and exercise rehabilitation yielded significant improvements in joint mobility among individuals with moderate to severe KOA. This discovery offers significant implications for clinical application. Furthermore, the FTSST was utilized to assess the functional capacity of the knee joint in practical situations. A shorter completion time of the FTSST correlated with improved knee joint functionality. Acupuncture and exercise rehabilitation were identified as effective interventions in reducing test completion time, suggesting their efficacy in enhancing knee joint function.

In addition, our research has demonstrated that exercise rehabilitation and combined therapy yield superior results in alleviating knee joint stiffness compared to acupuncture, as evidenced by the WOMAC stiffness score. The broader scope of action provided by exercise rehabilitation, such as roller therapy targeting the quadriceps femoris across a larger surface area, may account for its efficacy in addressing joint stiffness. Furthermore, research has shown that exercise rehabilitation and combined therapy have a beneficial impact on mental health, as evidenced by improvements in the SF-12 mental subscale. This underscores the importance of physical activity in enhancing mental well-being.

There are several limitations in this study that need to be addressed. Firstly, due to the nature of acupuncture and sports rehabilitation, it was challenging to implement a blind method. Secondly, this study was conducted at a single center, which may introduce bias in the results. To validate the findings, a multi-center study will be conducted. Additionally, the sample size in this study was small, and the follow-up period was limited to 8 weeks, which may not be sufficient to determine the long-term effects of the treatment. Furthermore, the absence of a placebo treatment group prevents the measurement of the placebo effect.

According to our research, individuals with moderate to severe chronic KOA who are between the ages of 45 and 70 can benefit from both acupuncture and exercise therapy. These therapies, whether used singly or in combination, showed considerable improvements in joint mobility, functional ability, and pain reduction, with positive effects that persisted for at least eight weeks. While exercise rehabilitation has a more gradual but long-lasting effect, acupuncture has been shown to alleviate pain quickly. This suggests that exercise rehabilitation may be able to provide long-term benefits in pain and functional abilities. Additionally, exercise rehabilitation is more advantageous in improving joint stiffness and the patient's mental state. By combining acupuncture and exercise rehabilitation, the advantages of both interventions can be integrated, potentially leading to synergistic benefits and enhanced overall treatment outcomes for patients with KOA. Based on these findings, our study supports the combination of acupuncture with exercise rehabilitation as a viable treatment option for patients with moderate to severe chronic KOA.

Abbreviation

AEs, Adverse events; ER, Exercise rehabilitation; FTSST, Five times sit to stand test; KOA, Knee osteoarthritis; MCID, minimal clinically important difference; NSAIDs, non-steroidal anti-inflammatory drugs; PLAGH, People's Liberation Army General Hospital; RCT, Randomized controlled trial; ROM, range of motion; SF-12, 12-item Short-Form Health Survey; PHS, Physical health Score; MPS, Mental health Score; SMA, Structure-based Medical Acupuncture therapy; VAS, Visual analogue pain scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Date Statement

The data of this study is not planned to be released to the public. If researchers are interested in the data of this study, they can contact the corresponding author of this article to obtain the original data of the study.

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Ethics and Dissemination

This protocol has been registered in the Chinese Clinical Trials Registry (registration number: ChiCTR2200061766). Investigators will obtain written informed consent from all participants. Patients will have enough time to ask questions and consider whether to participate in the study. We will publish the results of this trial in a peer-reviewed clinical journal.

Author Contributions

Each author has made substantial contributions to the research, including conception, study design, data acquisition, analysis, interpretation, drafting, revising, and critically reviewing the article. Additionally, all authors have provided final approval for publication in the "Journal of Pain Research" and have agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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