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CLINICAL TRIAL REPORT

Combination Treatment with Thread-Embedding Acupuncture and Electroacupuncture for Knee Osteoarthritis Patients with Postoperative Pain: A Randomized Controlled Feasibility Study

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Purpose: This study aimed to evaluate the effectiveness and safety of combination treatment with thread-embedding acupuncture (TEA) and electroacupuncture (EA) in patients with persistent knee pain after arthroscopic surgery, autologous chondrocyte implantation, or autologous osteochondral transplantation.

Patients and Methods: Twelve patients with knee osteoarthritis (KOA) who experienced postoperative pain were randomized to either the treatment group (TG) or control group (CG) in a 1:1 ratio. The TG received TEA once a week for four sessions and EA twice a week for eight sessions while continuing usual care, defined as standard conventional treatments. The CG received only usual care for four weeks. The primary outcome was the visual analogue scale (VAS) score at week 4 compared with the baseline. The secondary outcomes were the VAS scores at weeks 2, 6, and 8, the Korean version of the Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC), the EuroQol 5-Dimension 5-Level (EQ-5D-5L), and rescue medication consumption at weeks 2, 4, 6, and 8. Adverse events were assessed at each visit.

Results: The TG showed significant improvement in the VAS scores at weeks 4, 6, and 8 compared with the CG (week 4: −24.5; $p = 0.0106$, week 6: −19.667; $p = 0.0228$, week 8: −28.667; $p = 0.0036$). In the TG, significant differences were observed in K-WOMAC total scores at weeks 2, 4, 6, and 8 (week 2: 17.167; $p = 0.0083$, week 4: 23; $p = 0.0018$, week 6: 29.833; $p = 0.0009$, week 8: 30.5; $p = 0.0006$); however, there were no differences between the two groups. The two groups had no significant differences in the EQ-5D-5L and rescue medication consumption. No adverse events were observed in either groups during the study period.

Conclusion: This feasibility study suggests that adding combination treatment with TEA and EA to usual care might relieve pain in patients with KOA. Large-scale clinical trials are needed to confirm the long-term effects of combination treatment.

Keywords: thread-embedding acupuncture, electroacupuncture, osteoarthritis, knee, randomized controlled trial

Introduction

Knee osteoarthritis (KOA) is a disease accompanied by the degeneration and wear of the knee articular cartilage and proliferative changes in the osteocartilage,[1] with clinical symptoms such as knee pain, fatigue, movement disorders, swelling and tenderness around the joint, friction noise during exercise, and bone spur formation.[2] Risk factors include sex, age, and obesity, and the prevalence rate in women is approximately three times higher than in men.[3] Today, as

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living environments improve and lifespans increase, the morbidity rate of KOA is increasing, which has a significant impact on the lives of middle-aged and elderly populations and also causes an increase in medical expenses and socioeconomic costs.[4,5]

KOA has three main treatments: non-pharmacological therapy, medication, and surgery. Non-pharmacological therapy involves weight loss, stretching, and muscle strengthening exercises. If there is no response to non-pharmacological therapy, medication can be considered as the next option. If pain cannot be resolved with these treatments, surgery is performed as a final solution.[6] Surgery includes arthroscopic surgery, autologous chondrocyte transplantation, autologous osteochondral transplantation, osteotomy, and knee arthroplasty.[7] However, according to long-term follow-up studies of patients who underwent arthroscopic surgery, autologous chondrocyte transplantation, or autologous osteochondral transplantation, the effects of surgery did not last and the reoperation rate was high.[8–11] A safe and effective treatment is needed for patients who still have pain and discomfort after surgery, but whose knee has not deteriorated to the point of absolute instability requiring total knee replacement.

Thread-embedding acupuncture (TEA) and electroacupuncture (EA) are used as complementary and alternative treatments for musculoskeletal pain disorders.[12–15] TEA is a unique acupuncture method that embeds threads attached to needles into acupoints. It can provide the stimulating effect of general acupuncture and the continuous stimulation effect through the threads.[16] In a systematic literature review on TEA for patients with KOA,[17] three randomized controlled studies[18–20] showed significant treatment results in the TEA intervention group. EA is a method of treating diseases by applying electrical stimulation to needles and is widely applied in clinical practice to relieve acute and chronic pain.[16,21–23] Studies evaluating the effectiveness and safety of EA in patients with KOA have been reported.[24,25] In medical practice in Korea, EA is recommended as an effective treatment for knee pain.[26] However, a randomized clinical trial has not been conducted to date that provides evidence for combination treatment with TEA and EA in patients with KOA who suffer from pain and functional disorders after a considerable surgical recovery period. Both TEA and EA are categorized under acupuncture treatment and applied to diseases that require stronger stimulation by targeting specific acupoints. TEA involves prolonged stimulating effects induced by the implanted threads, while EA combines the effects of acupuncture and electrical stimulation. It was hypothesized that combining these two treatments could maximize the stimulation and enhance the synergistic effect. Before conducting a large-scale clinical study, we designed a preliminary feasibility trial to provide basic data on the effectiveness and safety of combination treatment with TEA and EA in patients with KOA complaining of knee pain, even after arthroscopic surgery, autologous chondrocyte transplantation, or autologous osteochondral transplantation.

Methods

Study Design

This was a two-arm, parallel, randomized controlled, assessor-blinded, single-center pilot trial. The subjects visited Daejeon University Daejeon Korean Medicine Hospital between May 2020 and November 2020. Subjects eligible for this study were randomly assigned 1:1 to the treatment group (TG) or control group (CG). The TG continued usual care by receiving four sessions of TEA once a week and eight sessions of EA twice a week for four weeks. The CG continued only usual care for four weeks. The protocol for this study was published in 2020.[27] This study was approved by the Institutional Review Board (IRB) of Daejeon University Daejeon Korean Medicine Hospital (DJDSKH-20-BM-01). This study was registered with the Clinical Research Information Service of the Republic of Korea (KCT0004804). All matters of this clinical trial were conducted in accordance with the Declaration of Helsinki.

Participants

The subjects were recruited through advertisements posted on hospital websites, bulletin boards, regional newspapers, and public transportation advertisement panels. All participants received a detailed explanation of the study from the Korean Medicine Doctor (KMD) and the Clinical Research Coordinator (CRC) at the first visit. The participants voluntarily agreed to participate in this clinical study, signed a consent form, and were provided with copy of written informed consent. A screening test was performed to determine eligibility for our study, including history taking and

questionnaire, measurement of vital signs, physical examination, blood test, electrocardiogram, knee X-ray, and urine test in case of a woman's chance of conceiving.

The inclusion criteria were as follows. An eligible subject 1) is aged over 40 years, 2) was diagnosed with KOA and underwent surgery (arthroscopic surgery, autologous chondrocyte transplantation, or autologous osteochondral transplantation) at least six months ago,[28–30] 3) has knee pain more than the visual analogue scale (VAS) 40mm at screening,[31] 4) voluntarily decides to participate and agrees to the consent form after having received a full explanation of the research objectives and processes, and 5) is able to provide patient preparation data on their own or with the support of a guardian or researcher.

The exclusion criteria were as follows. An excluded subject 1) has a history of knee arthroplasty on the affected knee, 2) has a history of severe trauma on the affected knee in the past 6 months, 3) had TEA within six months or EA treatment within two weeks on the knee,[12,13,32] 4) has a history of receiving injection treatments such as steroids or hyaluronic acid in the past three months, and prolotherapy or Platelet-Rich Plasma (PRP) in the past six months,[33,34] 5) has ESR>40mm/hr and RA Factor>20IU/mL on screening clinical examination,[31] 6) has musculoskeletal problems that cause more pain than knee pain in other body parts, 7) has hypersensitive reaction to previous acupuncture treatment, metal allergy, severe atopy, keloid, or other skin hypersensitivities, 8) has hemorrhagic disease, cardiovascular disease, or factors that may affect hemostasis, such as taking anti-coagulants or antiplatelets, 9) is pregnancy, nursing, or diagnosed with malignant tumors, 10) has severe diabetes or cardiovascular disease such as angina pectoris or congestive heart failure, 11) has senile dementia, severe mental or psychological disorders, 12) has inserted pacemaker, and 13) is considered to be inappropriate for the study by the researcher.

Randomization and Blinding

An independent statistician who was not involved in the conduct and evaluation of the trial created a randomization table using the statistical program SAS® Version 9.4 (SAS Institute. Inc., Cary, NC). The subjects and clinical researchers were not exposed to the randomization table to prevent bias. Because of the obvious interventional differences between the TG and CG, blinding the practitioners and subjects was not possible. To control bias as much as possible, the evaluator was a researcher who did not perform the intervention procedure or randomization, was blinded to prevent confirmation of the subjects' group assignment and conducted an efficacy assessment of the subjects.

Interventions

All participants were allowed to receive usual care to relieve knee pain, and the type and frequency of usual care received during the study period were recorded on a case report form (CRF). This study defined usual care as conventional treatments, such as medication, physical therapy, manual therapy, and exercise therapy. However, receiving other Korean medical treatments such as acupuncture, moxibustion, herbal medicine, and cupping was not permitted to improve knee pain. Invasive treatments (injections and surgical treatments) that were directly applied to the knee area were also prohibited.

Subjects in the TG continued usual care while receiving TEA once a week and EA twice a week for four weeks. A polydioxanone TEA (29036DB, 29066DB, Dongbang Medical Co., Seongnam, Republic of Korea) with a diameter of 29 gauge and a length of 30 or 60 mm was used (Figure 1). The appropriate length was selected considering the general penetration depth and direction of each acupoint and the subject's physique and muscle condition. The practitioner selected approximately ten acupoints from the acupoint pool of EX-LE4, ST35 (EX-LE5), EX-LE2, ST34, SP10, ST36, GB34, SP9, LR8, and BL40, considering the pain area, meridian, diagnosis, movement, and palpation with controlled finger pressure. For EA, 0.25×40 mm disposable needles (Dongbang Medical Co., Chungcheongnamdo, Republic of Korea) sterilized with gamma rays were used. Approximately ten acupoints were inserted, including the fixed acupoints of ST34, SP10, BL40, LR9, BL24, and BL25, and selecting a few from the acupoint pool of EX-LE4, ST35 (EX-LE5), ST31, ST32, GB29, and GB30. After inserting the needle, EA stimulation was applied to ST34-SP10, BL40-LR9, and BL24-BL25 using an EA device at an intensity of 2 hz for 20 minutes. A licensed KMD performed TEA and EA treatments with at least three years of clinical experience in TEA. The procedure site was sterilized with alcohol-treated

Figure 1 The polydioxanone thread-embedding acupuncture used in this trial (Left 60mm; Right 30mm).

cotton before and after the procedure to prevent infections. During the four-week treatment period, TEA and EA were administered simultaneously once a week, with EA being performed first, followed by TEA.

Subjects in the CG continued only usual care treatment they had previously received for four weeks. After the clinical study was completed, up to two sessions of TEA were administered to patients who desired compensatory treatment.

In this study, acetaminophen at a maximum dose of 3000 mg (6 T/day) or less per day was provided as a rescue medication and allowed to be taken only when the knee pain was so severe that it was unbearable during the study period. The participants were given a medication diary and instructed to complete it daily. They were also asked to bring a medication diary and remaining medication at the visit to check the dosage and frequency of medication use.

Outcome Measures

The evaluation was conducted in the first week (1 W, baseline), second week (2 W), fourth week (4 W), sixth week (6 W), and eighth week (8 W). The primary efficacy endpoint was the average change in the VAS score at 4 W compared with the baseline. The VAS valuates a subject's pain level by indicating where the pain is located among continuous values on a 100 mm straight line. The end point on the left indicates no pain, and that on the right indicates the maximum pain imaginable. Knee pain felt within the last 48 hours is expressed as a vertical line based on a subjective standard.[35,36]

The secondary efficacy endpoints were the average change in VAS scores at 2 W, 6 W, and 8 W compared with the baseline, the average change in the individual scores of three subscales (pain/stiffness/physical function) and the total scores for the Korean version of the Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC) at 2 W, 4 W, 6 W, and 8 W compared with the baseline, the average change in the Euroqol 5-dimension 5-level questionnaire (EQ-5D-5L) scores at 2 W, 4 W, 6 W, and 8 W, and the mean consumption of rescue medication at 2 W, 4 W, 6 W, and 8 W.

The K-WOMAC is an index that represents the overall joint function score of the knee joint and can evaluate the degree of functional limitation related to pain and disability of the knee joint. Of the 24 questions, five were about pain, two about stiffness, and 17 about physical function related to difficulties in performing daily activities. This is a self-administered evaluation tool in which patients complete a questionnaire to evaluate their condition over the past 48 hours. Each question is rated on a 5-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe, and 4=extreme).[37,38]

The EQ-5D-5L is a questionnaire used to assess quality of life. It evaluates health status in five areas: exercise ability, self-management, daily activities, pain/discomfort, and anxiety/depression. Each checked item is displayed as a number from 1 to 5 (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems). The 5 numbers' weighted combinations are expressed as an index between 0 and 1, where 0 indicates death and 1 indicates full health.[39,40]

Evaluating the consumption of the rescue medication provided to the subjects gives information about the analgesic effectiveness of the intervention. If pain is effectively controlled in the intervention group, the use of rescue medication decreases.[24,41,42]

The participants were asked to voluntarily report the presence or absence of adverse reactions and symptoms at any time, and the researcher evaluated the adverse reactions at each visit based on vital signs, questionnaires, and other test results.

Statistical Analysis

This preliminary pilot study was designed to evaluate the trial's feasibility and collect information on sample size calculations for the entire study. Therefore, without performing statistical calculations, we assumed a sample size of 14 people per group and 28 people, considering the number of subjects that could be recruited during the planned study period and the minimum range for evaluating effectiveness. Considering a dropout rate of 20%, the actual number of subjects recruited was 18 in each group, for a total of 36.

Data analysis was performed using the statistical program SAS® Version 9.4 (SAS Institute. Inc., Cary, NC). A two-sided test was performed for statistical analysis. Multiple imputations were performed when missing values occurred. The data obtained from the subjects were analyzed using the Full Analysis Set (FAS) and the per protocol (PP) set. The main analysis was performed using the FAS, and assistant confirmation was performed using the PP set. Descriptive statistics regarding the subjects' demographic characteristics and clinical baselines for each group were presented. The mean and standard deviation (SD) were given for continuous data. Then, an independent *t*-test or Wilcoxon rank-sum test was used for analysis. The frequency and percentage were given for categorical data, and the chi-square test or Fisher's exact test was used for analysis. The effectiveness endpoints were analyzed using analysis of covariance. The paired *t*-test or Wilcoxon signed-rank test was used to analyze the differences in each group's efficacy evaluation variable measurements before and after treatment. A repeated measures analysis of variance (RM-ANOVA) was performed to test for differences in trends over time. The significance level for each analysis was set at 0.05, and a confidence interval was presented with a power of 95%.

Results

Participants Recruitment

Thirteen participants were recruited from Daejeon University Daejeon Korean Medicine Hospital from May 22, 2020, to November 30, 2020, and 12 were eligible for participation according to this study's inclusion and exclusion criteria. The subjects were randomly assigned in a 1:1 ratio to the TG and CG. Of the 12 subjects who participated, eight completed the study and four dropped out. All four patients dropped out after completing the fourth week visit and evaluation owing

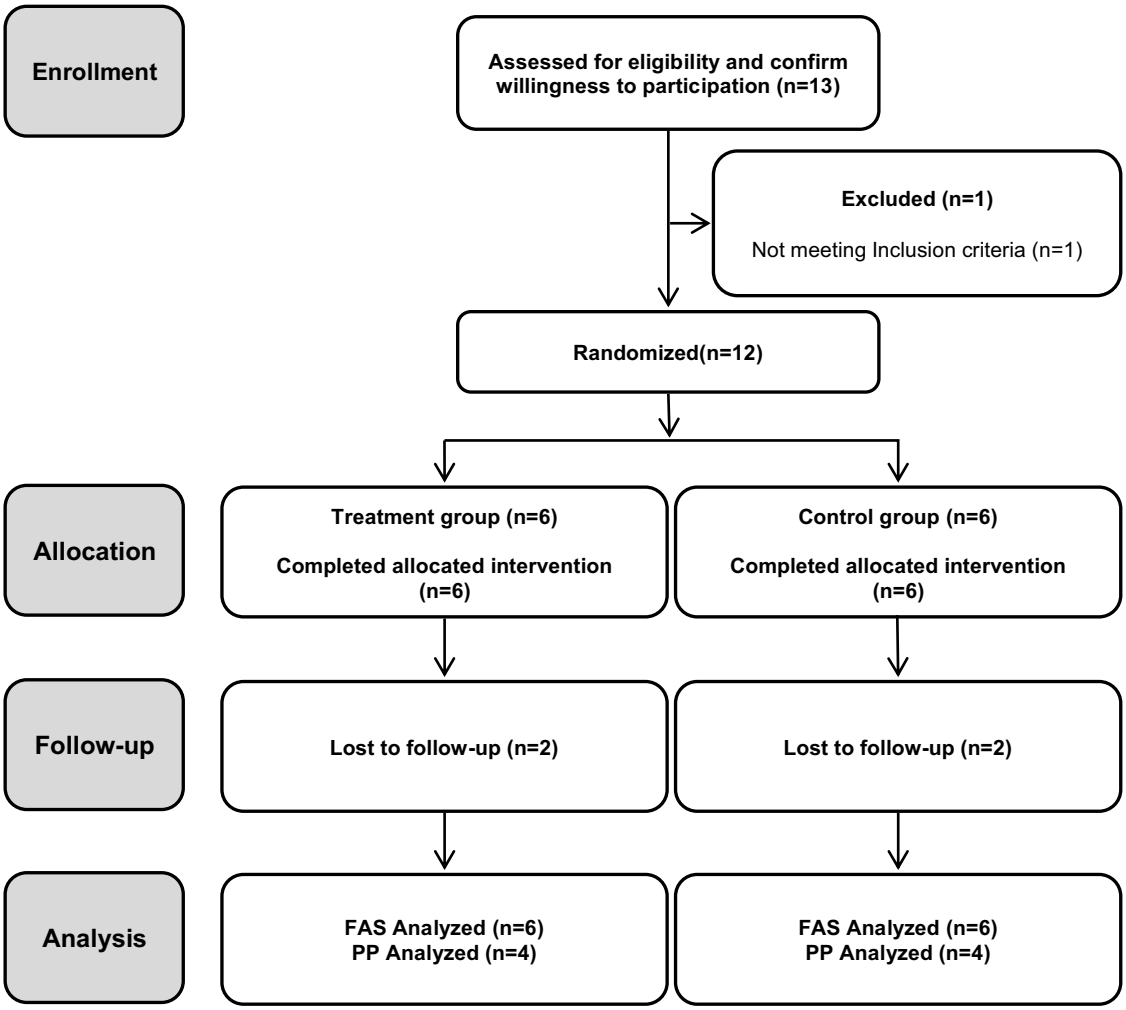

Figure 2 Study flow diagram.
Abbreviations: FAS, Full analysis set; PP, Per protocol.

to the early termination of the study. We planned to recruit 36 subjects; however, due to difficulties in recruiting participants, the study ended with 12 subjects (Figure 2).

Baseline Characteristics of the Participants

The baseline characteristics of the participants are summarized in Table 1. According to the results of homogeneity tests between the two groups, there were no significant differences in demographic and clinical variables.

Clinical Outcomes

Primary Outcomes: VAS (4 W)

In the TG, the average change in the VAS score at 4 W compared with the baseline decreased significantly by 23.5 points (4 W: −23.5 [95% confidence interval: −43.684 to −3.316]; p = 0.0303). The VAS score of the TG at 4W showed a statistically significant decrease compared with the CG (4 W: −24.5 [95% confidence interval: −45.418 to −3.582]; p = 0.0106) (Table 2).

Secondary Outcomes: VAS (2 W, 6 W, 8 W)

In the TG, the average change in the VAS scores at 6 W and 8 W compared with the baseline showed a statistically significant decrease of 21.5 and 29.667 points (6 W: −21.5 [95% confidence interval: −39.045 to −3.955]; p = 0.0254 and

Table 1 Demographic and Clinical Characteristics at Baseline

Characteristics		Treatment group (n=6)	Control group (n=6)	p-value[a]
		N(%)	N(%)	
Gender	Male	1(16.67%)	2(33.33%)	0.9999
	Female	5(83.33%)	4(66.67%)	
Job	Office worker	1(16.77%)	1(16.77%)	0.9999
	Service worker	1(16.77%)	2(33.33%)	
	Self-employment	1(16.77%)	0(0.00%)	
	Housewife	3(50.00%)	3(50.00%)	
Exercise	Yes	4(66.67%)	3(50.00%)	0.9999
	No	2(33.33%)	3(50.00%)	
Type of knee surgery	Arthroscopy	6(100.00%)	6(100.00%)	–
(multiple response)	Osteotomy	1(16.77%)	1(16.77%)	
Past history of knee pain treatment	Analgesic	3(50.00%)	2(33.33%)	–
(multiple response)	Physiotherapy	4(66.67%)	2(33.33%)	
	Manual therapy	3(50.00%)	3(50.00%)	
	Injection	1(16.77%)	0(0.00%)	
	Acupuncture	4(66.67%)	2(33.33%)	
	Moxibustion	2(33.33%)	2(33.33%)	
	Cupping therapy	2(33.33%)	0(0.00%)	
	Herbal medicine	2(33.33%)	0(0.00%)	
		Mean±SD	Mean±SD	p-value[b]
Age (year)		58.83±4.26	53.17±4.92	0.0587
Height (cm)		160.70±7.72	163.30±13.17	0.6816
Weight (kg)		68.77±7.44	74.83±14.22	0.3763
BMI (kg/m2)		26.65±2.29	27.98±3.72	0.4716
Exercise time (minute/week)		78.33±70.55	136.67±152.44	0.4229
Duration of knee pain (month)		76.33±48.57	80.83±64.49	0.8941
Days after surgery (month)		35.17±27.21	38.67±27.19	0.8281
VAS		54.17±18.78	53.00±15.09	0.9079
K-WOMAC	Pain	11.50±2.51	9.17±2.79	0.1585
	Stiffness	4.50±1.38	5.17±1.60	0.4576
	Physical function	34.67±11.31	35.17±12.30	0.9430
	Total	50.67±13.19	49.50±15.88	0.8926
EQ-5D-5L		0.66±0.18	0.72±0.05	0.4075

Notes: [a]Fisher's exact test, [b]Independent *t*-test.
Abbreviations: BMI, Body Mass Index; EQ-5D-5L, The Euroqol 5-dimension 5-level questionnaire; K-WOMAC, The Korean version of the Western Ontario and McMaster Universities Osteoarthritis Index; SD, standard deviation; VAS, Visual Analogue Scale.

8 W: −29.667 [95% confidence interval: −47.410 to −11.923]; p = 0.0077). The VAS scores of the TG at 6 W and 8 W showed a statistically significant reduction compared with that of the CG (6 W: −19.667 [95% confidence interval: −42.135 to 2.802]; p = 0.0228 and 8 W: −28.667 [95% confidence interval: −51.702 to −5.632]; p = 0.0036) (Table 2).

Secondary Outcomes: K-WOMAC

In the TG, the average change in the K-WOMAC total scores at 2 W, 4 W, 6 W, and 8 W compared with the baseline showed a statistically significant decrease of 17.167, 23, 29.833, and 30.5 points, respectively (p = 0.0083, p = 0.0018, p = 0.0009, and p = 0.0006). There were no statistically significant differences between the two groups.

In the "pain" category, the scores at 2 W, 4 W, 6 W, and 8 W compared with the baseline in the TG showed a statistically significant decrease of 4, 6.167, 7.833, and 7.167 points, respectively (p = 0.0066, p = 0.0065, p < 0.001, and p = 0.0015). In

Table 2 Adjusted Mean Difference of VAS

VAS	Treatment group (n=6)	Control group (n=6)	Mean difference[a] (95% CI)	p-value[b]
	Mean±SD (95% CI)	Mean±SD (95% CI)		
Baseline	54.17±18.78 (34.462, 73.872)	53.00±15.09 (37.168, 68.832)		
Week 2	53.33±18.79 (33.614, 73.052)	56.33±11.36 (44.411, 68.256)	−3.000 (−22.973, 16.973)	0.4677
Difference	−0.833 (−11.231, 9.564)	3.333 (−5.807, 12.474)		
p-value[c]	0.8449	0.3916		
Week 4	30.67±18.50 (11.252, 50.082)	55.17±13.66 (40.832, 69.501)	−24.500 (−45.418, −3.582)	0.0106*
Difference	−23.500 (−43.684, −3.316)	2.167 (−6.108, 10.441)		
p-value[c]	0.0303*	0.5307		
Week 6	32.67±19.23 (12.484, 52.849)	52.33±15.50 (36.067, 68.600)	−19.667 (−42.135, 2.802)	0.0228*
Difference	−21.500 (−39.045, −3.955)	−0.667 (−9.158, 7.824)		
p-value[c]	0.0254*	0.8480		
Week 8	24.50±20.11 (3.399, 45.601)	53.17±15.39 (37.012, 69.321)	−28.667 (−51.702, −5.632)	0.0036**
Difference	−29.667 (−47.410, −11.923)	0.167 (−7.726, 8.060)		
p-value[c]	0.0077**	0.9588		

Notes: [a]least squares mean difference, [b]Analysis of covariance, [c]Paired *t*-test, *Significant difference (*p < 0.05, **p < 0.01).
Abbreviations: CI, confidence interval; SD, standard deviation; VAS, Visual Analogue Scale.

the "stiffness" category, the score at 8 W compared with the baseline in the TG showed a statistically significant reduction of 2.667 points (p = 0.0383), and the score at 4 W compared with the baseline in the CG showed a statistically significant decrease of 1.667 point (p = 0.0108). In the "physical function" category, the scores at 2 W, 4 W, 6 W, and 8 W compared with the baseline in the TG showed statistically significant decreases of 12.167, 14.833, 19.833, and 20.667 points, respectively (p = 0.0139, p = 0.0017, p = 0.0030, and p = 0.0019). However, there were no statistically significant differences between the two groups in the average changes in the individual scores of the three subscales (Table 3).

Secondary Outcomes: EQ-5D-5L

In the TG, the EQ-5D-5L score was not statistically significant different from the baseline, and there was no statistically significant difference between the two groups (Table 4).

Table 3 Adjusted Mean Difference of K-WOMAC

K-WOMAC	Treatment group (n=6)	Control group (n=6)	Mean difference[a] (95% CI)	p-value[b]
	Mean±SD (95% CI)	Mean±SD (95% CI)		
Total				
Baseline	50.67±13.19 (36.829, 64.504)	49.50±15.88 (32.831, 66.169)		
Week 2	33.50±20.79 (11.680, 55.320)	44.17±22.69 (20.352, 67.981)	−10.667 (−38.663, 17.330)	0.3259
Difference	−17.167 (−27.607, −6.727)	−5.333 (−30.821, 20.154)		
p-value[c]	0.0083**	0.6137		
Week 4	27.67±19.12 (7.604, 47.729)	43.33±23.36 (18.815, 67.852)	−15.667 (−43.127, 11.794)	0.2033
Difference	−23.000 (−32.777, −13.223)	−6.167 (−34.940, 22.607)		
p-value[c]	0.0018**	0.6054		
Week 6	20.83±16.83 (3.168, 38.499)	38.50±24.30 (12.994, 64.006)	−17.667 (−44.560,9.226)	0.1721
Difference	−29.833 (−40.748, −18.919)	−11.000 (−41.603, 19.603)		
p-value[c]	0.0009***	0.3979		
Week 8	20.17±17.43 (1.876, 38.457)	38.33±25.02 (12.079, 64.587)	−18.167 (−45.901, 9.568)	0.1706
Difference	−30.500 (−40.734, −20.266)	−11.167 (−42.421, 20.088)		
p-value[c]	0.0006***	0.4005		

(*Continued*)

Table 3 (Continued).

K-WOMAC	Treatment group (n=6)	Control group (n=6)	Mean difference[a] (95% CI)	p-value[b]
	Mean±SD (95% CI)	Mean±SD (95% CI)		
Pain				
Baseline	11.50±2.51 (8.866, 14.134)	9.17±2.79 (6.242, 12.091)		
Week 2	7.50±4.37 (2.914, 12.086)	8.83±5.49 (3.069, 14.597)	−1.333 (−7.718, 5.051)	0.2322
Difference	−4.000 (−6.299, −1.701)	−0.333 (−6.145, 5.478)		
p-value[c]	0.0066**	0.8885		
Week 4	5.33±3.78 (1.369, 9.297)	8.83±5.04 (3.548, 14.119)	−3.500 (−9.227, 2.227)	0.3306
Difference	−6.167 (−9.705, −2.629)	−0.333 (−7.564, 6.897)		
p-value[c]	0.0065**	0.9103		
Week 6	3.67±2.42 (1.125, 6.209)	8.17±5.12 (2.798, 13.535)	−4.500 (−9.648, 0.648)	0.1511
Difference	−7.833 (−9.378, −6.289)	−1.000 (−8.210, 6.210)		
p-value[c]	<0.001***	0.7360		
Week 8	4.33±3.93 (0.206, 8.461)	8.17±5.12 (2.798, 13.535)	−3.833 (−9.703, 2.036)	0.2381
Difference	−7.167 (−10.091, −4.242)	−1.000 (−8.210, 6.210)		
p-value[c]	0.0015**	0.7360		
Stiffness				
Baseline	4.50±1.38 (3.053, 5.947)	5.17±1.60 (3.485, 6.848)		
Week 2	3.50±1.38 (2.053, 4.947)	4.00±1.67 (2.244, 5.756)	−0.500 (−2.472, 1.472)	0.6866
Difference	−1.000 (−3.201, 1.201)	−1.167 (−3.092, 0.759)		
p-value[c]	0.2956	0.1801		
Week 4	2.50±1.76 (0.652, 4.348)	3.50±1.76 (1.652, 5.348)	−1.000 (−3.265, 1.265)	0.5195
Difference	−2.000 (−4.393, 0.393)	−1.667 (−2.751, −0.583)		
p-value[c]	0.0844	0.0108*		
Week 6	2.33±1.75 (0.496, 4.171)	3.50±2.43 (0.951, 6.049)	−1.167 (−3.891, 1.557)	0.4519
Difference	−2.167 (−4.687, 0.353)	−1.667 (−4.209, 0.875)		
p-value[c]	0.0781	0.1527		
Week 8	1.83±1.47 (0.289, 3.378)	3.50±2.43 (0.951, 6.049)	−1.667 (−4.250, 0.917)	0.2394
Difference	−2.667 (−5.120, −0.213)	−1.667 (−4.209, 0.875)		
p-value[c]	0.0383*	0.1527		
Physical function				
Baseline	34.67±11.31 (22.800, 46.533)	35.17±12.30 (22.255, 48.078)		
Week 2	22.50±15.36 (6.382, 38.618)	31.33±16.03 (14.507, 48.159)	−8.833 (−29.030, 11.363)	0.3229
Difference	−12.167 (−20.599, −3.734)	−3.833 (−22.458, 14.791)		
p-value[c]	0.0139*	0.6194		
Week 4	19.83±13.99 (5.150, 34.517)	31.00±17.69 (12.440, 49.560)	−11.167 (−31.680, 9.347)	0.2451
Difference	−14.833 (−21.074, −8.592)	−4.167 (−25.811, 17.477)		
p-value[c]	0.0017**	0.6417		
Week 6	14.83±12.89 (1.306, 28.361)	26.83±17.00 (8.994, 44.673)	−12.000 (−31.406, 7.406)	0.2091
Difference	−19.833 (−29.346, −10.321)	−8.333 (−30.081, 13.415)		
p-value[c]	0.0030**	0.3699		
Week 8	14.00±12.85 (0.512, 27.488)	26.67±17.70 (8.086, 45.247)	−12.667 (−32.568, 7.235)	0.1963
Difference	−20.667 (−29.538, −11.795)	−8.500 (−30.848, 13.848)		
p-value[c]	0.0019**	0.3731		

Notes: [a]least squares mean difference, [b]Analysis of covariance, [c]Paired *t*-test, *Significant difference (*p < 0.05, **p < 0.01, ***p < 0.001).
Abbreviations: CI, confidence interval; K-WOMAC, The Korean version of the Western Ontario and McMaster Universities Osteoarthritis Index; SD, standard deviation.

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Table 4 Adjusted Mean Difference of EQ-5D-5L

EQ-5D-5L	Treatment group (n=6)	Control group (n=6)	Mean difference[a] (95% CI)	p-value[b]
	Mean±SD (95% CI)	Mean±SD (95% CI)		
Baseline	0.66±0.18 (0.465, 0.847)	0.72±0.05 (0.675, 0.774)		
Week 2	0.64±0.17 (0.458, 0.813)	0.68±0.22 (0.459, 0.910)	−0.049 (−0.298, 0.200)	0.8575
Difference	−0.020 (−0.137, 0.096)	−0.040 (−0.223, 0.142)		
p-value[c]	0.6726	0.5961		
Week 4	0.74±0.07 (0.670, 0.813)	0.66±0.24 (0.414, 0.911)	0.079 (−0.169, 0.327)	0.2879
Difference	0.085 (−0.060, 0.231)	−0.062 (−0.273, 0.148)		
p-value[c]	0.1926	0.4821		
Week 6	0.74±0.07 (0.667, 0.810)	0.67±0.24 (0.418, 0.921)	0.069 (−0.182, 0.320)	0.3070
Difference	0.083 (−0.045, 0.211)	−0.055 (−0.269, 0.160)		
p-value[c]	0.1572	0.5402		
Week 8	0.77±0.09 (0.675, 0.870)	0.70±0.20 (0.488, 0.909)	0.074 (−0.127, 0.275)	0.2004
Difference	0.116 (−0.003, 0.235)	−0.026 (−0.200, 0.148)		
p-value[c]	0.0537	0.7174		

Notes: [a]least squares mean difference, [b]Analysis of covariance, [c]Paired *t*-test.
Abbreviations: CI, confidence interval; EQ-5D-5L, The Euroqol 5-dimension 5-level questionnaire; SD, standard deviation.

Secondary Outcomes: Rescue Medication Consumption

The rescue medication dosages in the TG were 7.833, 6.833, 6, and 6 lower at 2W, 4W, 6W, and 8W, respectively, than those in the CG. However, when conducting a homogeneity test regarding the average dosage of rescue medication, there was no statistically significant difference between the two groups (Table 5).

Analysis of Trends Over Time

Trends over time were analyzed using RM-ANOVA. In the analysis of trends according to visit, significant trend changes over time were shown in the VAS score, K-WOMAC subscales for "pain" and "stiffness" categories, EQ-5D-5L, and rescue medication consumption ($p = 0.013$, $p = 0.0313$, $p = 0.0012$, $p = 0.0176$, and $p = 0.0436$). However, the interaction between time and group was not statistically significant for any clinical outcome (Figure 3).

Safety Assessment

No adverse reactions were reported in the 12 subjects who participated in the study (six in the TG and six in the CG).

Table 5 Analysis of Rescue Medication Consumption

Rescue medication consumption	Treatment group (n=6)	Control group (n=6)	Mean difference[a] (95% CI)	p-value[b]
	Mean±SD (95% CI)	Mean±SD (95% CI)		
Week 2	5.67±8.91 (−3.688, 15.022)	13.50±12.23 (0.669, 26.331)	−7.833 (−21.598, 5.931)	0.2335
Week 4	6.83±12.17 (−5.941, 19.607)	13.67±11.62 (1.470, 25.863)	−6.833 (−22.142, 8.475)	0.3434
Week 6	5.50±9.20 (−4.158, 15.158)	11.50±9.05 (2.003, 20.997)	−6.000 (−17.741, 5.741)	0.2814
Week 8	3.17±5.00 (−2.077, 8.410)	9.17±7.86 (0.919, 17.414)	−6.000 (−14.471, 2.471)	0.1456

Notes: [a]least squares mean difference, [b]Independent *t*-test.
Abbreviations: CI, confidence interval; SD, standard deviation.

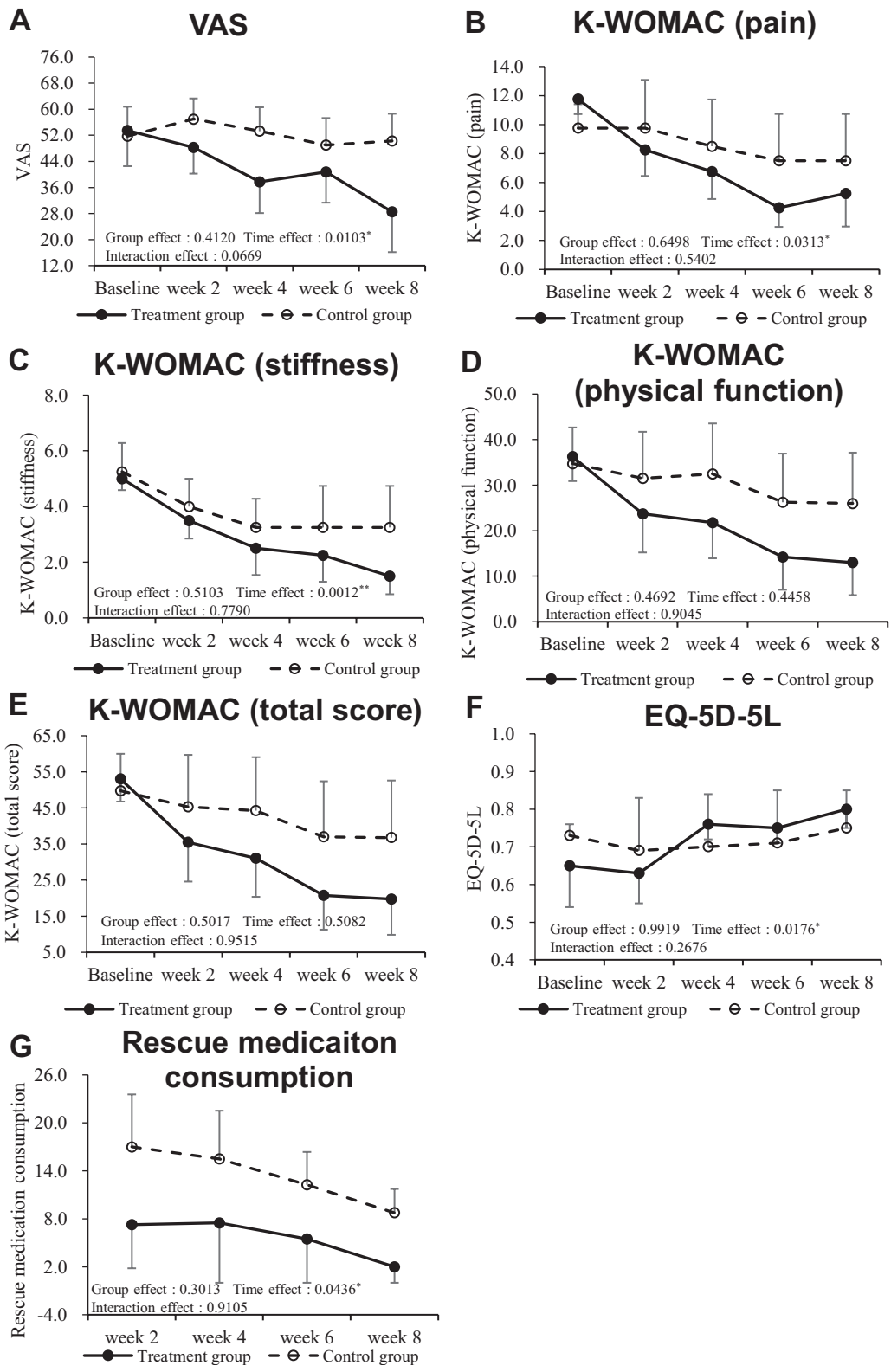

Figure 3 Change over time in the VAS, K-WOMAC (pain), K-WOMAC (stiffness), K-WOMAC (physical function), K-WOMAC (total score), EQ-5D-5L and rescue medication consumption. No significant interaction between time and group was found in the VAS (**A**), K-WOMAC (pain) (**B**), K-WOMAC (stiffness) (**C**), K-WOMAC (physical function) (**D**), K-WOMAC (total score) (**E**), EQ-5D-5L (**F**) and rescue medication consumption (**G**).

Notes: *p < 0.05, **p < 0.01.

Abbreviations: EQ-5D-5L, The Euroqol 5-dimension 5-level questionnaire; K-WOMAC, The Korean version of the Western Ontario and McMaster Universities Osteoarthritis Index; VAS, Visual Analogue Scale.

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Discussion

This pilot study aimed to evaluate the effectiveness and safety of adding combination treatment with TEA and EA to usual care in patients with KOA who complained of knee pain, even after arthroscopic surgery, autologous chondrocyte transplantation, or autologous osteochondral transplantation. We designed a preliminary randomized controlled trial to provide foundational information for more extensive clinical studies.

After checking the surgical history of the recruited subjects through documents such as medical certificates and surgical records, all 12 patients underwent arthroscopic surgery, and two underwent both osteotomy and arthroscopic surgery. Arthroscopic surgery has the advantages of a simple surgical procedure, a short rehabilitation period, and low cost; therefore, it is commonly performed in clinical practice.[7] Consequently, the participation rate of patients who underwent arthroscopic surgery tended to be high.

We evaluated the effectiveness of this intervention in routine clinical practice using a pragmatic research design. During the study period, two and five subjects received usual care in the TG and CG, respectively. In the TG, usual care was not essential but controlled through intervention. At the same time, the CG tended to actively receive usual care such as medication, physical therapy, exercise therapy, and self-stretching. This shows that combination treatment with TEA and EA can be used as an effective intervention in clinical practice for patients with KOA who suffer from persistent postoperative pain.

The primary efficacy endpoint, the VAS score at 4 W, was significantly reduced in the TG compared with that in the CG, and the VAS scores at 6 W and 8 W also reduced significantly. Compared with 4 W and 6 W, the gap in the VAS scores between the two groups at 8 W increased, showing a tendency for the pain improvement effect to persist after the end of the intervention. This suggests that combination treatment with TEA and EA is an effective method for improving postoperative knee pain. However, because the study was terminated after four weeks of follow-up from the last intervention date, it was impossible to confirm whether TEA's effect on knee pain lasted in the long term. According to randomized control trials that performed TEA intervention in patients with KOA, the results showed that the impact in the TEA treatment group was statistically superior after six months of treatment.[18,19] This suggests that TEA may produce better therapeutic results in the long term rather than immediately. Considering the characteristics of polydioxanone sutures, which take approximately six months to decompose and be completely absorbed,[43] the treatment effect is expected to be maintained for a certain period after the end of the intervention. In the future, a long-term follow-up study will be needed to determine the duration of the effect and pain change trends over time after TEA treatment of the knee.

In this study, the K-WOMAC and EQ-5D-5L scores tended to improve; however, there was no statistically significant difference between the two groups. This is inconsistent with other results showing significant treatment effects on functional disability and quality of life in previous studies that conducted TEA[19,20,44] and EA[45–48] interventions for KOA. Statistical significance was probably not achieved owing to the short study period and insufficient number of subjects. Future studies with a more extended study period and a more significant number of subjects should be conducted.

The two groups had no statistically significant difference in rescue medication consumption, but the CG took more rescue medications. However, several points should be considered regarding this finding. Because of the study design, blinding was not possible; therefore, there was also a bias toward the compensatory abuse of rescue medication in the CG. In addition, during the intervention period, some subjects in the TG took rescue medication for pain and discomfort such as stiffness and foreign body sensation immediately after the TEA procedure. If the analgesic effect continues for a considerable period even after the end of TEA intervention, the dose of rescue medication is expected to be significantly reduced. These findings suggest the need for long-term follow-up research on rescue medication consumption after TEA.

No adverse reactions related to TEA or EA were observed during this study period. In previous clinical studies in which TEA[49] and EA[50] were used as interventions in patients with KOA, no adverse reactions were reported. According to a systematic review of the safety of TEA,[51] the incidence of adverse reactions was 11.09%, which is relatively standard, but most were local and mild. The most common symptom was induration, followed by redness and swelling, bleeding and ecchymosis, persistent discomfort, fever, dizziness, and pain. In the case of EA, systematic reviews[52] and

meta-analyses[53] have demonstrated the safety of KOA treatment. Therefore, it is believed that combination treatment with TEA and EA is relatively safe.

The limitations of this study were as follows. First, the number of recruited participants was small, and some dropouts occurred. This study aimed to recruit 36 subjects but was terminated early due to the coronavirus disease 19 (COVID-19); therefore, the previously planned number of subjects could not be recruited. A follow-up study should be conducted with sufficient number of subjects to ensure the validity of the results. Second, blinding the practitioners and subjects was difficult because of the noticeable difference in the intervention, and the fact that the TG may favor the survey due to the risk of bias should be considered when interpreting the results. This suggests a study design that utilizes both TEA and EA sham tools to minimize the risk of performance bias. Third, the study was conducted over a relatively short period (eight weeks), making it difficult to confirm the duration of the effect of TEA. Therefore, future long-term observational studies should be conducted.

Despite these limitations, this is the first clinical pilot study to evaluate the effectiveness and safety of combination treatment with TEA and EA in patients with KOA who complained of knee pain after arthroscopic surgery, autologous chondrocyte transplantation, or autologous osteochondral transplantation. In addition, because this study was designed to reflect a practical clinical environment, it provides evidence that combination treatment with TEA and EA can be considered an adjuvant therapy in actual clinical settings. Based on the results of this study, we plan to conduct follow-up randomized controlled trials to verify the long-term effectiveness of combination treatment with TEA and EA on postoperative knee pain in patients with KOA.

Conclusion

This pilot study suggests that adding combination treatment with TEA and EA to usual care might be safe and effective for improving pain in patients with KOA. The combination treatment with TEA and EA significantly alleviated pain intensity, and no adverse reactions were observed during the eight-week study period. Further long-term, large-scale research is needed to validate the hypothesis of this preliminary study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree 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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