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Clinical and cost-effectiveness of collaborative treatment with Korean and Western medicine for headache: Protocol for a multicenter prospective observational study

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Abstract

Background: Headaches are among the most prevalent neurological conditions worldwide, significantly contributing to disability and socioeconomic burden. Conventional treatments for headaches often have limited efficacy and may cause adverse effects, particularly due to medication overuse. Collaborative treatment (CT), which combines Western medicine (WM) and Korean medicine (KM), has been proposed as an alternative approach; however, robust evidence on its clinical and cost-effectiveness remains limited.

Objective: This study aims to evaluate the clinical effectiveness and economic value of CT compared with usual care (UC) in patients with headaches in real-world clinical settings.

Methods: This prospective, two-arm, multicenter observational study will assess and compare the clinical effectiveness and economic value of CT versus usual care (UC) alone for patients with headaches. Adults aged 19 years or older with a primary diagnosis of headache visiting participating hospitals under Korea's national CT pilot project will be enrolled. Participants will receive either CT (WM plus KM) or UC (WM or KM) based on informed choice. Clinical and cost-related outcomes will be assessed at baseline, 6 weeks, and 12 weeks. Clinical outcomes include monthly headache days (MHD), the Numeric Rating Scale (NRS), the Headache Impact Test (HIT-6), the EuroQol-5 Dimensions (EQ-5D-5L), and the EuroQol-Visual Analogue Scale (EQ-VAS). The cost-effectiveness evaluation includes the Cost per QALY (Quality-Adjusted Life Years), the Incremental Cost-Effectiveness Ratio (ICER), and the Cost-Effectiveness Acceptability Curve (CEAC). Both intention-to-treat and per-protocol analyses will be performed.

Results: As of July 2025, this study protocol has received institutional review board (IRB) approval. Participant recruitment is scheduled to begin in August 2025, aiming to enroll 312 patients across multiple centers. Data collection is projected to be completed by late 2025.

Conclusions: This study will generate real-world evidence on whether CT provides superior clinical outcomes and greater cost-effectiveness compared to UC for headaches. The findings will address existing evidence gaps by integrating multidimensional clinical and economic measures, supporting informed decision-making for health policy, and contributing to the advancement of CT models for headache management within Korea's medical system and beyond. Clinical Trial: The study protocol was registered with the Clinical Research Information Service (CRIS) of Korea (https://cris.nih.go.kr/ Registration No: KCT0010812, Date: July 28, 2025)

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Keywords: headaches; collaborative treatment; cost-effectiveness; QALY

Introduction

Headache disorders are among the most prevalent neurological conditions worldwide, affecting over 52% of the global population and contributing substantially to disability and healthcare costs [1, 2]. According to the Global Burden of Disease (GBD) 2019 study, headaches rank as the leading cause of years lived with disability globally [1, 3]. In South Korea, National Health Insurance Service (NHIS) data from 2021 indicate that 580,292 patients were treated for migraine and 543,750 for other headache syndromes such as tension-type headache (TTH), with total healthcare expenditures exceeding 226 billion KRW [4]. Additionally, chronic headaches can lead to reduced productivity, depression, and insomnia [5, 6]. These substantial impacts underscore the urgent need for structured,

multidisciplinary national strategies and alternative approaches for the management and treatment of headaches [5, 7].

Pharmacological treatments for headaches—such as nonsteroidal anti-inflammatory drugs (NSAIDs) and tricyclic antidepressants—often demonstrate limited long-term efficacy and may cause adverse effects [8-10]. Chronic headache, in particular, is frequently resistant to pharmacotherapy, and overuse of analgesics can exacerbate headache symptoms [8, 11]. In this context, collaborative treatment (CT) combining Western medicine (WM) and Korean medicine (KM) has attracted increasing interest due to its potential synergistic effects, integrating the pharmacological benefits of WM with the holistic and individualized therapies of KM—such as acupuncture, pharmacopuncture, herbal medicine, and cupping therapy [12-15]. Emerging evidence suggests that collaborative care can reduce headache frequency and intensity more effectively than monotherapy alone [14, 16]. However, robust clinical data comparing the effectiveness and cost-efficiency of CT for various health conditions, including headaches, remain limited [17-19]. Since 1951, Korea has maintained a dual medical system that legally recognizes both WM and KM [20]. While this structure preserves patient choice and cultural tradition, it can also result in overlapping resources and practice-related disputes [21]. To address these challenges, pilot programs were introduced to support WM–KM collaboration [22]. Despite these initiatives, barriers persist. Treatments from both disciplines provided on the same day for the same condition are typically not jointly reimbursed under NHIS, resulting in higher out-of-pocket costs for patients [23]. Additionally, limited information exchange and the absence of standardized protocols hinder effective interdisciplinary coordination. To overcome these obstacles, the Korean government launched pilot programs that expanded insurance coverage for CT, resulting in improvements in patient and provider satisfaction and a reduction in treatment duration [24, 25].

Since its launch in 2016, Korea's pilot program for CT has progressed through four stages and is now preparing for its fifth phase [23, 25]. The program has gradually evolved from parallel practice to protocol-based models for specific conditions, along with a unified reimbursement system and strengthened institutional support for CT [19, 25, 26]. Notable advancements include the introduction of inter-institutional electronic medical record sharing systems and joint training programs for WM and KM practitioners. Nonetheless, persistent challenges—such as fragmented delivery systems, insufficient clinical experience with interdisciplinary practice, and the lack of unified clinical guidelines—continue to limit the wider adoption of collaborative care models. In response, this study aims to investigate whether CT provides greater clinical effectiveness and cost-efficiency for patients with headache compared to usual care (UC) alone. To achieve this, we will conduct a prospective, multicenter observational study using validated patient-centered instruments focusing on headache-related disability, quality of life, and self-rated health status, alongside an economic evaluation based on healthcare costs and utility measures.

Methods

Study design and ethical approval

This is a prospective, two-arm, observational, multicenter study of patients with headaches at medical institutions participating in the fifth phase of the national pilot project for CT [23]. The study protocol was developed following the SPIRIT guidelines (Supplement File 1). The study adheres to the principles outlined in the Declaration of Helsinki and follows Good Research Practices as recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [27]. The study protocol was registered with the Clinical Research Information Service (CRIS) of Korea (https://cris.nih.go.kr/ Registration No: KCT0010812, Date: July 28, 2025). Ethical approval was obtained from the ethical review board of all the following institutions: Wonkwang University Gwangju Oriental Medicine Hospital (WKIRB-2025-10), Dongshin University Mokpo Oriental Hospital(DSMOH25-4). The study will be conducted as part of the Registry for Korean Medicine

and Western Medicine Collaborative Treatment (REKOMENT), with participant recruitment scheduled from the date of IRB approval to December 12, 2025. The detailed study schedule, as outlined in the SPIRIT guidelines, is illustrated in Figure 1.

Participants and treatments

The study participants comprise patients diagnosed with headaches who visit hospitals participating in the fifth phase of the CT pilot project and receive either CT or UC alone [23]. Patients receiving UC are those treated exclusively with either KM or WM, whereas CT refers to treatment involving both KM and WM. The detailed treatment procedures and guidelines for headaches with WM and/or KM in participating hospitals under the fifth phase of the national CT pilot project are based on clinical evidence and recommendations outlined in clinical practice guidelines for headaches in Korea [9, 28, 29]. Participants can freely choose either UC alone or CT, in consultation with their practitioners. If a participant opts for CT, one practitioner will initiate a collaborative treatment request to the other practitioner. Treatment choices can be adjusted at any time through consultation with practitioners, and all treatments will be recorded and monitored. Patients who agree to participate will be given detailed information about the study and all safety-related aspects before providing informed consent. After obtaining written consent, a medical doctor (MD) or a Korean medicine doctor (KMD) will assess the participant's eligibility. Those who meet the inclusion criteria will be enrolled in the study and assigned an enrollment number to ensure anonymity. To ensure fair and open participation, announcements about the study will be made publicly available at the participating institutions.

Inclusion criteria

1. Adults aged 19 years or older.
2. Individuals with a primary diagnosis of headache who are first-time outpatients at one of the participating institutions, as systematically defined by the International Classification of Diseases, 10th Revision (ICD-10): G43 (migraine), G44.0 (cluster headaches and other trigeminal autonomic cephalgia's (TAC), G44.2 (TTH), and G44.8 (other specified headache syndromes).
3. Individuals who voluntarily agree to participate in the study, or whose legal representatives have provided both written and verbal informed consent.

Exclusion criteria

1. Individuals covered by automobile insurance (ineligible for treatment under the CT pilot project) [23].
2. Individuals with difficulty understanding the research questionnaire.
3. Individuals with difficulty adhering to the study schedule and follow-up assessments.
4. Individuals deemed unsuitable for participation at the discretion of the investigator.
5. Individuals participating in the national pilot project for herbal medicine coverage under the National Health Insurance [23].

Sample size estimation

The sample size was estimated based on NRS values obtained from our internal pilot study (N = 59; mean ± SD for group 1: 1.85 ± 1.66, group 2: 2.48 ± 2.13), which was registered with the Clinical Research Information Service (CRIS) of Korea (Registration No: KCT0010198, registration date: November 14, 2024). Using the G*Power program with a two-sided significance level of 0.05, power of 80% ($\alpha = 0.05$), and adjusting for a 10% discontinuation rate, the total required sample size for the study was determined to be 312 participants.

Data collection and management

Data for the study will be collected through participant surveys using a standardized Case Report Form (CRF). The CRF is designed to capture participants' baseline characteristics, hospital medical records, and administrative data from each participating institution. This includes sociodemographic information, medical history, clinical indicators, and cost-related details. Administrative and medical data will be utilized to assess treatment costs associated with headaches, types and frequencies of treatment, medical expenses, duration of healthcare utilization, and types of services used. Trained and experienced researchers at each institution will be responsible for collecting both baseline and follow-up data. Face-to-face or telephone interviews will be conducted. All data will be entered and managed using the iCReaT system, developed by the Korea National Institute of Health. To protect participant confidentiality, all collected documents will use identification codes instead of personal names and will be stored as encrypted files with access limited to authorized researchers. The Monitoring Center for Korean Medicine and Western Medicine Collaboration (MCMC) will independently oversee data handling, storage, and validation throughout the study. This center, established under the Ministry of Health and Welfare as part of the fifth phase of the national pilot project, will serve as the study's executive data management body. The monitoring center personnel will ensure compliance with the observational study protocol, authorize any modifications to the registry protocol, oversee the accuracy and appropriateness of data collection, and verify that informed consent has been properly obtained from all participants.

Measures

Baseline characteristics

The participants' baseline information will be collected on the first day of their hospital visit. This includes age, gender, monthly household income (in KRW), history of treatment for headaches and other medical conditions, medication use, occupation and employment status, insurance status, and onset duration (duration from headache onset to first hospital visit).

Clinical effectiveness

The clinical effectiveness of the treatment will be evaluated using monthly headache days (MHD) [30], the Numeric Rating Scale (NRS) [31], the Headache Impact Test (HIT-6) [32, 33], the EuroQol-5 Dimensions (EQ-5D-5L) [34], and the EuroQol-Visual Analogue Scale (EQ-VAS) [35], with assessments conducted at each study time point: baseline, 6 weeks, and 12 weeks. Evidence indicates that increases in MHD are linked to lower health-related quality of life (HRQOL), and that a reduction in MHD by ≤ 4 contributes to improved patient health outcomes [30, 36]. Thus, assessing MHD in this study is crucial for evaluating treatment efficacy. The NRS measures overall pain intensity and discomfort associated with headache, with patients rating their pain on a scale from 0 (no pain) to 10 (worst pain imaginable) [31, 37].

The HIT-6 is a widely used, validated tool designed to measure the impact of headaches on a patient's ability to function normally in daily life, comprising six items, each with five graded response options [32, 33]. Each response is assigned a score ranging from 6 to 13 points per item, resulting in total scores that range from 36 to 78, with higher scores indicating greater impact or burden of headaches [38]. The patient's HRQOL will be evaluated using the Korean version of the EQ-5D-5L [39]. The EQ-5D-5L assesses HRQOL across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [34, 40]. The EQ-VAS will be used to measure the patient's self-perceived health status on a scale from 0 to 100 [35, 41]. Higher scores on the EQ-5D-5L and EQ-VAS indicate better HRQOL and overall health, respectively.

Cost-effectiveness

Cost utilization for both treatments will be comprehensively assessed, including direct medical costs, direct non-medical costs, and indirect costs such as productivity losses, derived from CRF and hospital administrative data. The cost-effectiveness of the treatments will be evaluated using several measures: cost per quality-adjusted life-years (QALYs) [42, 43], the incremental cost-effectiveness ratio (ICER) [44], and the cost-effectiveness acceptability curve (CEAC) [45]. The cost per QALY will be estimated using the area under the curve (AUC) method [42, 46], based on utility scores captured through EQ-5D-5L and EQ-VAS. The ICER, representing the economic value of CT compared with UC, is determined by dividing the incremental cost by the incremental QALYs gained [44, 47]. The CEAC illustrates the probability that a treatment is cost-effective across a range of willingness-to-pay (WTP) thresholds per QALY, with the horizontal axis denoting WTP values and the vertical axis representing the corresponding probabilities [45, 48].

Safety

This study establishes standardized guidelines for reporting adverse events during the study period. All abnormal symptoms, adverse effects, or illnesses occurring in participants—regardless of their relation to the treatment received—will be documented. Recorded data will include a description of the event, time of onset, severity assessment by the practitioner, and relationship to treatment. The research team will assess participant eligibility and determine the need for withdrawal. Additional visits may be scheduled for further evaluation. For participants who withdraw, the reasons will be documented, assessed, and followed up on accordingly.

Statistical analyses

Baseline data will be summarized using descriptive statistics such as percentages, frequencies, and means (standard deviations) for both the UC and CT groups. The UC group refers to participants receiving treatment exclusively with either KM or WM, whereas the CT group includes those receiving both KM and WM. Data normality will be evaluated using the Shapiro-Wilk test and Q-Q plots. Between-group differences will be assessed using Chi-square tests (Fisher’s exact test) for categorical data, and the Student’s t-test or ANOVA for continuous data. When normality or equal variances assumptions are violated, the Mann–Whitney U and Kruskal–Wallis tests will be performed.

Per-protocol (PP) and intention-to-treat (ITT) analyses will be conducted to assess clinical and cost-effectiveness. To establish the ITT dataset, the proportion and mechanism of missing data will be evaluated using Little’s test. If the missingness is identified as missing completely at random (MCAR) or missing at random (MAR), as defined by Rubin [49], multiple imputation will be performed [49, 50]. Mean changes in clinical outcomes over time will be compared between groups as part of the effectiveness analysis. Furthermore, a generalized linear mixed model (GLMM) will be employed to assess between-group effects at each time point, adjusting for baseline covariates. Subgroup analyses will be performed according to headache type (migraine, tension-type, or other) and headache severity (episodic or chronic).

Utility values from EQ-5D-5L and EQ-VAS will be used to estimate QALYs, using the AUC method [42]. Deterministic analyses for the ICER will be performed using both ITT and PP data from a limited societal perspective (LSP) and a societal perspective (SP). A probabilistic sensitivity analysis (PSA) will also be carried out using parameter distributions and estimates. To account for sampling uncertainty in the ICER point estimates, 95% confidence intervals will be calculated using the bootstrapping method or a seemingly unrelated regression (SUR) model. All statistical analyses will be conducted using Stata MP (version 14.0) and SAS (version 9.4), with the significance level set at p-value < 0.05.

Results

This trial protocol was approved by the institutional review board in July 2025. Participant recruitment is planned to commence in August 2025, with a target enrollment of 312 patients across multiple clinical centers. Baseline data to be collected will include sociodemographic characteristics, clinical history, and treatment preferences. Clinical outcomes (monthly headache days, numeric rating scale scores, Headache Impact Test-6), health-related quality of life (EQ-5D-5L, EQ-VAS), and economic measures (QALYs, ICER, CEAC) are planned to be systematically collected during the study period. Data collection is expected to be completed by late 2025.

Discussion

This study will prospectively assess and compare the clinical and cost-effectiveness of CT combining KM and WM versus UC alone in patients with headaches. By incorporating real-world data from multiple medical institutions participating in the fifth phase of the national CT pilot project, the study integrates multidimensional patient-centered measures to provide evidence supporting effective and sustainable CT integration in headache treatment.

Previous studies on KM, WM, or CT for headaches have shown potential benefits, including pain reduction and improved quality of life [9, 13, 14, 17, 51]. However, the evidence remains limited and inconsistent, often relying on single-center designs, short follow-up periods, and lacking cost-effectiveness analyses, thereby reducing both generalizability and methodological rigor [12, 13, 52]. While pharmacological interventions in WM are effective, they frequently cause notable side effects [8, 9]. Conversely, electroacupuncture has proven effective in mitigating chronic headache severity, especially when other therapeutic options have not yielded results [53]. Therefore, this study addresses these gaps through a robust multicenter observational design and comprehensive clinical and economic outcome measures, providing a thorough evaluation of CT's value in headache management.

The strength of this study lies in its real-world, multicenter design within Korea's national healthcare framework, enhancing the generalizability of the findings. To our knowledge, this is the first study to comprehensively evaluate both the clinical and cost-effectiveness of CT for headache. This dual focus on clinical and economic outcomes aims to support evidence-based decision-making in CT for headache care. However, there are several limitations that should be acknowledged. First, as an observational study with non-randomized allocation and patient-driven treatment preferences, there is potential for residual confounding and selection bias. Second, variations in clinical practice across institutions may lead to heterogeneity in treatment delivery (e.g., choice of specific KM or WM modalities), which could affect the consistency of outcomes. Third, the study's follow-up duration may not fully capture long-term outcomes or recurrence rates, which are particularly relevant for chronic headache management. Fourth, cost data derived from patient self-reports may be subject to underreporting or misclassification, especially for indirect and non-medical costs. Lastly, as this study is embedded within Korea's dual healthcare system, the findings may have limited generalizability to countries with different healthcare structures or reimbursement models.

In conclusion, this study is expected to generate robust, actionable evidence on the clinical effectiveness and cost-effectiveness of CT for headache. The findings will contribute to the growing body of evidence supporting collaborative approaches in chronic disease management, including headaches, and may help inform policy development for CT-based healthcare delivery in Korea and beyond.

Dissemination

The findings of this study will be disseminated through academic conferences and seminars and published in peer-reviewed journals. In addition, the results will inform the development of clinical practice guidelines for the use of CT in the treatment of headaches. Progress updates will be reported

annually, and ongoing information and additional resources will be made available through MCMC's dedicated website.

Data Availability

No datasets were generated or analyzed during the current study. However, upon completion, all relevant data will be made available by the corresponding author upon reasonable request.

Authors' Contribution

JK and JY conducted literature review and wrote the original draft. LK contributed to study design, conducted literature review and developed the manuscript structure, and performed critical clinical review. SRA contributed to study design, performed data analysis, provided statistical review, and wrote the statistical sections of the manuscript. CH performed critical clinical review, contributed ethical perspectives to support IRB approval, and revised the manuscript for intellectual and clinical content. JK and JY contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

None declared

Abbreviations

CT: Collaborative Treatment
WM: Western Medicine
KM: Korean Medicine
UC: Usual Care
QALY: Quality-Adjusted Life Year
NHIS: National Health Insurance Service
GLMN: Generalized Linear Mixed Model
PP: Per-Protocol
ITT: Intention-to-Treat
LSP: Limited Societal Perspective
SP: Societal Perspective
SUR: Seemingly Unrelated Regression

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	STUDY PERIOD			
	Enrolment	**Baseline / Allocation**	**Treatment / Follow-up**	
TIMEPOINT	0	0	6 weeks	12 weeks
ENROLMENT:				
Informed consent	**X**			
Inclusion and exclusion criteria	**X**			
Socio-demographic information, medical history		**X**		
ASSESSMENTS:				
MHD		**X**	**X**	**X**
NRS		**X**	**X**	**X**
HIT-6		**X**	**X**	**X**
EQ-5D-5L		**X**	**X**	**X**
EQ-VAS		**X**	**X**	**X**
Cost information			**X**	**X**
Hospital medical records and administrative data				**X**

Figure 1. Schedule of enrolment and assessments according to SPIRIT guidelines. MHD, monthly headache days; NRS, numeric rating scale; HIT-6, hit impact test; EQ-5D-5L, EuroQol-5 dimensions; EQ-VAS, EuroQol-visual analogue scale.

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Figures

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Schedule of enrolment and assessments according to SPIRIT guidelines. MHD, monthly headache days; NRS, numeric rating scale; HIT-6, hit impact test; EQ-5D-5L, EuroQol-5 dimensions; EQ-VAS, EuroQol-visual analogue scale.

	STUDY PERIOD			
	Enrolment	Baseline / Allocation	Treatment / Follow-up	
TIMEPOINT	0	0	6 weeks	12 weeks
ENROLMENT:				
Informed consent	X			
Inclusion and exclusion criteria	X			
Socio-demographic information, medical history		X		
ASSESSMENTS:				
MHD		X	X	X
NRS		X	X	X
HIT-6		X	X	X
EQ-5D-5L		X	X	X
EQ-VAS		X	X	X
Cost information			X	X
Hospital medical records and administrative data				X

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CONSORT (or other) checklists

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