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Original Article

Effectiveness and safety of hominis placental pharmacopuncture for chronic temporomandibular disorder: A multi-center randomized controlled trial

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ABSTRACT

Background: Hominis placental (HPP) extract has been approved by the Ministry of Food and Drug Safety in Korea for treating chronic liver diseases and postmenopausal syndrome. However, its efficacy and safety for treating chronic temporomandibular disorder (TMD) remains unclear. We aimed to assess the effectiveness and safety of HPP for treating chronic TMD compared with physical therapy (PT).

Methods: This study is a 2-arm parallel, multi-center, randomized controlled trial. We enrolled 82 chronic TMD patients from 2 Korean medicine hospitals between December 2019 and January 2021. We included patients with chronic TMD and randomly assigned them to undergo HPP or PT. The primary outcome was the difference in the scores for temporomandibular joint (TMJ) pain at baseline and week 6. The secondary outcomes were the scores for TMJ pain and bothersomeness, TMJ range of motion, the Korean version of Beck's depression index-II, jaw functional limitation scale (JFLS) score, patient global impression of change (PGIC) scores, EuroQoL 5-dimension 5-level score, and short form-12 health survey (SF-12) scores.

Results: Compared with PT, HPP showed significantly superior effects on TMJ pain and bothersomeness, protrusive movement pain, JFLS (verbal, emotional, and global), SF-12, and PGIC scores at week 6 ($P < 0.05$). Compared with the PT group, the HPP group showed a significantly higher recovery rate (≥50 % reduction in the scores for TMJ pain at the 24-week follow-up).

Conclusion: HPP was more effective than PT managing pain and improving function and quality of life. Our findings demonstrate the effectiveness and safety of HPP for TMD treatment.

Trial registration: This study has been registered at clinicalTrials.gov (NCT04087005), Clinical Research Information Service (CRIS) (KCT0004437), and Ministry of Food and Drug Safety (No. 31886).

1. Introduction

Temporomandibular disorder (TMD) is characterized by various clinical symptoms involving the temporomandibular joint (TMJ), masticatory muscle, and surrounding areas. The most common TMD symptoms include TMJ and masticatory muscle pain, TMJ asymmetry, restricted TMJ movement, and TMJ crepitus. Other less common symptoms include ear pain, tinnitus, dizziness, neck pain, and headaches. Some patients might present acute mild symptoms, while others might present chronic pain as well as other physical, behavioral, and psychological symptoms similar to those in patients with chronic pain syndrome in other body parts.[1] The prevalence rate of TMD is especially high among individuals aged 30–49 years; moreover, it is at least thrice higher among women than among men.[2] In Korea, the prevalence of TMD persisting ≥ 3 months is 3.1 %.[3]

The diagnostic tools for TMD include the American Academy of Orofacial Pain criteria[4] and the International Headache Society classification[5]; moreover, the most widely used diagnostic tool is the research diagnostic criteria for TMD (RDC/TMD).[6] The RDC/TMD is used to assess the degree of mandibular opening, range of motion (ROM), severity of pain and bothersomeness, and other symptoms. This multidimensional tool classifies TMDs as muscle and joint problems (Axis 1) or psychological problems (Axis 2). In Axis 1, the TMDs are subclassified as myofascial pain (group 1), disc displacements (group 2), and other joint conditions

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(group 3). Axis 2 assesses pain severity along with the presence and severity of accompanying neuropsychiatric symptoms.

Conventional treatments for TMD include drug therapy, physical therapy (PT), and surgical intervention.[1] Drug therapy includes oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, opioids, steroids, tricyclic antidepressants, selective serotonin reuptake inhibitors, anxiolytics, and anticonvulsants,[7,8] as well as injection of topical analgesics, corticosteroids, hyaluronic acid, ketamine, and botulinum toxin.[9] PT includes heat therapy and transcutaneous electrical nerve stimulation (TENS) for reducing TMJ pain, as well as for neck and jaw exercises; posture exercises; and manual therapy for the jaw, neck, and face to improve TMJ ROM.[7,8,10] Surgical interventions include arthroscopy, arthrocentesis, arthrotomy, and TMJ reconstruction.[11] However, due to the risk of adverse events (AEs), including deafferentation pain, surgical interventions should only be considered for patients who have been unresponsive to conservative treatment for 3–6 months and those with serious impairments in activities of daily living or with anatomic lesions. Other treatment methods for TMD include splinting,[12] cognitive behavioral therapy, counseling, and biofeedback.[7,8]

Acupuncture is the most widely used treatment option in complementary and alternative medicine for TMD.[8] Acupuncture can effectively treat musculoskeletal diseases, especially TMJ pain and functional impairment.[7,13] Pharmacopuncture therapy combines acupuncture and herbal medicine, with the injection of herbal extracts into acupoints.[14-16] The aqueous extract of the human placenta, known as hominis placental extract, is utilized as an injectable medicine for treating chronic liver diseases[17] and postmenopausal syndrome[18] in Korea. HPP is a rich source of bioactive substances such as polydeoxyribonucleotides, RNA, DNA, peptides, amino acids, enzymes, and trace elements.[19] HPP has been reported to have therapeutic effects, including anti-inflammatory, anti-viral, anti-oxidative, anti-mutagenic and analgesic properties.[20-22] It has been verified and approved by the Ministry of Food and Drug Safety for these conditions and is marketed as a drug. However, the efficacy and safety of hominis placental pharmacopuncture (HPP) for treating chronic TMD remains unclear. Therefore, this randomized clinical trial (RCT) aimed to assess the effectiveness and safety of HPP for chronic TMD compared with PT.

2. Methods

2.1. Study design and setting

This two-armed parallel, multi-center, RCT recruited 82 patients from the Jaseng Hospital of Korean Medicine and Kyung Hee University Korean Medicine Hospital in Guangdong, South Korea between December 2019 and January 2021. The study protocol was approved by the Institutional Review Board of two centers (JASENG 2017–09–002–002 and KHNMCOH 2019–08–002) and the Ministry of Food and Drug Safety for Investigational New Drug approval (No. 31,886) before participant recruitment. The study protocol was registered with ClinicalTrials.gov (NCT04087005) and Clinical Research Information Service (KCT0004437). Participants were recruited through posters placed inside and outside of the hospitals as well as advertisements on hospital websites and subway stations.

2.2. Participation timeline

Each participant completed an informed consent form (ICF) after receiving information regarding the trial during the first visit. Subsequently, the participants were screened based on the inclusion/exclusion criteria, with eligible participants being randomly allocated to the HPP or PT groups and undergoing 10 therapy sessions (twice per week for 5 weeks) as per the assigned group. The primary endpoint was assessed upon treatment completion (week 6), with follow-up hospital visits or telephone interviews being conducted at 9, 13, and 25 weeks after baseline. Treatment compliance was assessed based on the number of attended HPP and TENS sessions. Supplementary Table 1 presents the trial schedule for the participants.

2.3. Inclusion criteria

1. Unilateral/bilateral TMJ pain
2. Visual analog scale (VAS) score ≥ 40 mm at the pain site (for patients with bilateral pain, the site with more severe pain was chosen)
3. Intermittent/persistent TMJ pain for ≥ 3 months
4. Diagnosis of myofascial TMD (Axis I: Group 1) based on the RDC/TMD[6] or belonging to Group 1 as well as Groups 2 and/or 3
5. Age 19–70 years as of the date of ICF signing
6. Consent for participation and ICF submission

2.4. Exclusion criteria

1. Current pain episode having being caused or exacerbated by a traffic accident or traumatic injury
2. Diagnosis of Axis I: Group 2 and/or 3, but not Group 1, based on the RDC/TMD
3. Having undergone TMJ-related surgery
4. Having other chronic diseases that may influence the therapeutic effects or the interpretation of the results (e.g., rheumatoid arthritis, neoplastic disease, stroke, myocardial infarction, etc.)
5. Current intake of steroids, immunosuppressants, psychiatric drugs, or other drugs that may influence the findings.
6. Having received NSAIDs or other drugs that may affect pain within the past week or having received HPP therapy within the past month
7. Pregnant or lactating women
8. Having participated in another clinical trial within the past month or planning to participate in another clinical trial within 6 months of study enrollment or during the follow-up period of our study
9. A history of hypersensitivity to HPP
10. Having diabetes with uncontrolled blood sugar levels (fasting blood sugar ≥ 180 mg/dl)
11. Aspartate or alanine aminotransferase levels twice or higher than the normal range established by the test center
12. Creatinine levels twice or higher than the normal range established by the test center
13. Possibility of having an organic disease
14. Having cardiac, hepatic, or renal complications as well as other serious complications
15. Having psychosomatic disease
16. Inability to undergo HPP therapy due to inflammation or wounds in the acupoints
17. Individuals considered ineligible by the researcher for other reasons

2.5. Randomization and allocation concealment

Group allocation was performed at a 1:1 ratio (41 per group) through block randomization using nQuery Advisor 7.0 (SAS 9.0, or SPSS 21.0). Specifically, we generated a random sequence through block randomization, with the size of each block being randomly set to 2, 4, and 6. The randomization results were sealed in nontransparent envelopes and delivered to each center, where they were kept in a double-lock locker. Before the intervention, the envelopes were opened in front of each participant for group allocation based on the randomization number, which was recorded in an electronic chart and could not be subsequently changed.

2.6. Blinding

Since each group received a different treatment, the participants and therapist could not be blinded. A baseline assessment was performed by

a researcher blinded to the group allocation who was instructed not to have treatment-related discussions with the participants.

2.7. Interventions

2.7.1. Experimental group: HPP group

Participants in the HPP group underwent 10 sessions of HPP therapy, receiving treatment twice per week for 5 weeks, using JHG002 manufactured at the Jaseng Namyangju Extramural Herbal Dispensary in accordance with Korean Good Manufacturing Practice. JHG002 was produced through human placental extraction, sourced from the drug master file (DMF) provided by Kyungnam Pharm. Ltd., Korea. The DMF for human placental medicine adhered to regulations set by the Korean Food and Drug Administration. Human placentas, collected by Kyungnam Pharm with maternal consent at full-term delivery, underwent extraction and sterilization processes. The treatment protocol for HPP, including the total treatment period, number of treatment sessions, dose per injection, and injection site, was based on a previous trial.[13] A trained Korean medicine (KM) doctor with ≥ 2 years of clinical experience injected JHG002 into the designated site using a disposable syringe (0.5 mL syringe, 31 gauge*5/16'' needle) following the standard protocol. The participants got a treatment in a supine or lateral position for their safety. The intervention was bilaterally applied at eight acupoints (0.1 mL of JHG002 per acupoint) to a depth of 8 mm, regardless of the pain site. The acupoint were SI19 (*Tinggong; Cheonggung*), GB20 (*Fengchi; Pungji*), GB21 (*Jianjing; Gyeonjeong*), TE17 (*Yifeng; Yepung*), ST7 (*Xiaguan; Hagwan*), ST6 (*Jiache; Hyeopgeo*), LI18 (*Futu; Budol*), and EX-HN5 (*Taiyang; Taeyang*). The dose per acupoint was adjustable to 0.05–0.1 mL based on the patient's reaction, including pain and bothersomeness.

2.7.2. Control group: PT group

The PT group underwent TENS therapy twice per week for 5 weeks using high-frequency, low-intensity stimulation at 50–100 Hz, with an intensity comfortable for the patient (up to 15 mA). During each visit, this procedure was bilaterally performed for 15 min using the same TENS equipment (BioTron-DX, D.M.C., Osan, Korea).

2.8. Concomitant treatment

All participants were educated on the cause, prevention, treatment, and management of TMD as well as on the self-stretching method.[23] During the treatment period, participants were restricted from receiving treatments that may affect TMD. However, they could receive treatment for severe pain after notifying the principal investigator. The type and frequency of such treatments were recorded on a case report form. There were no restrictions regarding specific treatments during the follow-up period.

2.9. Discontinuation criteria

1. Occurrence of any serious AE (SAE) during the trial or when continuing treatment could harm the participants.
2. Having a newly occurring disease during the study period that could influence the study outcome.
3. Participant's request for discontinuation during the trial period
4. Participant's violation of the study protocol (treatment compliance ≤ 60 %)
5. Complications during the therapy sessions
6. Pregnancy during the study period
7. When the principal investigator determines that the study cannot continue due to other reasons

2.10. Outcome measure

2.10.1. Primary outcome

2.10.1.1. Visual analog scale (VAS) score for TMJ pain. The primary outcome was the difference in the VAS score for TMJ pain between the baseline and primary endpoint (week 6). Using the VAS, participants were instructed to indicate the TMJ pain level experienced within the past week on a 100-mm line, with one end indicating "no pain" and the other indicating "worst pain imaginable".[24]

2.10.2. Secondary outcomes

2.10.2.1. Numeric rating scale (NRS) score for TMJ pain and bothersomeness. The intensity of TMJ pain and bothersomeness experienced in the past week were assessed using the NRS on a 0–10 scale (0, no pain and bothersomeness; 10, worst imaginable pain and bothersomeness imaginable).[24]

2.10.2.2. TMJ range of motion. The degree of mouth opening and excursive movement was measured using a Therabite Range of Motion Ruler according to the guidelines of the International RDC/TMD Consortium.[25]

2.10.2.3. Korean-Beck depression inventory (K-BDI)-II. The BDI-II is a 21-item depression index for sadness, guilt, suicidal ideation, and loss of interest.[26] We used the K-BDI-II, which has confirmed reliability and validity.[27] Each item is rated on a 0–3 scale, with higher total scores indicating more severe depressive tendencies (1–10 points, normal; 10–16 points, mild mood disturbance; 17–20 points, borderline clinical depression; 20–30 points, moderate depression; 30–40 points, severe depression; and ≥ 40 points, extreme depression).

2.10.2.4. Jaw functional limitation scale (JFLS). The JFLS is a 20-item scale used to assess jaw function within the past month (mastication, mobility, verbal, and emotional).[28] We used the official Korean version of the JFLS, which has verified reliability.[29]

2.10.2.5. The 5-level version of EuroQol-5 Dimension(EQ-5D-5L). The EQ-5D-5L is the most widely used tool for indirectly calculating the weights of certain health aspects with respect to QoL based on multidimensional assessment. It assesses five dimensions regarding the current health status (mobility, self-care, usual activities, pain, and anxiety/depression), with weights being assigned based on the level of each dimension. A preference score was calculated based on these weights and specific constants. We used the Korean version of the EQ-5D-5L, which has verified validity.[30]

2.10.2.6. Short form-12 health survey (SF-12) version 2. The SF-12 is a condensed version of the short form-36 health survey, which is widely used to assess health-related QoL (HRQoL). The SF-12 comprises 12 items regarding eight dimensions, with higher scores indicating better HRQoL.[31] We used the Korean version of the SF-12, which has verified reliability and validity.[32]

2.10.2.7. Patient global impression of change (PGIC). The PGIC uses a seven-point Likert scale to assess the patient's overall impression regarding the post-intervention improvement in TMD-induced dysfunction (1, very much improved; 4, no change; and 7, very much worse). Although this tool was originally developed for psychology, it has been used in other medical fields.[33]

2.11. Laboratory test

To determine the suitability of participants and assess AEs, the following clinical pathology tests were performed at the start and end of the treatment period: complete blood count, liver function tests (aspartate transaminase, alanine transaminase, and alkaline phosphatase),

blood urea nitrogen, creatinine, erythrocyte sedimentation rate, and C-reactive protein. Moreover, women of childbearing age underwent a urine human chorionic gonadotropin test. Laboratory findings were recorded in the case report form (CRF). In case of abnormal findings, additional tests, and/or treatment, the researcher decided whether the participant was to be discontinued.

2.12. Adverse events (AEs)

All AEs and SAEs were investigated during each visit and recorded in the CRF. Since the group allocation may be revealed during AE assessment, the AE assessment was performed using a separate CRF. Based on the Spilker classification, all AEs were classified as follows[34]: 1) mild: the AE does not impair normal functioning, causes minimal discomfort, and is tolerable; 2) moderate: the AE significantly impairs normal function; and 3) severe: the AE impedes the participant from having a normal life. Based on the World Health Organization-Uppsala Monitoring Centre causality scale, the causal relationship of the AE with the intervention was classified as definitely related, probably related, possibly related, probably not related, definitely not related, and unknown.

2.13. Sample size

The sample size was calculated based on previous studies and clinical experience. The significance level was set to $\alpha = 0.05$ (two-sided test), type II error (β) was set to 0.2, and test power was set to 80 %. Since there have been no studies on pharmacopuncture therapy and PT for treating TMD, the effect size for between-group comparisons of the VAS scores was set to Cohen's $d = 0.65$[35] (moderate-to-high) based on clinical experience. Accordingly, the sample size was estimated to be 39 per group. Since the planned main analysis was an analysis of covariance (ANCOVA) adjusted for baseline values, we conservatively assumed the correlation value between the baseline and primary endpoint to be 0.4 based on previous study.[36] Calculation of the sample size based on this assumption [(1–0.4 * 0.4) * 78] revealed that the minimum sample size required was 65.[37] To account for a dropout rate of 20 %, we determined a total sample size of 82 (41 per group). The sample size was calculated using G*Power 3.1.7.

2.14. Data collection and management

This study used an e-CRF from the Internet-based Clinical Research and Trial Management System operated by the Korea Disease Control and Prevention Agency. The researcher from the lead organization trained assessors and researchers in each center by distributing the standard operating procedure for the study, which included instructions regarding CRF preparation and data entry. After data entry, only the data manager was allowed access to the data.

2.15. Statistical analysis

We performed within- and between-group comparisons of the effectiveness and safety. The assessment was performed using intention-to-treat (ITT) analysis as the main analysis, while participants with compliance ≥ 60 % were included in the per-protocol (PP) analysis. For baseline characteristics, continuous and categorical variables are expressed as the mean ± standard deviation (SD) and n (%), respectively. Between-group comparisons of baseline characteristics were performed using the chi-square test, Fisher's exact test, and independent *t*-test.

The effectiveness endpoint was the degree of changes in continuous outcomes (VAS, NRS, K-BDI, JFLS, EQ5D-5L, and SF-12 scores) between baseline and each time point. Regarding effectiveness assessment, between-group comparisons of continuous and categorical variables were performed using ANCOVA adjusted for baseline values and logistic regression analysis, respectively. Regarding the safety endpoint, we performed between-group comparisons of the percentage of participants who presented AEs.

For additional analysis, we performed between-group comparisons of the area under the curve (AUC) values for the effectiveness variables. Moreover, we performed a survival analysis, with recovery being defined as $a \geq 50$ % decrease in the VAS score from baseline. Furthermore, we performed subgroup analyses based on sex, age, body mass index,[38] symptom severity, RDC/TMD diagnosis (Group Ia, Ib), VAS score for TMJ pain, range of active maximum mouth opening (MMO), K-BDI-II score,[39] EQ-5D-5 L score, SF-12 (physical component summary, mental component summary [MCS]) score,[40] and current working status. Missing values were processed through multiple imputation; moreover, sensitivity analysis was performed using a mixed model for repeated measures (MMRM) and the last observation carried forward (LOCF). Statistical analyses were performed using SAS version 9.4 statistical package (SAS Institute, Cary, NC, USA) and R version 4.1.1 (© The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at values of $p < 0.05$.

3. Results

3.1. Flowchart of the participant selection process

After screening 220 patients, we enrolled 82 participants between December 2019 and January 2021, who were randomly allocated to the HPP ($n = 40$) and PT ($n = 42$) groups. Four and five participants in the HPP and PT groups, respectively, withdrew consent during the intervention period, while one participant from each group withdrew consent during the follow-up period. Accordingly, 40 and 42 participants in the HPP and PT groups, respectively, were included in the ITT analysis. Contrastingly, PP analysis was performed including 36 and 37 participants in the HPP and PT groups, respectively, who had received at least seven treatment sessions during the intervention period (Fig. 1).

3.2. Baseline characteristics

There were no significant between-group differences in the baseline characteristics (Table 1).

3.2.1. Primary and secondary outcomes

Compared with PT, HPP showed significantly superior effects on the VAS and NRS scores for TMJ pain, NRS scores for TMJ bothersomeness, protrusive movement pain, JFLS score (verbal and emotional), JFLS score (global), SF-12 score (MCS), and PGIC score at the primary endpoint. Moreover, there was a significant between-group difference in the NRS scores for TMJ bothersomeness at the 9-week follow-up; VAS scores for TMJ pain and pain during active MMO, as well as right and left lateral excursive movement, and protrusive movement at the 13-week follow-up; pain during active MMO, as well as right and left lateral excursive movement; JFLS (mobility) scores; JFLS (global) scores; and PGIC scores at the 25-week follow-up (Table 2, Fig. 2). Compared with the PT group, the HPP group showed more favorable outcomes in the linear mixed-model analysis using MMRM (Supplementary Table 2) and in the analysis set with multiple imputation for missing values through LOCF (Supplementary Table 3). Specifically, the significant between-group differences in the VAS and NRS scores for TMJ pain were consistent throughout the follow-up period. PP analysis showed similar results until the 13-week follow-up (Supplementary Table 4).

AUC analysis of the cumulative values revealed that compared with the PT group, the HPP group showed significantly lower VAS and NRS scores for TMJ pain, NRS scores for TMJ bothersomeness, JFLS (mastication) scores, JFLS (mobility) scores, JFLS (verbal and emotion) scores, and JFLS (global) scores (Table 3).

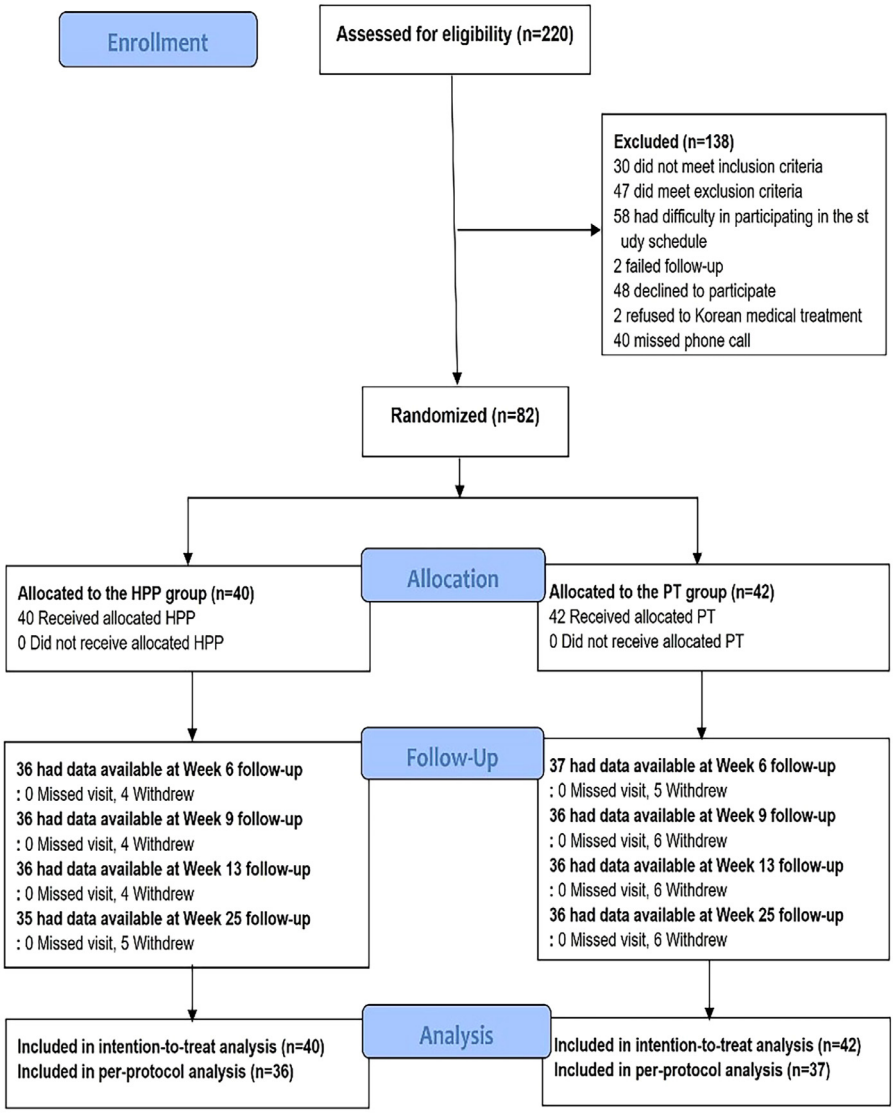

Fig. 1. Study flowchart. HPP, hominis Placental Pharmacopuncture; PT, Physical Therapy.

3.3. Survival analysis

The median times to recovery in the HPP and PT groups were 5 weeks (95 % CI: 4–12) and 24 weeks (95 % CI: 8–NA), respectively (log-rank test, $P = 0.008$). The hazard ratio for the number of patients who recovered within the 24-week period was 1.95 (95 % CI: 1.12–3.39), which favored the HPP group (Fig. 3).

3.4. Subgroup analysis

Subgroup analyses revealed that HPP resulted in greater improvement of TMJ pain among participants with higher JFLS (global) scores, which indicated poorer TMJ function; however, no other factors significantly influenced the HPP effectiveness (Supplementary Fig. 1).

3.5. Adverse events

In the HPP group, one participant complained of a localized rash at the injection site, which disappeared after 9 days without treatment. In the PT group, one participant experienced increased post-treatment TMJ pain, which was improved by an analgesic tablet (Tylenol 500 mg) on the same day. Both AE cases were mild. There were no cases of treatment-related SAEs.

4. Discussion

We found that HPP significantly improved TMJ pain indicators, functional scale scores, and QoL in patients with chronic TMD, which was maintained throughout the follow-up period. For moderate chronic TMJ pain, the minimal clinically important difference in the VAS score for TMJ pain is 11.4,[41] which is lower than our value at the primary endpoint (13.77). This suggests that compared with conventional treatment, HPP had a statistically and clinically better treatment effect on TMJ pain.

Pharmacopuncture therapy combines acupuncture with herbal medicine, which provides the physical stimulation effect of needling and the chemical effects of the herbal medicine injected into acupoints.[16] Since herbal extracts are directly absorbed into the target site without passing the digestive system, pharmacopuncture therapy allows immediate effects, treatment of individuals who cannot receive oral administration, and easy dose adjustment.[42]

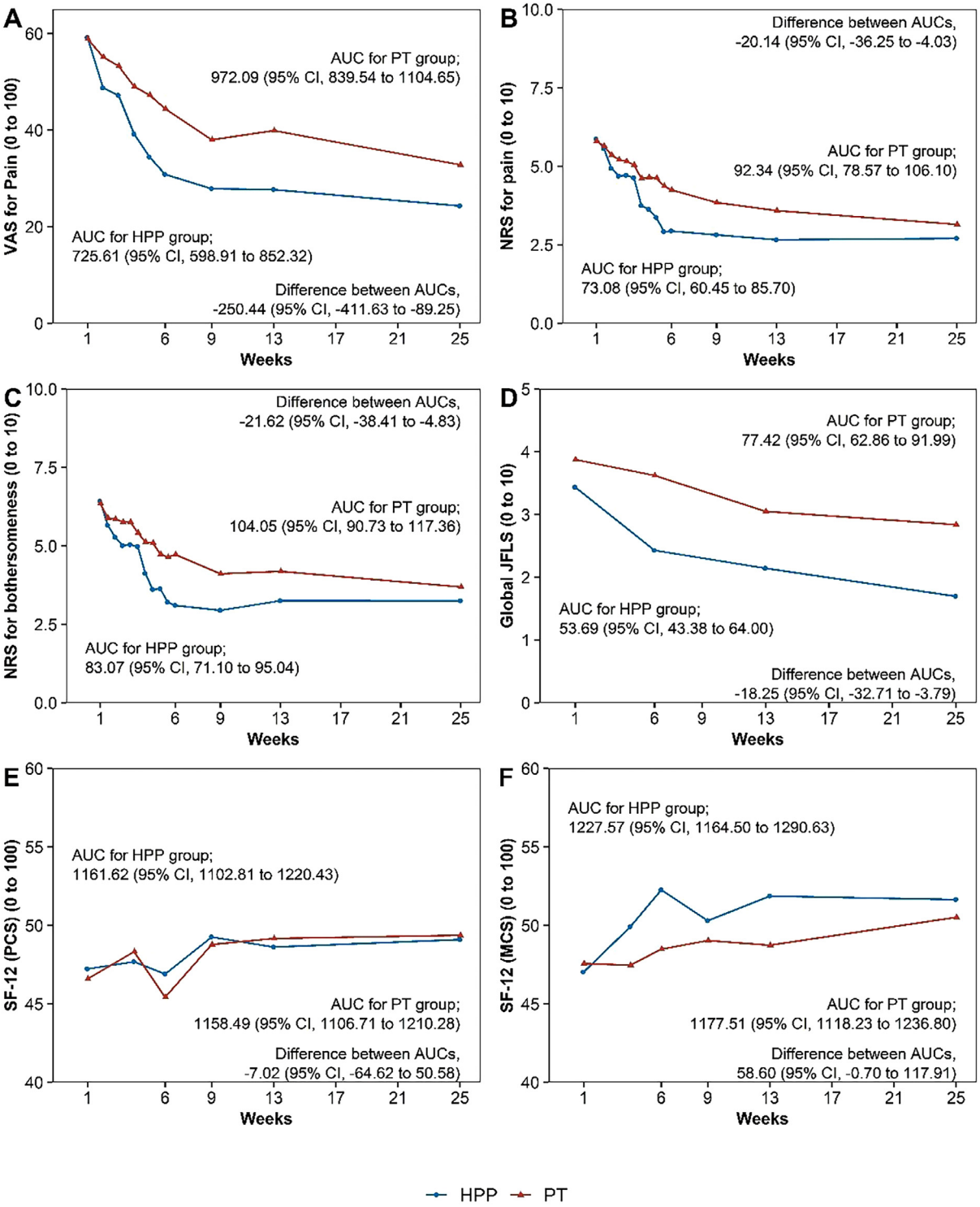

Fig. 2. Temporal changes in outcomes and AUC values. A, VAS score for TMJ pain; B, NRS score for TMJ pain; C, NRS score for TMJ bothersomeness; D, JFLS (global) score; E, SF-12 score (PCS); F, SF-12 score (MCS). Throughout the study period, the dots and error bars show the mean scores and 95 % Cis, respectively. Multiple imputations were used to process missing values. AUC values were obtained by applying the trapezoidal rule to the HPP and PT data. Between-group comparisons of the AUC values were analyzed using independent *t*-tests.

AUC, area under the curve; CI, confidence interval; HPP, hominis placental pharmacopuncture; JFLS, jaw functional limitation scale; MCS, mental component summary; NRS, numerical rating scale; PCS, physical component summary; PT, physical therapy; SF-12, short form-12 health survey; VAS, visual analog scale.

Table 1
Baseline characteristics of the participants.

Characteristics		HPP (n = 40)	PT (n = 42)	P*
Sex	Female	28 (70.0)	30 (71.4)	>0.999
	Male	12 (30.0)	12 (28.6)	
Age (years)		40.6 ± 12.7	43.2 ± 12.2	0.335
Height (cm)		166.1 ± 8.3	165.4 ± 8.8	0.699
Body weight (kg)		62.0 ± 11.3	60.9 ± 10.6	0.638
BMI (kg/m^2)		22.3 ± 2.5	22.1 ± 2.5	0.749
Pain duration (months)		98.1 ± 88.6	114.7 ± 100.5	0.430
Severity of symptoms	Moderate	19 (47.5)	26 (61.9)	0.189
	Severe, no treatment needed	16 (40.0)	9 (21.4)	
	Severe, treatment needed	5 (12.5)	7 (16.7)	
RDC/TMD†	Group I a	17 (42.5)	18 (42.9)	>0.999
	Group I b	23 (57.5)	24 (57.1)	
VAS score for TMJ pain (mm)		59.2 ± 14.1	58.9 ± 13.7	0.930
NRS score for TMJ pain		5.9 ± 1.5	5.8 ± 1.8	0.860
NRS score for bothersomeness		6.4 ± 1.9	6.4 ± 1.8	0.866
K-BDI-II score		13.3 ± 8.8	12.4 ± 8.4	0.612
JFLS - Mastication score		4.4 ± 1.9	4.9 ± 2.0	0.344
JFLS - Mobility score		3.3 ± 2.1	3.8 ± 2.2	0.362
JFLS - Verbal and emotion score		2.5 ± 2.5	3.0 ± 2.5	0.395
JFLS - Global score		3.4 ± 2.0	3.9 ± 2.0	0.330
Range of active maximum mouth opening (mm)		37.0 ± 9.5	37.9 ± 10.5	0.691
Pain during active maximum mouth opening	None	7 (17.5)	6 (14.3)	0.975
	Right side	9 (22.5)	10 (23.8)	
	Left side	10 (25.0)	10 (23.8)	
	Both sides	14 (35.0)	16 (38.1)	
Range of right lateral excursive movement (mm)		8.9 ± 3.9	10.1 ± 3.5	0.149
Pain during right lateral excursive movement	None	22 (55.0)	21 (50.0)	0.221
	Right side	9 (22.5)	4 (9.5)	
	Left side	6 (15.0)	12 (28.6)	
	Both sides	3 (7.5)	5 (11.9)	
Range of left lateral excursive movement (mm)		9.7 ± 4.5	10.6 ± 3.6	0.337
Pain during left lateral excursive movement	None	22 (55.0)	23 (54.8)	0.834
	Right side	7 (17.5)	5 (11.9)	
	Left side	8 (20.0)	9 (21.4)	
	Both sides	3 (7.5)	5 (11.9)	
Range of protrusive movement (mm)		4.4 ± 1.9	5.0 ± 2.6	0.269
Protrusive movement pain	None	28 (70.0)	25 (59.5)	0.749
	Right side	2 (5.0)	3 (7.1)	
	Left side	6 (15.0)	7 (16.7)	
	Both sides	4 (10.0)	7 (16.7)	
EQ-5D-5 L score		0.81 ± 0.08	0.81 ± 0.09	0.841
SF-12 score	PCS	47.2 ± 8.1	46.6 ± 7.6	0.717
	MCS	47.0 ± 9.6	47.6 ± 9.1	0.792

The values are shown as mean ± SD or N (%).
BMI, body mass index; EQ-5D-5 L, European quality of life–5 dimension 5 levels; JFLS, jaw functional limitation scale; HPP, hominis placental pharmacopuncture; K-BDI-II, Korean-Beck depression inventory-II; MCS, mental component summary; NRS, numerical rating scale; PCS, physical component summary; PT, physical therapy; RDC/TMD, research diagnostic criteria for temporomandibular disorders; SF-12, short form-12 health survey; TMJ, temporomandibular joint; VAS, visual analog scale.
* Between-group comparisons of the distribution of baseline characteristics. Continuous variables were analyzed using the independent t-test. Categorical variables were analyzed using the chi-square test and Fisher exact test.
† Group Ia – myofascial pain alone; Group Ib – myofascial pain with limited mouth opening.

Hominis placenta, a key ingredient for pharmacopuncture, is a human placental extract rich in bioactive substances, including polydeoxyribonucleotides, RNA, DNA, peptides, amino acids, enzymes, and trace elements.[19,43] Hominis placenta has demonstrated therapeutic effects through its anti-inflammatory, antiviral, antioxidative, antimutagenic, and analgesic properties.[20-22] Moreover, hominis placenta promotes nerve regeneration[44] and wound healing.[45,46]

A systematic review[17] revealed that most clinical trials involving HPP focused on musculoskeletal diseases (24 %) and nervous system diseases (24 %), followed by studies on gynecological, respiratory, psychiatric, and dermatological conditions. A recent RCT examined the use of HPP in the treatment of hot flushes.[18] Regarding musculoskeletal diseases, HPP can effectively reduce pain and improve function in patients with chronic ankle sprain,[47] improve shoulder joint immobilization in patients with complex regional pain syndrome,[48] and improve pain and function after high-dose treatment in patients with spinal stenosis.[49] However, most of these studies were case reports; moreover, the effectiveness of HPP alone could not be determined given the limitations of the combination therapy design. Additionally, other studies did not report AEs. There remain no clinical trials on the effectiveness of HPP in patients with TMD.

The mean age of our participants was the early 40 s; further, approximately 70 % of the participants were women and the mean duration of TMJ pain was approximately 9 years. Approximately 50 % and 40 % of the participants had moderate and severe pain, respectively. Additionally, approximately 42 % and 57 % of the participants were classified as Group Ia and Group Ib, respectively. Compared with the PT group, the HPP group showed significantly superior improvement in the VAS and NRS scores for TMJ pain, NRS scores of TMJ bothersomeness, protrusive movement pain, JFLS scores (verbal and emotional), JFLS scores

Table 2
Primary and secondary outcomes according to the treatment (ITT set)*.

Outcome	Intervention	Week 6	Week 9	Week 13	Week 25
VAS score for TMJ pain† (mm)	HPP	30.83 (23.08–38.59)	27.88 (20.33–35.42)	27.68 (20.41–34.95)	24.29 (17.31–31.27)
	PT	44.42 (35.96–52.88)	37.99 (29.32–46.67)	39.90 (31.62–48.17)	32.83 (23.96–41.69)
	Difference	13.77 (2.87–24.66)	10.26 (−1.88–22.39)	12.36 (1.77–22.94)	8.69 (−2.85–20.24)
	P value	0.014	0.095	0.023	0.136
NRS score for TMJ pain†	HPP	2.94 (2.13–3.75)	2.82 (2.07–3.57)	2.66 (1.93–3.39)	2.70 (2.01–3.40)
	PT	4.25 (3.42–5.07)	3.85 (3.06–4.64)	3.59 (2.82–4.36)	3.15 (2.34–3.97)
	Difference	1.35 (0.20–2.49)	1.06 (−0.02–2.14)	0.97 (−0.08–2.01)	0.48 (−0.52–1.47)
	P value	0.022	0.054	0.069	0.340
NRS score for TMJ bothersomeness†	HPP	3.10 (2.34–3.86)	2.94 (2.33–3.56)	3.25 (2.60–3.90)	3.25 (2.49–4.00)
	PT	4.72 (3.93–5.51)	4.11 (3.37–4.84)	4.19 (3.39–4.99)	3.69 (2.87–4.51)
	Difference	1.65 (0.52–2.78)	1.19 (0.19–2.18)	0.96 (−0.09–2.02)	0.47 (−0.64–1.58)
	P value	0.005	0.020	0.072	0.402
Range of active maximum mouth opening† (mm)	HPP	40.04 (36.80–43.28)	40.18 (36.99–43.38)	41.36 (38.42–44.30)	41.16 (37.96–44.36)
	PT	38.48 (34.49–42.47)	40.29 (36.80–43.78)	38.79 (35.02–42.57)	40.38 (36.59–44.17)
	Difference	−2.16 (−6.77–2.45)	−0.45 (−4.82–3.92)	−3.10 (−7.23–1.03)	−1.27 (−5.71–3.18)
	P value	0.349	0.834	0.137	0.568
Pain during active maximum mouth opening‡	HPP	0.75 (0.61–0.88)	0.62 (0.47–0.78)	0.52 (0.37–0.68)	0.44 (0.29–0.60)
	PT	0.79 (0.66–0.92)	0.78 (0.65–0.91)	0.75 (0.62–0.89)	0.66 (0.52–0.81)
	Difference	0.82 (0.27–2.45)	0.46 (0.15–1.38)	0.36 (0.14–0.97)	0.40 (0.16–1.00)
	P value	0.712	0.163	0.043	0.050
Range of right lateral excursive movement† (mm)	HPP	10.42 (8.77–12.08)	10.66 (9.12–12.20)	11.27 (9.49–13.05)	11.75 (10.17–13.33)
	PT	10.40 (8.60–12.21)	10.90 (9.41–12.40)	11.48 (9.83–13.14)	10.26 (8.79–11.72)
	Difference	−0.99 (−3.23–1.25)	−0.58 (−2.62–1.47)	−0.65 (−2.95–1.65)	−2.25 (−4.26–−0.24)
	P value	0.374	0.570	0.569	0.029
Pain during right lateral excursive movement‡	HPP	0.42 (0.27–0.58)	0.40 (0.25–0.55)	0.32 (0.18–0.47)	0.30 (0.16–0.44)
	PT	0.50 (0.35–0.65)	0.50 (0.35–0.65)	0.50 (0.35–0.65)	0.45 (0.30–0.60)
	Difference	0.77 (0.30–1.96)	0.69 (0.27–1.73)	0.49 (0.19–1.25)	0.53 (0.21–1.34)
	P value	0.577	0.423	0.132	0.177
Range of left lateral excursive movement† (mm)	HPP	11.90 (10.19–13.62)	12.41 (10.70–14.11)	12.51 (10.69–14.33)	12.89 (10.95–14.82)
	PT	11.89 (10.25–13.52)	12.46 (10.77–14.16)	12.44 (10.66–14.21)	12.17 (10.11–14.22)
	Difference	−0.73 (−2.71–1.26)	−0.55 (−2.70–1.59)	−0.67 (−2.93–1.59)	−1.34 (−3.82–1.14)
	P value	0.467	0.605	0.553	0.284
Pain during left lateral excursive movement‡	HPP	0.42 (0.27–0.58)	0.40 (0.25–0.55)	0.35 (0.20–0.50)	0.28 (0.14–0.41)
	PT	0.62 (0.47–0.77)	0.52 (0.37–0.67)	0.57 (0.42–0.72)	0.50 (0.35–0.65)
	Difference	0.44 (0.18–1.11)	0.60 (0.24–1.50)	0.39 (0.16–1.00)	0.37 (0.14–0.96)
	P value	0.081	0.274	0.049	0.042
Range of protrusive movement† (mm)	HPP	5.62 (4.79–6.44)	5.41 (4.70–6.11)	5.44 (4.73–6.16)	5.96 (5.19–6.72)
	PT	5.01 (4.07–5.96)	5.18 (4.38–5.99)	5.22 (4.21–6.23)	5.19 (4.13–6.25)
	Difference	−0.88 (−2.14–0.37)	−0.52 (−1.51–0.47)	−0.49 (−1.71–0.74)	−1.06 (−2.27–0.14)
	P value	0.163	0.295	0.429	0.083
Protrusive movement pain‡	HPP	0.28 (0.14–0.41)	0.32 (0.18–0.47)	0.24 (0.11–0.38)	0.25 (0.11–0.38)
	PT	0.52 (0.37–0.67)	0.47 (0.31–0.62)	0.48 (0.32–0.63)	0.40 (0.25–0.55)
	Difference	0.35 (0.13–0.97)	0.60 (0.23–1.57)	0.37 (0.14–0.98)	0.51 (0.19–1.34)
	P value	0.043	0.295	0.046	0.166
K-BDI-II score†	HPP	10.10 (7.30–12.91)	—	9.24 (6.57–11.91)	8.92 (5.97–11.87)
	PT	10.66 (7.99–13.33)	—	10.35 (7.37–13.33)	9.66 (6.77–12.54)
	Difference	1.19 (−1.80–4.19)	—	1.73 (−1.53–4.99)	1.27 (−2.61–5.14)
	P value	0.427	—	0.290	0.511
JFLS - Mastication score†	HPP	3.39 (2.66–4.12)	—	2.73 (2.10–3.36)	2.39 (1.70–3.08)
	PT	4.55 (3.71–5.39)	—	3.92 (3.07–4.77)	3.61 (2.73–4.49)
	Difference	0.92 (−0.12–1.97)	—	1.02 (−0.05–2.08)	1.05 (−0.02–2.13)
	P value	0.083	—	0.060	0.055
JFLS - Mobility score†	HPP	2.45 (1.80–3.10)	—	2.09 (1.49–2.70)	1.67 (1.19–2.15)
	PT	3.34 (2.55–4.13)	—	2.86 (2.15–3.58)	2.83 (2.02–3.64)
	Difference	0.68 (−0.23–1.60)	—	0.62 (−0.26–1.50)	1.01 (0.12–1.90)
	P value	0.139	—	0.165	0.027
JFLS - Verbal and emotion score†	HPP	1.52 (0.85–2.18)	—	1.42 (0.74–2.10)	1.17 (0.56–1.78)
	PT	2.90 (2.04–3.76)	—	2.41 (1.55–3.27)	2.23 (1.43–3.02)
	Difference	1.13 (0.18–2.07)	—	0.77 (−0.26–1.81)	0.90 (−0.02–1.82)
	P value	0.020	—	0.139	0.054
JFLS - Global score†	HPP	2.43 (1.82–3.03)	—	2.14 (1.57–2.72)	1.70 (1.19–2.20)
	PT	3.62 (2.81–4.44)	—	3.05 (2.29–3.81)	2.84 (2.08–3.60)
	Difference	0.94 (0.00–1.88)	—	0.72 (−0.19–1.62)	0.97 (0.06–1.87)
	P value	0.049	—	0.120	0.037
EQ-5D-5 L score†	HPP	0.82 (0.77–0.87)	0.83 (0.79–0.88)	0.84 (0.81–0.88)	0.86 (0.82–0.91)
	PT	0.79 (0.73–0.85)	0.82 (0.78–0.86)	0.85 (0.81–0.89)	0.85 (0.81–0.89)
	Difference	−0.03 (−0.11–0.05)	−0.01 (−0.08–0.05)	0.00 (−0.05–0.05)	−0.02 (−0.08–0.04)
	P value	0.425	0.628	0.932	0.501
SF-12 score (PCS)†	HPP	46.90 (43.27–50.54)	49.26 (46.24–52.27)	48.62 (45.24–52.00)	49.10 (45.89–52.31)
	PT	45.43 (42.13–48.72)	48.78 (45.75–51.82)	49.17 (46.20–52.14)	49.37 (46.54–52.21)
	Difference	−1.05 (−5.56–3.46)	−0.08 (−4.10–3.94)	0.94 (−3.48–5.37)	0.65 (−3.21–4.52)
	P value	0.638	0.970	0.665	0.734

(*continued on next page*)

Table 2 (*continued*)

Outcome	Intervention	Week 6	Week 9	Week 13	Week 25
SF-12 score (MCS)†	HPP	52.26 (49.45–55.08)	50.30 (46.79–53.81)	51.87 (48.59–55.16)	51.65 (48.25–55.04)
	PT	48.49 (45.11–51.87)	49.04 (45.42–52.66)	48.74 (45.32–52.16)	50.52 (47.55–53.48)
	Difference	−4.11 (−8.02–−0.21)	−1.57 (−5.89–2.75)	−3.51 (−7.50–0.49)	−1.44 (−5.36–2.49)
	P value	0.039	0.469	0.084	0.466
PGIC score†	HPP	2.25 (2.00 to 2.50)	—	—	2.29 (1.92 to 2.66)
	PT	3.34 (2.93 to 3.75)	—	—	3.20 (2.71 to 3.68)
	Difference	−1.09 (−1.59 to −0.59)	—	—	−0.91 (−1.53 to −0.28)
	P value	< 0.001	—	—	0.005

CI, confidence interval; EQ-5D-5 L, European quality of life-5 dimension 5 levels; ITT, intention-to-treat; JFLS, jaw functional limitation scale; K-BDI-II, Korean-Beck depression inventory-II; MCS, mental component summary; NRS, numerical rating scale; PCS, physical component summary; PGIC, patient global impression of change; SF-12, short form-12 health survey; TMJ, temporomandibular joint; VAS, visual analog scale.

* Effectiveness outcomes were analyzed using analysis of covariance, with adjustment for all baseline characteristics except PGIC score. The primary endpoint was week 6. Missing values were processed through multiple imputations.

† VAS, NRS, range of mouth opening, K-BDI-II, JFLS, EQ-5D-5 L, PCS, MCS, WPAI, and PGIC scores were considered continuous variables. The mean and 95 % CI values were presented for estimates stratified by groups at each time point, with between-group comparisons of the post-intervention change from baseline.

‡ Presence/absence of pain was considered a dichotomous variable. The proportion of patients with pain is shown. The mean and 95 % CI values were presented for estimates stratified by groups at each time point; moreover, we compared the odds ratios for pain at each time point.

Table 3
AUC of outcomes according to the treatment (ITT set)*.

Outcome	HPP	PT	Difference (95 % CI)	P value
VAS scores for TMJ pain	725.61 (598.91–852.32)	972.09 (839.54–1104.65)	−250.44 (−411.63–−89.25)	0.003
NRS scores for TMJ pain	73.08 (60.45–85.70)	92.34 (78.57–106.10)	−20.14 (−36.25–−4.03)	0.017
NRS scores of TMJ bothersomeness	83.07 (71.10–95.04)	104.05 (90.73–117.36)	−21.62 (−38.41–−4.83)	0.014
K-BDI-II score	235.21 (181.31–289.11)	251.15 (194.18–308.12)	−31.18 (−81.78–19.42)	0.232
JFLS - Mastication score	71.73 (60.02–83.44)	98.36 (83.05–113.67)	−21.52 (−37.99–−5.04)	0.013
JFLS - Mobility score	52.96 (42.58–63.34)	73.65 (59.17–88.12)	−16.03 (−31.01–−1.05)	0.040
JFLS - Verbal and emotion score	35.90 (23.36–48.45)	61.14 (45.23–77.05)	−19.52 (−35.25–−3.79)	0.018
JFLS - Global score	53.69 (43.38–64.00)	77.42 (62.86–91.99)	−18.25 (−32.71–−3.79)	0.016
EQ-5D-5 L score	20.13 (19.48–20.78)	19.90 (19.17–20.64)	0.27 (−0.58–1.13)	0.530
SF-12 score (PCS)	1161.62 (1102.81–1220.43)	1158.49 (1106.71–1210.28)	−7.02 (−64.62–50.58)	0.812
SF-12 score (MCS)	1227.57 (1164.50–1290.63)	1177.51 (1118.23–1236.80)	58.60 (−0.70–117.91)	0.057

AUC, area under the curve; CI, confidence interval; EQ-5D-5 L, European quality of life-5 dimension 5 levels; ITT, intention-to-treat; JFLS, jaw functional limitation scale; K-BDI-II, Korean-Beck depression inventory-II; MCS, mental component summary; NRS, numerical rating scale; PCS, physical component summary; SF-12, short form-12 health survey; VAS, visual analog scale.

* AUC was derived using outcomes throughout the study period. The AUC was calculated using the trapezoidal rule. The mean and CI values for each group are presented. Between-group differences in the AUC values were analyzed using analysis of covariance, with adjustment for baseline values. Missing values were processed through multiple imputation.

(global), SF-12 score (MCS), and PGIC scores. The AUC analysis of the cumulative values throughout the study period revealed that compared with the PT group, the HPP group showed significantly higher VAS and NRS scores for TMJ pain, NRS scores for TMJ bothersomeness, JFLS (mastication) score, JFLS (mobility) score, JFLS (verbal and emotion) score, and JFLS (global) score. Compared with the PT group, the HPP group showed a significantly faster recovery rate, which was sustained for up to 25 weeks.

This study has several limitations. First, we could not blind the therapist and participants since each group received a different intervention. To minimize bias, outcome assessment was performed by a researcher not involved in the intervention who was blinded to group allocation. Second, although psychological factors are major predictors of the therapeutic effect in patients with TMD,[50] we did not perform stratified allocation according to these factors at the randomization stage. Nonetheless, to minimize the influence of such psychological factors, we applied random allocation and performed subgroup analyses according to K-BDI scores to examine the influence of psychological factors.

This study has several strengths. First, we applied clearly defined inclusion/exclusion criteria. In previous studies,[51-53] the diagnostic criteria for TMD were ambiguous; moreover, they did not differentiate between acute and chronic TMD, which impeded the homogeneity of the patient groups. Contrastingly, we used the validated Korean version[29] of the RDC/TMD, which is a widely used diagnostic tool for chronic TMD. Second, in this study, the choice of intervention, HPP, was guided by the criteria of stability and safety. Specifically, HPP was selected as the intervention due to its composition of a singular stable ingredient and its established use as an injectable in marketed medicines (Melsmon® and Unicenta®),[54] indicating a relative safety level. Third, we selected an appropriate control intervention; specifically, based on the TMD treatment guidelines,[8] > 90 % of patients with TMD can be managed with conservative treatment, including PT and drug therapy. Furthermore, a Cochrane review[55] reported that the effectiveness of NSAIDs, benzodiazepines, anticonvulsants, and muscle relaxants in treating TMD was unclear. Based on these previous studies,[56,57] we selected PT (TENS) as the control intervention.

In conclusion, our findings confirmed the effectiveness and safety of HPP for chronic TMD, which could inform the KM standard clinical practice guidelines. Moreover, our study design and methodology could be referenced in future clinical trials on other musculoskeletal diseases and pharmacopuncture types.

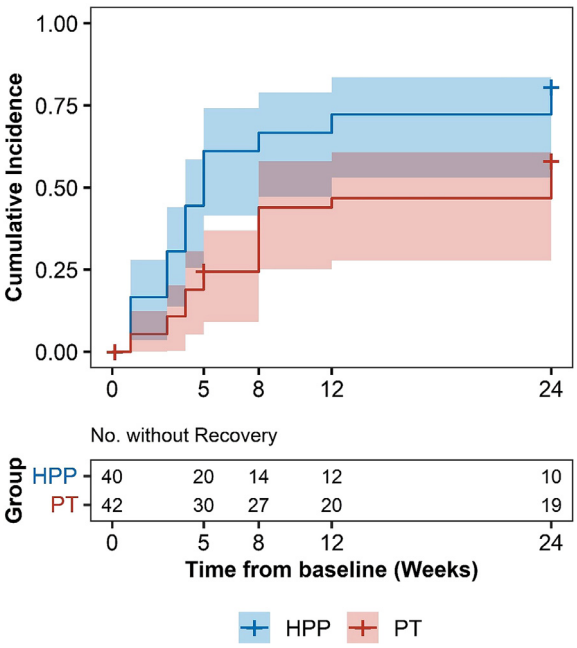

Fig. 3. Cumulative incidence curves of recovery according to group. Recovery was defined as $\alpha \geq 50$ % reduction in the VAS score for TMJ pain from baseline. The cumulative incidence curve for recovered events was derived for each group. The number of patients without recovery at the corresponding time points was recorded in the table under the graph. The hazard ratio was tested using the proportional hazard assumption with time and group interactions; moreover, the assumption was satisfied.
HPP, hominis placental pharmacopuncture; PT, physical therapy; VAS, visual analog scale.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Kyoung Sun Park: Methodology, Writing – original draft, Writing – review & editing. **Eun-San Kim:** Formal analysis. **Koh-Woon Kim:** Conceptualization, Methodology. **Jae-Heung Cho:** Conceptualization, Methodology, Funding acquisition. **Yoon Jae Lee:** Conceptualization, Methodology, Writing – review & editing. **In-Hyuk Ha:** Conceptualization, Writing – review & editing, Funding acquisition.

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Ethical statement

This research was reviewed and approved by the Institutional Review Board of each center (JASENG 2017-09-002-002 and KHNMCOH 2019-08-002) and the Ministry of Food and Drug Safety for Investigational New Drug approval (No. 31886). Informed consent was obtained from all participants.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101044.

Supplementary Table 1. Schedule for the participants

Supplementary Table 2. Primary and secondary outcomes according to treatment with imputation of missing values by mixed-model repeated measures (ITT set)

Supplementary Table 3. Primary and secondary outcomes according to treatment with imputation of missing values by LOCF

Supplementary Table 4. Primary and secondary outcomes according to treatment (PP Set)

Supplementary Fig. 1. Subgroup analysis with a primary outcome

References

1. Scrivani SJ, Keith DA, Kaban LB. Temporomandibular disorders. *N Engl J Med*. 2008;359(25):2693–2705.
2. Manfredini D, Guarda-Nardini L, Winocur E, Piccotti F, Ahlberg J, Lobbezoo F. Research diagnostic criteria for temporomandibular disorders: a systematic review of axis I epidemiologic findings. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;112(4):453–462.
3. Sim S-H, Ha M. Association between psychological factors and temporomandibular disorders in Korean adults: the fouth Korean national health and nutritional examination survey (2009). *J Korea Soc Dent Hyg*. 2013;13(5):739–747.
4. Okeson JP, Adler RC, Anderson GC, et al. *Orofacial Pain*. Differential diagnosis and management considerations of temporomandiubular disorders. Chicago: Quintessence; 1996.
5. McMillan AS, Nolan A, Kelly PJ. The efficacy of dry needling and procaine in the treatment of myofascial pain in the jaw muscles. *J Orofac Pain*. 1997;11(4):307–314.
6. John MT, Dworkin SF, Mancl LA. Reliability of clinical temporomandibular disorder diagnoses. *Pain*. 2005;118(1–2):61–69.
7. List T, Axelsson S. Management of TMD: evidence from systematic reviews and meta–analyses. *J Oral Rehabil*. 2010;37(6):430–451.
8. Gauer RL, Semidey MJ. Diagnosis and treatment of temporomandibular disorders. *Am Fam Physic*. 2015;91(6):378–386.
9. Machado E, Machado P, Wandscher V, Marchionatti A, Zanatta F, Kaizer O. A systematic review of different substance injection and dry needling for treatment of temporomandibular myofascial pain. *Int J Oral Maxillofac Surg*. 2018;47(11):1420–1432.
10. Kalamir A, Pollard H, Vitiello AL, Bonello R. Manual therapy for temporomandibular disorders: a review of the literature. *J Bodyw Mov Ther*. 2007;11(1):84–90.
11. De Leeuw R, Klasser G, eds. *Orofacial Pain*. Chicago: Quintessence; 2008.
12. Zhang C, Wu J-Y, Deng D-L, et al. Efficacy of splint therapy for the management of temporomandibular disorders: a meta-analysis. *Oncotarget*. 2016;7(51):84043.
13. Kim K-W, Ha I-H, Lee YJ, et al. A clinical practice guideline for temporomandibular disorders in traditional Korean medicine: an evidence-based approach. *Eur J Integr Med*. 2018;23:123–133.
14. Lee YJ, Shin J-S, Lee J, Kim M-r, Park KB, Lee HD, et al. Usage report of pharmacopuncture in musculoskeletal patients visiting Korean medicine hospitals and clinics in Korea. *BMC Complement Altern Med*. 2016;16(1):292.
15. Park J, Lee H, Shin B-C, Lee MS, Kim B, Kim J-I. Pharmacopuncture in Korea: a systematic review and meta-analysis of randomized controlled trials. *Evid-Base Complem Alternat Med*. 2016;2016:4683121.
16. Kim M-r, Lee SM, Lee YJ, Ha I-H. Clinical research on pharmacopuncture in Korea: a scoping review. *Perspect Integr Med*. 2023;2(1):8–23.
17. Ryoo D-W, Kim H-G, Kim S-J, Baek S-W, Jeong S-M, Yoon J-Y, et al. Systematic review of hominis placenta pharmacopuncture in English and Korean Literature. *J Acupunct Res*. 2017;34(4):153–158.
18. Choi S-J, Kim D-I, Yoon SH, Choi C-M, Yoo J-E. Randomized, single-blind, placebo–controlled trial on Hominis placenta extract pharmacopuncture for hot flashes in peri- and post-menopausal women. *Integr Med Res*. 2022;11(4):100891.
19. Tonello G, Daglio M, Zaccarelli N, Sottofattori E, Mazzei M, Balbi A. Characterization and quantitation of the active polynucleotide fraction (PDRN) from human placenta, a tissue repair stimulating agent. *J Pharm Biomed Anal*. 1996;14(11):1555–1560.
20. Angelucci C, Lama G, Sica G. The growth of malignant and nonmalignant human cells is modulated by a human placental extract. *Anticancer Res*. 1999;19(1A):429–436.
21. Togashi S-I, Takahashi N, Iwama M, Watanabe S, Tamagawa K, Fukui T. Antioxidative collagen-derived peptides in human-placenta extract. *Placenta*. 2002;23(6):497–502.
22. Datta P, Bhattacharyya D. Spectroscopic and chromatographic evidences of NADPH in human placental extract used as wound healer. *J Pharm Biomed Anal*. 2004;34(5):1091–1098.
23. Rocabado M. The importance of soft tissue mechanics in stability and instability of the cervical spine: a functional diagnosis for treatment planning. *Cranio*. 1987;5(2):130–138.

24. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthrit Care Res*. 2011;63(S11):S240–S252.
25. Dworkin SF. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomandib Disord*. 1992;6:301–355.
26. Dozois DJ, Dobson KS, Ahnberg JL. A psychometric evaluation of the Beck Depression Inventory–II. *Psychol Assess*. 1998;10(2):83.
27. Lee YH, Song JY. A study of the reliability and the validity of the BDI, SDS, and MMPI-D scales. *Korea J Clin Psychol*. 1991;10(1):98–113.
28. Ohrbach R, Larsson P, List T. The jaw functional limitation scale: development, reliability, and validity of 8-item and 20-item versions. *J Orofac Pain*. 2008;22(3):219–230.
29. Yuwei Z, Jin-Woo C, Richard O, Sung-Chang C. Reliability of a Korean version of the jaw functional limitation scale (JFLS) in dental college students. *J Oral Med Pain*. 2004;29(2):197–203.
30. Kim S-H, Ahn J, Ock M, et al. The EQ-5D-5L valuation study in Korea. *Quality of Life Research*. 2016;25(7):1845–1852.
31. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health (Bangkok)*. 1997;19(2):179–186.
32. Kim S-H, Jo M-W, Ahn J, Ock M, Shin S, Park J. Assessment of psychometric properties of the Korean SF-12 v2 in the general population. *BMC Public Health*. 2014;14(1):1086.
33. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1):9–19.
34. Spilker B. *Interpretation of adverse reactions. Guide to Clinical Studies*. New York: Raven Press; 1991:565–587.
35. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Routledge; 2013.
36. Walters SJ, Jacques RM, IBdA Henriques-Cadby, Jane Candlish NT, Xian MTS. Sample size estimation for randomised controlled trials with repeated assessment of patient-reported outcomes: what correlation between baseline and follow-up outcomes should we assume? *Trials*. 2019;20:566.
37. Borm GF, Fransen J, Lemmens WAJJ. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol*. 2007;60(12):1234–1238.
38. Kim B-Y, Kang SM, Kang J-H, Kang SY, Kim KK, Kim K-B, et al. 2020 Korean society for the study of obesity guidelines for the management of obesity in Korea. *J Obes Metab Syndr*. 2021;30(2):81.
39. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: beck depression Inventory-II (BDI-II), center for epidemiologic studies depression scale (CES-D), geriatric depression scale (GDS), hospital anxiety and depression scale (HADS), and patient health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)*. 2011;63(S11):S454–S466.
40. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *J Clin Epidemiol*. 1998;51(11):1171–1178.
41. Emshoff R, Bertram S, Emshoff I. Clinically important difference thresholds of the visual analog scale: a conceptual model for identifying meaningful intraindividual changes for pain intensity. *Pain*. 2011;152(10):2277–2282.
42. Committee AMTC. *The Acupuncture and Moxibustion Medicine*. Seoul:Jipmoondang; 2012.
43. Shibasaki T, Odagiri E, Shizume K, Ling N. Corticotropin-releasing factor-like activity in human placental extracts. *J Clin Endocrinol Metabol*. 1982;55(2):384–386.
44. Seo Tb, Han Is, Yoon Jh, Seol Ic, Kim Ys, Jo Hk, et al. Growth-promoting activity of Hominis Placenta extract on regenerating sciatic nerve 1. *Acta Pharmacol Sin*. 2006;27(1):50–58.
45. Wu CH, Chang GY, Chang WC, Hsu CT, Chen RS. Wound healing effects of porcine placental extracts on rats with thermal injury. *Brit J Dermatol*. 2003;148(2):236–245.
46. Shukla V, Rasheed M, Kumar M, Gupta S, Pandey S. A trial to determine the role of placental extract in the treatment of chronic non-healing wounds. *J Wound Care*. 2004;13(5):177–179.
47. Lee D-E, Park W-H, Cha Y-Y. The Case Report of Chronic Ankle Sprain Improved with Hominis Placenta Pharmacopuncture Treatment. *J Korea Med Rehabil*. 2016;26(3):171–181.
48. Cho TH, Park KM. Effect of placental extract on immobilization of shoulder joint in a complex regional pain syndrome patient. *J Korea Acupunct Moxibust Soc*. 2012;29(4):93–97.
49. Song KC, Seo JY, Cho MU, Song SB, Choi BS, Ryu WH, et al. Case report of patients diagnosed with spinal stenosis treated by hominis placenta megadose pharmacopuncture combined with Korean medicine treatment. *J Physiol Pathol Korea Med*. 2018;32(2):141–147.
50. Manfredini D, Favero L, Del Giudice A, Masiero S, Stellini E, Guarda-Nardini L. Axis II psychosocial findings predict effectiveness of TMJ hyaluronic acid injections. *Int J Oral Maxillofac Surg*. 2013;42(3):364–368.
51. de Abreu Venâncio R, Guedes Pereira Alencar F, Zamperini C. Different substances and dry-needling injections in patients with myofascial pain and headaches. *CRANIO®*. 2008;26(2):96–103.
52. de Abreu Venancio R, Guedes Pereira Alencar F, Zamperini C. Botulinum toxin, lidocaine, and dry-needling injections in patients with myofascial pain and headaches. *CRANIO®*. 2009;27(1):46–53.
53. Dıraçoğlu D, Vural M, Karan A, Aksoy C. Effectiveness of dry needling for the treatment of temporomandibular myofascial pain: a double-blind, randomized, placebo controlled study. *J Back Musculoskelet Rehabil*. 2012;25(4):285–290.
54. Kim S, Lee S, Ahn K-H, et al. Multicenter, double-blind, parallel, non-inferiority clinical study to compare the efficacy and safety of unicenta and melsmon for menopausal symptom improvement. *Medicina (B Aires)*. 2023;59(8):1382.
55. Mujakperuo HR, Watson M, Morrison R, Macfarlane TV. Pharmacological interventions for pain in patients with temporomandibular disorders. *Cochrane Database Syst Rev*. 2010(10):CD004715.
56. Hoffmann RG, Kotchen JM, Kotchen TA, Cowley T, Dasgupta M, Cowley Jr AW. Temporomandibular disorders and associated clinical comorbidities. *Clin J Pain*. 2011;27(3):268–274.
57. Yang H-Y, Kim M-E. Prevalence and treatment pattern of korean patients with temporomandibular disorders. *J Oral Med Pain*. 2009;34(1):63–79.