



Original Article

Safety of herbal medicine decoction for facial palsy: Coarsened exact matching analysis of the national health insurance database

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ABSTRACT

Background: Herbal medicine decoctions (HMD) are potential treatments for Bell's palsy (BP), but real-world evidence regarding the safety is limited. This study investigated whether HMD use for BP was associated with risk of adverse events using a nationwide claims-based database in South Korea.

Methods: This retrospective cohort study used data from the Korean Health Insurance Review and Assessment database. We applied coarsened exact matching, through which 1627 BP patients who received at least one HMD prescription between November 2020 and February 2022 were matched with 1627 BP patients who did not use HMD. Difference-in-differences logistic regression modeling compared the incidences of safety outcomes between HMD users and non-users.

Results: No significant differences were observed in the risk of hepatotoxicity, renal failure, allergic events, hospitalization, and emergency department visits between HMD users and non-users with BP, assessed at 3, 6, 9 and 11 months after HMD prescription. All effect estimates and corresponding 95 % confidence intervals included the null value.

Conclusions: There was no significant difference in the risk of safety outcomes between HMD users and non-users with BP. Further research is warranted to understand the safety of specific herbal formulas or individual herbs using broader safety measures.

1. Introduction

Bell's palsy (BP), the most prevalent cause of facial paralysis, is characterized by an acute onset of spontaneous unilateral peripheral facial nerve paralysis or paresis with an unidentified cause.^{1,2} BP affects individuals of all ages and sexes, with an annual incidence rate of 10–50 cases per 100,000 individuals globally with varying rates across different populations,³ imposing substantial physical, psychological, and economic burdens due to facial dysfunction, reduced social engagement, and healthcare-related costs.⁴ Recent studies have highlighted the potential role of herbal medicine decoction (HMD) in the treatment of BP, documenting a decreased risk of stroke (HMD users vs.

non-users) among Taiwanese sample⁵ and non-differential risk of adverse events (HMD-prednisone combined vs. prednisone only) among Chinese sample.⁶ However, these previous studies were either with a small number of patients ($n = 90$) over a short follow-up period (4 weeks), or did not evaluate safety outcomes.^{5,6} This necessitates further investigation to understand the safety of HMD used for BP.

In South Korea, the practices of Traditional Korean Medicine (KM) has been partly covered by the National Health Insurance (NHI), including KM diagnosis, non-pharmacological therapies (e.g., acupuncture, manual therapy, cupping, and moxibustion), herbal medications in extracts-forms, psychological consultations, and physical therapies, but not HMD.⁷ However, in November 2020, the Korean

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government implemented a pilot initiative to expand the NHI benefit coverage to include the use of HMD for three major diseases, including Bell's palsy.^{8–14} This nationwide initiative offers an opportunity to understand the safety of HMD prescribed for BP using real-world database established through the claims-and-reimbursement process primarily by the Korean National Health Insurance Review and Assessment (HIRA). Particularly, we used the difference-in-differences (DID) natural experimental design. This approach aligns with an increasing body of research on drug safety assessment using real-world data (RWD), such as claims databases,^{15,16} which encompass extensive clinical safety outcome measures. Therefore, we aimed to determine the safety of HMD for BP by comparing individuals diagnosed with BP who underwent HMD treatment through the benefit-expansion initiative with those diagnosed with BP but did not receive HMD treatment, using RWD from the Korean HIRA database.

2. Methods

2.1. Data source

The Korean Ministry of Health and Welfare launched the first-wave nationwide pilot initiative of the national health insurance (NHI) benefit expansion for HMD in November 2020.⁸ The benefit package consisted of a 50 % reduction in the total healthcare service fee, which covered the prescription and provision of HMD to treat and manage chronic conditions such as BP, cerebrovascular disease sequelae, and dysmenorrhea at primary care KM clinics from November 2020 to October 2023.⁸ Patients were eligible for the treatment of one pre-specified condition. Furthermore, the initiative mandated that all medicinal herbs be produced and distributed in compliance with Good Manufacturing Practice for Herbs regulations, which have been implemented since 2015 by the Korea Food and Drug Administration.⁸

This study used data encompassing January 1, 2015 and February 28, 2022, from the HIRA database of South Korea.¹⁷ The Korean National Health Insurance Service provides mandatory public health insurance to a majority of Korean citizens. The HIRA, responsible for claims reviews and quality assessments of services provided under the NHI, has accumulated healthcare utilization claims for the entire population of the country (approximately 50 million). The HIRA database contains both inpatient and outpatient medical records, including patient demographics, clinical diagnoses as classified by the International Classification of Diseases, tenth revision (ICD-10), medical procedures, and drug prescriptions.¹⁸

2.2. Study population

The BP cohort was defined according to the eligibility criteria of the HMD benefit-expansion pilot program. Patients were included if they had outpatient visits with a primary diagnosis of BP (G51.0) at primary care KM clinics during the benefit expansion period (November 1, 2020, and February 28, 2022). Inclusion criteria followed the HMD benefit-expansion pilot program, covering both new and existing BP patients. Data from 2015 onward were used to capture patients' medical histories and comorbidities. HMD users were defined as individuals who received at least one HMD prescription for BP under the initiative; concomitant use of Western medications and non-pharmacological therapies was permitted. Non-users were those who received only conventional (Western) BP treatment and no HMD. For HMD users, the index date was their first HMD prescription post-expansion; for non-users, it was randomly selected from their BP-related outpatient visits during the same period, to ensure time-proximal comparability. The nationwide single payer claims system ensured that all study variables had complete data.

To reduce potential confounding from additional healthcare utilization, we excluded HMD users who visited a KMD for reasons other than BP within one year after their index date. Similarly, we excluded

non-users who had any KMD visits during the same timeframe to maintain a clear distinction between the groups in terms of HMD exposure status. It resulted in 3538 among 6856 users and 25,821 among 57,204 non-users. All patients were followed up for 1 year from their respective index dates to assess subsequent outcomes (Fig. 1). Because we used claims data from a single-payer system, all individuals could be followed throughout the study period without attrition; therefore, there was no loss to follow-up.

2.3. Exposure assessment

The duration-response relationship was assessed based on the cumulative exposure duration for 30 days starting from the index date, using the proportion of days covered (PDC), calculated by dividing the sum of the durations of all prescriptions over 30 days by the total number of days in the same period. For the first visit, the NHI covers a 10-day prescription and patients pay only the copayment. Patients can have an additional prescription with full payment, which is also recorded in the HIRA database, even though the NHI does not pay for the second prescription.⁸ Considering that the initiative allows two prescriptions, we categorized HMD users as one-time users ($PDC < 0.34$) or two-time users ($PDC \geq 0.34$).

2.4. Outcome definition

The HIRA database includes information on diagnostic codes (ICD-10), hospitalization records, emergency department visits, procedures, and prescriptions. This comprehensive structure enables robust, real-world capture of safety indicators, such as hepatotoxicity and renal failure that are recognized in the literature and national surveillance as the most frequent and clinically important adverse events associated with herbal medicine use.^{19–22} Such events are identifiable via standardized diagnostic codes and service claims across all insurance-insured encounters. The HIRA database's nationwide scope and mandatory reporting ensure that these safety outcomes are representative, systematically monitored, and suitable for population-level analyses in post-market herbal medicine safety research.

Hepatotoxicity and renal failure events were considered the primary outcomes considering that these are the most commonly cited adverse effects associated with herbal medicine use in the literature.^{19–21} They were defined as the presence of either inpatient or outpatient diagnoses based on ICD-10 codes (hepatotoxicity K71; and renal failure N10, N12, N14.1, N14.2, N15.8, N15.9, N17.0, N17.1, N17.2, N17.8, and N17.9).

Secondary outcomes included allergic drug reactions, hospital admissions (except for KM hospitals), and emergency department visits. Allergic drug reactions were determined based on inpatient or outpatient diagnoses (D72.1, L27.0, L27.1, L29.8, L29.9, L50.0, L50.9, R21, T78.2, T78.3, T78.4, T88.6, and T88.7) based on previous studies.^{23,24}

Post-exposure outcomes were measured at 1, 3, 6, and 11 months, beginning 30 days after the index date. To avoid short-term or seasonal fluctuations, pre-exposure outcomes were measured at the same intervals beginning one year before the index date. All study patients had >12 months of pre-exposure claims data, enabling robust adjustment for prior health conditions and healthcare utilization.

2.5. Potential confounders for matching

To account for confounding in both treatment assignment and outcomes, we matched HMD user and non-users on their sociodemographic characteristics and clinical characteristics, as well as prior healthcare utilization patterns. In addition, we used the period between cohort entry and the index date (the interval from the benefit expansion start (November 1, 2020)) to address possible discrepancies in the timing of cohort entry. Sociodemographic characteristics included sex (male or female), age, and residential status. The duration of BP at the index date was assessed in terms of years (<1 year to >5 years). To balance

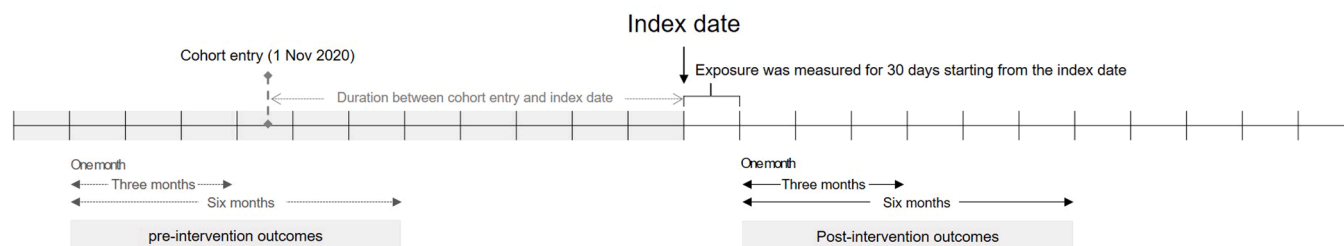


Fig. 1. Construction of the pre- and post-exposure periods of the matched.

comorbidities, we calculated the Charlson Comorbidity Index (CCI) for each participant as the sum of a weighted index ranging from 1 to 6 points and assigned to 17 disease groups based on the presence of comorbidities identified through ICD-10 codes in the year preceding the index date. A score of 0 indicates no comorbidities, whereas higher scores represent an increased risk of comorbidities.^{25,26} Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, liver disease, diabetes, hemiplegia, paraplegia, renal disease, and cancer were included as additional matching variables. Furthermore, we obtained information on allergic responses, hepatic failure, and renal failure from the claims data using the corresponding ICD-10 codes.

We also several healthcare utilization variables—hospital admissions, emergency care utilization, and KM healthcare service use during the year before each patient's index date. Hospital admissions and emergency care utilization are not only potential outcome measures but also may reflect prior adverse health events and greater underlying morbidity, which could confound treatment decisions and outcomes. Prior KM healthcare service use may proxy unobserved patient preferences and exposure to HMD, further mitigating confounding by indication.

To strengthen the DID design and explicitly address the parallel trend assumption, we additionally included emergency department visits that occurred during the 6-month window beginning 1 year prior to the index date, as our preliminary analysis indicated significant differences in pre-treatment trends between HMD users and non-users. This inclusion ensured selection of controls whose pre-treatment trends were similar to those of the treated group—an approach increasingly advocated to reinforce DID validity when parallel trends are otherwise in question.

2.6. Empirical strategy

We used the Coarsened Exact Matching (CEM) method and a quasi-experimental DID design to compare the incidence of outcomes between HMD users and non-users before and after the index date. CEM is a multidimensional matching algorithm that is applied to cells generated by dividing continuous variables into discrete intervals or by regrouping categorical variables into fewer coarsened categories. The CEM algorithm creates a strata based on the coarsened values of the matching variables, ensuring that the matched data falls within areas of shared empirical support and balancing the empirical distributions of the matching variables between the treated and control groups. One of the established benefits of CEMs is their capacity to decrease the level of reliance on the model.²⁷

We employed CEM to eliminate potential bias that may occur owing to the exaggerated person-time of a comparator as well as the aforementioned potential confounders. Each HMD user was matched to a non-user with similar sociodemographic and medical characteristics. Matching was performed at a 1:1 ratio to maximize comparability while retaining sufficient sample size.

The DID approach estimates the change in outcome incidence owing to HMD use in HMD users by offsetting the change in outcome incidence among non-users. The DID estimator is derived as follows:

$$\ln(\Pr(Y_i = 1|X)/(1 - \Pr(Y_i = 1|X))) = \beta_0 + \beta_1 Post_i + \beta_2 One\ prescription_i + \beta_3 Two\ prescriptions_i + \beta_4 One\ prescription_i \cdot Post_i + \beta_5 Two\ prescriptions_i \cdot Post_i + e_i$$

Y_i is a binary outcome variable representing hepatotoxicity, renal failure, allergic drug reactions, hospital admissions, and emergency department visits, taking a value of 1 if the individual experienced each event and 0 otherwise. "One prescription" and "two prescriptions" are dummy variables that assume a value of 1 if an individual used HMD once and twice under the initiative, respectively, and 0 otherwise. "Post" is a dummy variable that assumes the value of 1 if the outcome measurement was made in the post-policy period (after the index date) and 0 otherwise. The interaction term coefficients, β_4 and β_5 , represent our estimates of interest, indicating DID in the outcome variable attributable to one- and two-time prescriptions of herbal medicine, respectively. Considering the nature of the data, we employed logistic regression and ran separate models for each outcome measure.

The robustness of DID analyses assumes a "parallel trend" in outcomes between the treatment and control groups.²⁸ We evaluated whether there were significant differences in the trends of each outcome indicator between HMD users and non-users by using the interaction term between treatment status and the period preceding the index date, specifically focusing on the previous 1 and 2 years. Data analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA).

2.7. Ethics

As this study used de-identified data provided by the HIRA after anonymization according to strict confidentiality guidelines, the ethics review was exempted by the Institutional Review Board of Sangji University (IRB number: SJIRB-Human-22-003). The study design and reporting followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

3. Results

3.1. Descriptive characteristics

A total of 29,359 eligible patients, including 3538 herbal medicine users and 25,821 non-users, were included in this study. After conducting CEM, the user and non-user cohorts consisted of 1627 patients each (matching ratio = 45.99 % of user) (Fig. 2). The baseline characteristics of the users and non-users in the CEM-matched cohorts were well balanced between the two groups (Table 1).

3.2. Results from logistic DID analysis

Table 2 displays the coefficients for safety events associated with one- and two-time prescriptions of HMD compared to non-use in the CEM-matched cohort. The findings indicate that HMD use did not

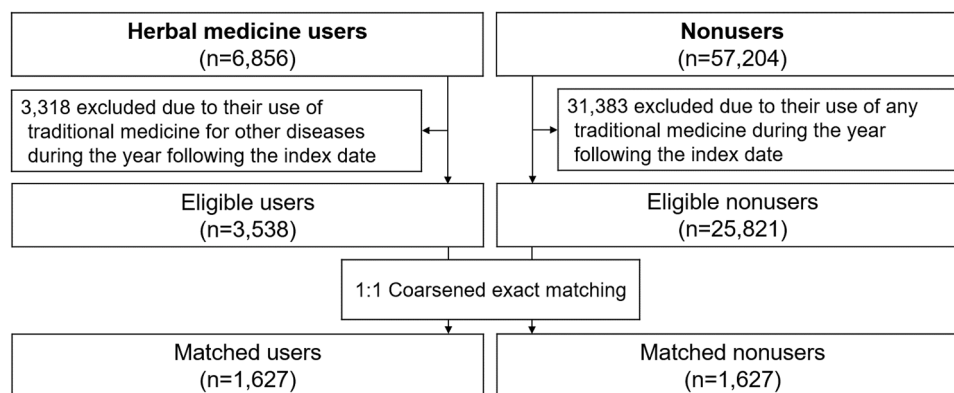


Fig. 2. Selection of study participants and construction of the matched cohort.

Table 1

Baseline characteristics of herbal medicine users and non-users in the CEM-matched cohort.

Characteristics ^a	Control (n = 1627)	Treatment (n = 1627)	P value ^b
	No. (%)	No. (%)	
One-time prescription	–	1342 (82.5)	NA
Two-time prescriptions	–	285 (17.5)	NA
Sex	–	–	1.0
Male	951 (58.5)	951 (58.5)	–
Female	676 (41.5)	676 (41.5)	–
Age, mean (SD), y	50.0 (14.2)	50.3 (14.3)	0.4
Duration of BP, mean (SD), y	1.1 (0.7)	1.1 (0.7)	0.8
Duration from cohort entry, mean (SD), d	228.5 (148.2)	226.2 (148.9)	0.7
Region	–	–	1.0
Seoul	480 (29.5)	480 (29.5)	–
Busan	81 (5.0)	81 (5.0)	–
Incheon	82 (5.0)	82 (5.0)	–
Daegu	71 (4.4)	71 (4.4)	–
Gwangju	26 (1.6)	26 (1.6)	–
Daejeon	27 (1.7)	27 (1.7)	–
Ulsan	8 (0.5)	8 (0.5)	–
Gyeonggi	629 (38.7)	629 (38.7)	–
Gangwon	23 (0.7)	23 (0.7)	–
Chung-buk	13 (0.8)	13 (0.8)	–
Chung-nam	48 (3.0)	48 (3.0)	–
Jeon-buk	13 (0.8)	13 (0.8)	–
Jeon-nam	10 (0.6)	10 (0.6)	–
Gyeong-buk	46 (2.8)	46 (2.8)	–
Gyeong-nam	77 (4.7)	77 (4.7)	–
Jeju	3 (0.2)	3 (0.2)	–
Sejong	1 (0.1)	1 (0.1)	–
Allergic responses	7 (0.4)	7 (0.4)	1.0
Hepatic failure	0	0	NA
Renal failure	0	0	NA
Admissions to hospitals	264 (16.2)	264 (16.2)	1.0
Emergency department visits	39 (2.4)	39 (2.4)	1.0
Use of KM	1067 (65.6)	1067 (65.6)	1.0
Emergency department visits (6 months)	3 (0.2)	3 (0.2)	1.0
Charlson Comorbidity Index, mean (SD)	0.2 (0.5)	0.2 (0.5)	0.6
Comorbidities			
Myocardial infarction	0	0	1.0
Congestive heart failure	0	0	NA
Peripheral vascular disease	1 (0.1)	1 (0.1)	1.0
Cerebrovascular disease	15 (0.9)	15 (0.9)	1.0
Dementia	0	0	NA
Liver disease	8 (0.5)	8 (0.5)	1.0
Diabetes	111 (6.8)	111 (6.8)	1.0
Hemiplegia or paraplegia	0	0	NA
Renal disease	0	0	NA
Cancer	4 (0.2)	4 (0.2)	1.0

Abbreviations: BP, Bell's palsy; CEM, coarsened exact matching; d, days; KM, Korean medicine; NA, not applicable; SD: standard deviation; y, years.

^a Sex, age, residence, duration of Bell's palsy, and duration from cohort entry were measured at the time of the index date; the Charlson Comorbidity Index, the presence of comorbidities, hepatic and renal failure, allergic responses, hospital admissions, emergency department visits, and the use of traditional medicine were identified in the year preceding the index date; emergency department visits were measured starting from 1 year before their index date to meet the parallel trend assumption of the difference-in-differences analysis.

^b P values represent the significance of the chi-square test for sex, region, and others with t-statistics.

Table 2
Difference-in-differences analysis. Safety events in herbal medicine users compared to non-users by observation period^a.

Observation periods	One month	Three months	Six months	Eleven months
Variables	β coefficient (95 % CI)	β coefficient (95 % CI)	β coefficient (95 % CI)	β coefficient (95 % CI)
Hepatic failure				
One-time prescription	-0.2 (-186.0 to 185.7)	-0.2 (-186.0 to 185.7)	-0.2 (-186.0 to 185.7)	-0.2 (-186.0 to 185.7)
Two-time prescriptions	0.04 (-262.4 to 262.5)	0.04 (-262.4 to 262.5)	0.04 (-262.4 to 262.5)	0.04 (-262.4 to 262.5)
Post-period	2.6 (-234.9 to 240.1)	2.6 (-234.9 to 240.1)	2.6 (-234.9 to 240.1)	2.6 (-234.9 to 240.1)
One-time · post-period	-2.9 (-295.1 to 289.4)	-2.9 (-295.1 to 289.4)	-2.9 (-295.1 to 289.4)	-2.9 (-295.1 to 289.4)
Two-time · post-period	-3.2 (-438.2 to 431.8)	-3.2 (-438.2 to 431.8)	-3.2 (-438.2 to 431.8)	-3.2 (-438.2 to 431.8)
Renal failure				
One-time prescription	-0.2 (-177.1 to 176.7)	0.0 (-163.3 to 163.3)	0.0 (-163.3 to 163.3)	0.0 (-163.3 to 163.3)
Two-time prescriptions	0.04 (-249.8 to 249.9)	0.0 (-240.4 to 240.4)	0.0 (-240.4 to 240.4)	0.0 (-240.4 to 240.4)
Post-period	2.9 (-223.2 to 229.0)	6.5 (-170.8 to 183.8)	6.5 (-170.8 to 183.8)	6.5 (-170.8 to 183.8)
One-time · post-period	-3.2 (-281.4 to 275.0)	3.0 (-196.6 to 202.6)	3.0 (-196.6 to 202.6)	3.0 (-196.6 to 202.6)
Two-time · post-period	-3.5 (-417.6 to 410.5)	-6.5 (-338.9 to 325.9)	-6.5 (-338.9 to 325.9)	-6.5 (-338.9 to 325.9)
Allergic responses				
One-time prescription	-3.2 (-171.7 to 165.4)	2.9 (-130.3 to 136.0)	-0.2 (-1.5 to 1.0)	-0.3 (-1.0 to 0.5)
Two-time prescriptions	-3.2 (-257.5 to 251.2)	-6.2 (-272.6 to 260.1)	0.6 (-0.8 to 2.1)	0.4 (-0.6 to 1.4)
Post-period	7.2 (-129.2 to 143.7)	5.3 (-127.9 to 138.4)	2.0 (1.0 to 3.0)	1.4 (0.7 to 2.1)
One-time · post-period	2.4 (-166.1 to 170.9)	-3.1 (-136.3 to 130.1)	0.3 (-1.0 to 1.6)	0.4 (-0.5 to 1.3)
Two-time · post-period	3.3 (-251.0 to 257.6)	6.1 (-260.3 to 272.4)	-0.9 (-2.6 to 0.7)	-0.7 (-1.9 to 0.6)
Admissions to non-traditional medicine hospitals				
One-time prescription	-0.1 (-1.0 to 0.7)	-0.4 (-0.8 to -0.01)	-0.1 (-0.5 to 0.2)	0.01 (-0.1 to 0.2)
Two-time prescriptions	-0.5 (-1.9 to 0.8)	0.3 (-0.2 to 0.8)	-0.2 (-0.7 to 0.3)	-0.03 (-0.3 to 0.2)
Post-period	0.4 (-0.4 to 1.3)	0.3 (-0.1 to 0.7)	0.2 (-0.2 to 0.5)	-1.1 (-1.3 to -0.8)
One-time · post-period	0.2 (-0.8 to 1.2)	0.2 (-0.3 to 0.7)	0.02 (-0.4 to 0.4)	-0.1 (-0.4 to 0.2)
Two-time · post-period	0.3 (-1.4 to 1.9)	-0.1 (-0.8 to 0.6)	0.3 (-0.3 to 0.9)	-0.02 (-0.4 to 0.4)
Emergency department visits				
One-time prescription	-3.0 (-227.0 to 220.9)	-7.2 (-181.6 to 167.2)	-0.7 (-1.8 to 0.4)	-0.4 (-0.7 to -0.1)
Two-time prescriptions	-3.2 (-351.8 to 345.4)	4.1 (-83.1 to 91.3)	0.9 (-0.2 to 2.0)	0.6 (0.2 to 1.0)
Post-period	-3.1 (-265.5 to 259.4)	-0.5 (-208.9 to 207.8)	-4.2 (-204.9 to 196.6)	-6.2 (-145.8 to 133.4)
One-time · post-period	2.9 (-318.1 to 323.9)	11.0 (-246.3 to 268.3)	4.2 (-196.6 to 204.9)	3.6 (-136.0 to 143.2)
Two-time · post-period	3.2 (-475.0 to 481.5)	-10.8 (-399.2 to 377.5)	-8.0 (-409.4 to 393.4)	-7.2 (-286.5 to 272.0)

Abbreviations: β , beta; CI, confidence interval.^a Utilizing the coarsened exact matching cohort analysis, no additional covariates were incorporated as all potential confounders exhibited similar characteristics, as shown in Table 1.

increase the risk of hepatotoxicity or renal failure during the 1-, 3-, 6-, or 11-month observation periods, without significant coefficients for both one- and two-time prescriptions. For instance, during the 3-month follow-up period, the DID effect estimates and 95 % CIs comparing two-time users to non-users were -3.2 (95 % CI: -438.2, 431.8) for hepatotoxicity and -6.5 (95 % CI: -338.9, 325.9) for renal failure. Furthermore, there were no significant increases in allergic drug reactions, admissions to Western medicine hospitals, or emergency department visits among HMD users who received either one- or two-time prescriptions across all observation periods.

Supplement 1 presents the results of a robustness check that assessed the validity of the parallel trend assumption in the DID analysis. No significant differences were found between the treatment groups (both one- and two-time prescriptions) and the control group in any outcome measure.

3.3. Frequently used herbal medicine formula and herbal component

The five most frequently prescribed herbal formulas, constituting more than half of all the formulas prescribed from the HMD initiative: Ligigeopoong-san (19.4 %), Gamiboik-tang (13.1 %), Gamigeopoongligi-san (12.5 %), Gamiboheol-tang (4.9 %), and Gamihwangkee-tang (4.1 %). These formulas include 36 individual medicinal herbs. The most frequently used herbs, in order, are Glycyrrhizae Radix et Rhizoma, Citri Unshius Pericarpium, Pinelliae Tuber, Osterici seu Notopterygii Radix et Rhizoma, and Zingiberis Rhizoma Recens.

4. Discussion

4.1. Summary of key findings

We investigated the safety of herbal medicine decoction (HMD) on

Bell's palsy (BP), utilizing the Korean HIRA database based on the First-Wave Nationwide Benefit Expansion Initiative of HMD and found that HMD users did not exhibit any significant difference in the change rate of various safety endpoints (e.g., hepatic/renal toxicity and allergic reactions, emergency department visits, and hospitalization) over 1, 3, 6, and 11 months of follow-up, compared to their matched non-users. To the best of our knowledge, this is the first study to investigate the safety of HMD for BP using real world data from clinical settings.

4.2. Comparison with previous studies

Our findings are generally consistent with findings from previous studies.^{6,13,14} Chen et al. (2022) conducted a retrospective review of 90 patients with peripheral facial paralysis in China.⁶ They compared efficacy and safety outcome measures between individuals ($n = 45$) who received electroacupuncture and Qianzhengsan decoction, an herbal formula decoction, together with prednisone tablets over a 4-week follow-up period and those in the control group ($n = 45$) who received prednisone tablets only.⁶ The findings revealed that the efficacy endpoints, such as overall response rate, facial nerve function, and facial nerve electromyography, were more favorable in individuals who received combined treatment. The study also demonstrated no significant differences in safety endpoints, including adverse events, between the two groups.⁶

Furthermore, Ton et al. (2019) conducted a population-based retrospective cohort study investigating the potential effectiveness of TCM modalities, including acupuncture and/or herbal medicine, among 238 patients with BP utilizing a National Health Insurance Database in Taiwan.⁵ They compared individuals ($n = 119$) who received TCM treatment modalities (e.g., herbal medicine only 18.5 %, herbal medicine and acupuncture combined 57.1 %, acupuncture only 24.4 %) with those ($n = 119$) who did not receive TCM treatment.⁵ The findings of the study indicated that users of TCM modalities had a decreased risk of

developing stroke (adjusted HR 0.19, 95 % CI 0.06–0.59) compared to non-users.⁵

4.3. Clinical and scientific implications

The findings of our study suggest that the use of herbal medicine decoctions, compared to the use of conventional Western medicine, does not make significant difference in terms of safety outcomes when measured through medical claims at real world clinical practice settings. While this can provide evidence of non-difference in safety outcomes in real world practice for the two larger approaches for Bell's palsy, it does not necessarily indicate equality in the efficacy.

Moreover, due to the nature of the clinical practice of traditional medicine that emphasizes the disease/symptom pattern differentiation, there are multiple numbers of herbal medicine decoctions used for Bell's palsy in this pilot initiative. While this provides an opportunity to examine the safety of the larger group of herbal medicine decoctions, further research is needed to gain a deeper understanding of the safety profile of each single herbal medicine decoction and herbal component.

From this point of view, prior research has provided evidence of safety of single herbal component that was frequently used in this pilot initiative. For instance, previous reviews have reported that formulas/preparations containing *Glycyrrhizae Radix et Rhizoma* (e.g., *Paeoniae-glycyrrhiza* decoction and *glycyrrhizic acid* preparation) have significant clinical and biological safety.^{29,30} Similarly, the safety of formulas or preparations containing *Citri Unshius Pericarpium*,^{31,32} *Pinelliae Tuber*,^{33,34} *Osterici seu Notopterygii Radix et Rhizoma*,³⁵ *Zingiberis Rhizoma Recens*³⁶⁻³⁸ or their compounds have been demonstrated. While the findings of our study, based on a clinical claims dataset, are generally consistent with those from previous laboratory-based studies, further research is warranted to better understand the safety of specific herbal formulas and individual herbal components.

4.4. Strengths and limitations

To the best of our knowledge, this is the first study to investigate the safety of HMD for BP using a large nationwide sample derived from a national insurance database. The use of a DID natural experimental study design, along with the CEM approach, enabled us to effectively address the potentially unequal distribution of health- and trait-related factors that could affect safety outcomes between HMD users and non-users at the time of study enrollment. Furthermore, we examined various safety outcomes linked to the NHI database, including health-care utilization owing to hepatic/renal toxicity and allergic reactions, emergency department visits, and hospitalization.

However, this study had several limitations. First, we focused on evaluating the overall safety of HMDs prescribed for BP through a nationwide initiative rather than isolating the specific impacts of individual herbs or formulas. Likewise, detailed information on individual Western medication was not extracted, as the analysis aimed to capture overall treatment safety. Future research should further investigate the safety profiles of individual herbal components and formulations. Second, although patients in the treatment group received a diverse range of herbal medicine decoctions under real-world clinical practice, many herbal preparations are not reimbursed by the Korean National Health Insurance system and therefore are not captured in the claims data. This limitation should be considered when interpreting the findings. Relatedly, since diverse herbal medicine decoctions were used in this study, we were not able to specify individual herbal formulas or components for the safety evaluation in this study, warranting further investigation. Third, we did not assess BP complications or symptom progression as outcome measures, since the study was designed around predefined safety endpoints. Fourth, since the reference of the safety evaluation for HMD use is the use of conventional Western medicine, further investigation with a placebo control is warranted. In addition, several outcome estimates were accompanied by wide confidence intervals, reflecting the

low frequency of rare adverse events. While our findings did not indicate increased risk, the imprecision highlights the need for larger-scale or longer-term studies to confirm the safety of HMD for BP. Although we selected non-users with pre-exposure utilization trends similar to HMD users, the parallel trends assumption fundamental to DID analysis cannot be definitively confirmed. Finally, because we used data derived from a claims database, our study lacked information concerning biochemical measures of hepatic and renal functions and immune markers, which would complement the claims-based outcomes.

4.5. Conclusions and suggestions for future research

Our findings indicate that no significant difference in safety outcomes was observed between HMD and conventional Western medicine when used for the treatment and management of facial palsy. However, further research is warranted to clarify the underlying mechanisms and refine the HMD safety profiles. Future studies should explore specific herbal formulas or individual herbal components through subgroup analyses or focusing on a specific herbal formula or component, while incorporating broader safety assessments, including biochemical measures of organ function and immuno-endocrinological processes.

Author contributions

Conceptualization: S.Kim, Park; Data curation: Yoon, Bae, Moon; Formal analysis: S.Kim, Yoon; Funding acquisition: Jang; Methodology: S.Kim, Y.Kim, Park; Project administration: Jang, Bae, Moon; Supervision: S.Kim; Writing – original draft: S.Kim, Y.Kim; Writing – review & editing: All authors.

Ethics statement

Since this study used de-identified data provided by the Korean National Health Insurance Review & Assessment (HIRA) after anonymization according to strict confidentiality guidelines, the ethics review was exempted by the Institutional Review Board of Sangji University (IRB number: SJIRB-Human-22-003).

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Declaration of competing interest

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.imr.2025.101279](https://doi.org/10.1016/j.imr.2025.101279).

Supplement 1. Robustness of analysis: testing parallel trend assumption of difference-in-difference.

Data availability

The data that support the findings of this study are available from the HIRA, but restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available.

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