

Safety of Concomitant Use of Corticosteroids and Traditional Korean Herbal Medicine for Facial Nerve Palsy: A Retrospective Study of Effects on Liver and Renal Function

Jee Young Lee¹, Jung-Hyun Kim², Bonhyuk Goo^{2,*}, Sang-Soo Nam^{3,*}

¹Department of Korean Internal Medicine, Integrative Cancer Center, Cha Il-san Medical Center, Goyang, Republic of Korea; ²Department of Acupuncture and Moxibustion, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; ³Department of Acupuncture and Moxibustion, Kyung Hee University College of Korean Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea

*These authors contributed equally to this work

Correspondence: Bonhyuk Goo, Department of Acupuncture and Moxibustion, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea, Email goobh99@naver.com; Sang-Soo Nam, Department of Acupuncture and Moxibustion, Kyung Hee University College of Korean Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea, Email dangun66@gmail.com

Purpose: Bell's palsy is a peripheral neuropathy that requires early administration of high-dose corticosteroids as initial treatment. There is a lack of clinical evidence on the effects of herbal medicines on liver and renal function, as well as their interactions with conventional medicines. This study aimed to assess the safety of using herbal medicine and corticosteroids.

Patients and Methods: To evaluate the effects of herbal medicine with corticosteroid liver and renal function, we analyzed the medical records of patients with facial nerve palsy. We defined drug-induced liver injury (DILI) according to Hy's law and assessed causality using the Roussel Uclaf Causality Assessment Method. Kidney injury was defined by the Kidney Disease Improving Global Outcomes guidelines.

Results: A total of 1076 patients were evaluated. Among 32 patients (3.0%) who showed abnormally increased liver function, 29 patients (2.7%) had possible DILI, and 3 patients (0.3%) had probable DILI, respectively, after concomitant use of steroids and herbal medicine. No case of drug-induced acute kidney injury occurred. There were no sequelae or irreversible damage to liver or renal function.

Conclusion: The results of this study suggest that concomitant use of steroids and herbal medicine was safe for renal function but may be associated with hepatotoxicity in rare cases. Thus, proper monitoring is required when prescribing steroids and herbal medicines concurrently.

Keywords: herbal medicine, corticosteroids, facial nerve palsy, liver function, renal function

Introduction

Steroid use is becoming increasingly widespread in the general population.¹ Steroids can downregulate the hyperactivation of the immune system^{2,3} and are widely used to treat many immune-related diseases, including rheumatoid arthritis, dermatitis, and allergic disorders. They are also used to manage adverse events after monoclonal antibody therapies using immune checkpoint inhibitors or severe pneumonic inflammation after COVID-19.⁴ Furthermore, corticosteroids are administered to relieve acute nerve compression, especially metastatic spinal cord compression, and facial nerve compression.^{5,6}

Natural therapeutic agents, including herbs and healthcare supplements, are considered relatively safe because their use overlaps daily food intake. However, although these natural remedies have been used safely for years, their safety has not been indicated in academic research, especially in intervention studies.⁷ Nevertheless, awareness of the safety of these natural products is gradually increasing. Interactions between herbs and conventional medicine are another clinically significant issue. For instance, warfarin has the potential to interact with herbs and dietary supplements.⁸ Herbs that could interact with conventional medicines include Chinese wolfberry, ginkgo biloba, American ginseng, ginger, and St. John's wort.⁹ Considering how potentially harmful some drug interactions can be, it is necessary to re-examine the interactions between herbal medicines and commonly

used conventional drugs. Specifically, it is necessary to confirm whether concomitant use of herbal medicines and corticosteroids, including glucocorticoids, is safe. Steroids are among the most common causes of iatrogenic illnesses. Steroid use is associated with several adverse events, including osteoporosis, infection, edema, weight changes, skin changes, sleep disturbances, gastrointestinal bleeding, ulcers, and cataracts.^{10,11} Glucocorticoids may cause hepatic adverse events such as drug-induced liver injury (DILI), hepatic steatosis, or cirrhosis.^{12,13} However, whether the combined use of steroids and herbal medicines is safe and whether it aggravates liver damage remains unclear.

Therefore, this study was conducted to confirm the safety of concurrent administration of herbal medicines to a homogenous group of patients using steroids and to determine whether concomitant use of herbal medicines and steroids is associated with a risk of liver or renal damage.

Materials and Methods

Study Design and Study Population

This was a retrospective study of the safety of the concomitant use of herbal medicines and corticosteroids in patients with facial nerve palsy. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital at Gangdong (approval number and date: KHNMC0H 2021-02-005, March 12, 2021). The flowchart of the study is shown in Figure 1.

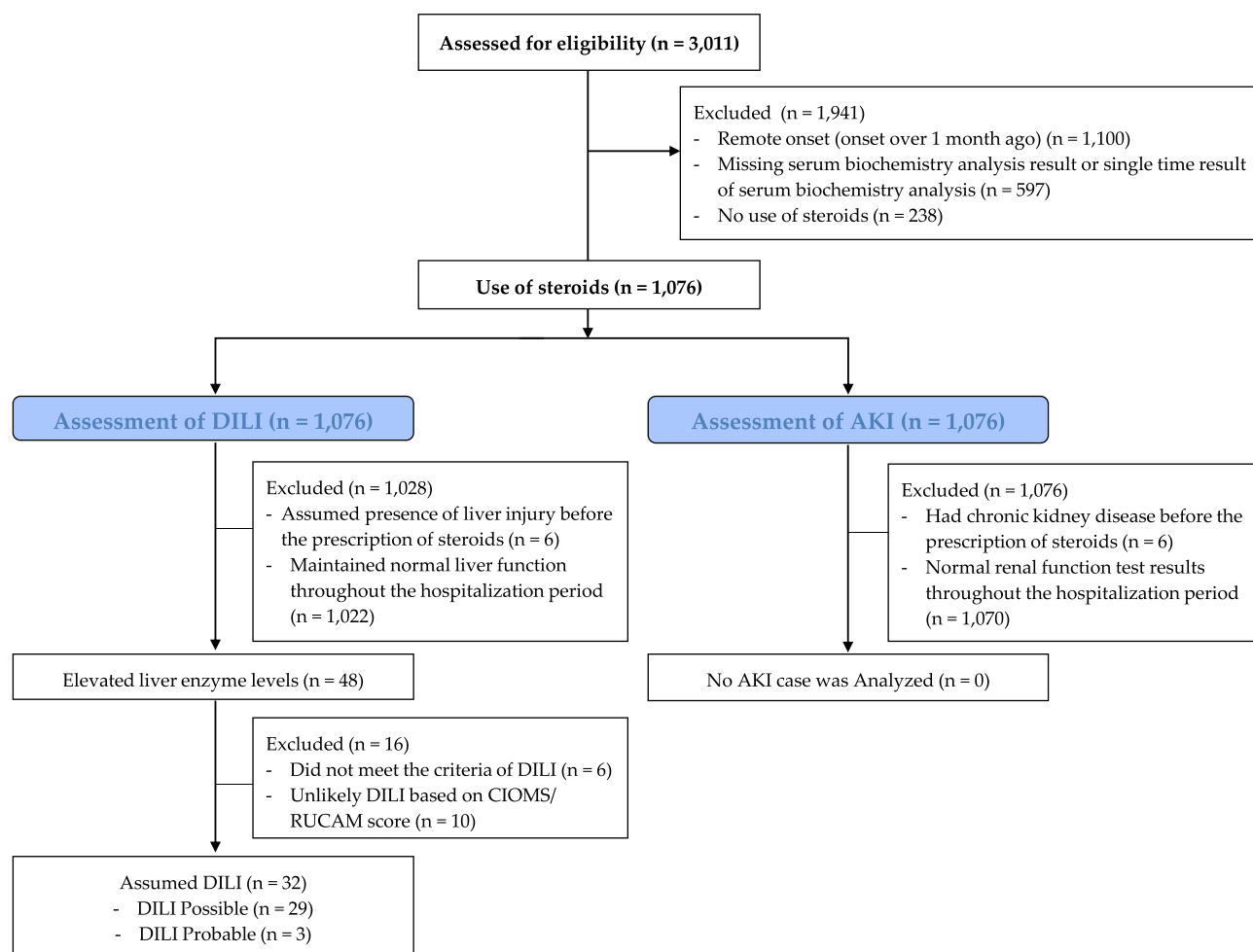


Figure 1 Flow diagram.

Abbreviations: DILI, drug-induced liver injury; AKI, acute kidney injury; CIOMS, The Council for International Organization of Medical Sciences; RUCAM, Roussel Uclaf Causality Assessment Method.

Any patient who visited the Facial Palsy Center at the Kyung Hee University Korean Medicine Hospital in Gangdong, Republic of Korea, was eligible for the study. The study period was from January 1, 2011, when the electronic medical record system was established and combined treatment of facial nerve palsy was initiated, to June 30, 2020. Patients who were diagnosed with facial nerve palsy within one month from the time of onset and received at least a single dose of corticosteroids, including methylprednisolone (MPD) and prednisolone, were considered eligible for inclusion. Patients with no laboratory liver or renal function test results were excluded. All medical data were recorded electronically and stored on a computer server. To maintain data consistency, we established a standard procedure for data collection and extracted and collated information according to the procedure. In this procedure, a trained independent researcher extracted data from complete medical records, and a professional coordinator coded the data. Another independent investigator conducted data cleaning by reviewing missing data and possible bias. An independent statistician performed the statistical analyses to ensure data consistency.

The following data were obtained from the medical records: demographic data, including age and sex; medical history of facial palsy; comorbidities, including diabetes mellitus, hypertension, cerebrovascular and cardiovascular disease, liver and renal disease, cancer history, and dyslipidemia. Results of liver and renal function tests performed at three time points (at admission and initiation of corticosteroid therapy, on the transfer date and initiation of herbal medicines, and at discharge) were obtained. If available, physical examination and imaging results and data on the duration of admission and administration of each medication were obtained.

Interventions

Steroids and antiviral agents were administered to patients by an otolaryngologist. The dosage and tapering schedule were planned according to the Korean clinical practice guidelines for acute facial nerve palsy. The dosage and schedule protocol was as follows: Systemic corticosteroid therapy was initiated within 72 hours of symptom onset. Prednisolone or MPD was prescribed, and doses were calculated using the steroid conversion table. The starting dose was 1 mg/kg/day, which was maintained for 5 days, after which tapering was recommended. A total treatment duration of 10 to 14 days was recommended. The specific schedule was determined according to the guidelines and based on the clinical feasibility of each case. Some patients were not allowed to take the drug for up to 10–14 days for the following reasons: late visit after the onset of facial nerve palsy, medical fragility, or contraindicated by physicians.

Assessment of Acute Liver Injury

According to the American College of Gastroenterology guidelines, the normal alanine transaminase (ALT) levels for males range from 29 IU/L to 33 IU/L, whereas those for females range from 19 IU/L to 25 IU/L; levels above these values require further evaluation.¹⁴ Elevated ALT levels refer to an increase of more than five times the upper limit of normal (ULN) ALT levels.¹⁵ In the present study, 33 IU/L and 25 IU/L were considered the ULN ALT levels for males and females, respectively. The ULN alkaline phosphatase (ALP) level was set at 147 IU/L.

Liver injury was defined according to Hy's law. Hepatocellular liver injury was defined as abnormal liver function with suspected symptoms of liver injury, more than three times the ULN serum ALT or aspartate transaminase (AST) levels, with or without an increase in serum total bilirubin to more than twice the ULN. Cholestatic liver injury was defined as ALP levels more than twice the ULN. The reaction type was defined using the R ratio (ratio of serum ALT to ALP levels), calculated as $R = (\text{ALT value}/\text{ALT ULN}) / (\text{ALP value}/\text{ALP ULN})$.

Acute liver injuries were categorized as hepatocellular, cholestatic, and mixed injuries. The hepatocellular injury was defined as having ALT levels more than twice the ULN or $R \geq 5$. Cholestatic injury was defined as having ALP levels more than twice the ULN or $R \leq 2$. Mixed injury was defined as $2 < R < 5$ and having ALP levels more than twice the ULN, with increased ALT levels.

If acute liver injury was present, causality was assessed using the Roussel Uclaf Causality Assessment Method (RUCAM) score and classified as highly probable (>8), probable (6–8), possible (3–5), unlikely (1–2), or excluded (0).¹⁶

Assessment of Acute Kidney Injury

Kidney injury was defined in accordance with the Kidney Disease Improving Global Outcomes criteria. Acute kidney injury (AKI) was defined as an increase in the serum creatinine concentration or an abnormal urinalysis result that developed within hours to days. Consensus criteria for AKI include an increase in serum creatinine level by ≥ 0.3 mg/dL ($27 \mu\text{mol/L}$) relative to a known baseline value within 48 hours, an increase to ≥ 1.5 times the known or presumed baseline value within seven days, or a decrease in urine volume to < 0.5 mL/kg over six hours.¹⁷

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences for Windows (version 18.0; IBM, Armonk, NY, USA). General patient characteristics and blood test results are expressed as numbers (percentages), whereas continuous data are expressed as means $\pm$ standard deviations. The average age and duration of hospitalization in the liver injury and normal groups were analyzed using the Mann–Whitney *U*-test. Unless stated otherwise, continuous variables were analyzed using Student’s *t*-test. Statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

Based on the inclusion and exclusion criteria, 3011 patients were identified. All the patients were Korean. A total of 1100 patients for whom glucocorticoids were not recommended because they were past the acute stage of facial nerve palsy, and 597 patients with unavailable blood test results were excluded. Additionally, 238 patients with acute disease who had contraindications for glucocorticoids were excluded. The remaining 1076 patients were assessed for DILI and AKI. DILI and AKI were evaluated separately.

The 1076 patients (males, 42.0%) were patients diagnosed with facial nerve palsy who either took herbal medicine concomitantly with steroids or took herbal medicine following steroid therapy as prescribed by an otolaryngologist. All the patients took herbal medicines at least once (100.0%). All patients with possible or probable DILI were prescribed MPD. The mean number of prescription days was insignificant; however, the prescribed doses tended to be high. *Yupung-dan* was the most commonly prescribed herbal medicine (94.9%); however, several other types of herbal medicines were prescribed as well. Table 1 shows the herbal medicines prescribed to more than 5% of the patients. *Yupung-dan*, *Boigyangwi-tang*, *Gamiigigeopung-san*, *Hwangnyeonhaedok-tang*, *Daehwang* agents (*Rhei Rhizoma* or *Rhei Rhizoma-Erigeron canadensis* combination) were prescribed to the patients.

Rhei Rhizoma agents were prescribed to 24.1% of the patients in the possible DILI group and 66.7% in the probable DILI group (5.7% overall prescription rate). The duration of treatment with herbal medicines was generally 1–3 days.

Table 1 Demographic Details of the Patients with Facial Nerve Palsy

Demographics	All Participants (n = 1076)	Possible DILI (n = 29)	Probable DILI (n = 3)
Number of participants	1076 (100.0)	29 (2.70)	3 (0.28)
Age	49.4 $\pm$ 15.9	50.7 $\pm$ 11.4	62.3 $\pm$ 8.7
Male	452 (42.0)	5 (17.2)	1 (33.3)
Duration of steroid use (days)	3.0 (1–26)	3.0 (1–11)	2.0 (2–8)
Diagnosis			
Bell’s palsy	993 (92.3)	26 (89.7)	3 (100)
Ramsay Hunt’s syndrome	83 (7.7)	3 (10.3)	0 (0.0)

(Continued)

Table 1 (Continued).

Demographics	All Participants (n = 1076)	Possible DILI (n = 29)	Probable DILI (n = 3)
Comorbidities			
Hypertension	268 (24.9)	0 (0.0)	0 (0.0)
Diabetes mellitus	173 (16.1)	0 (0.0)	0 (0.0)
Dyslipidemia	108 (10.0)	0 (0.0)	1 (25.0)
Hepatitis B virus	26 (2.4)	0 (0.0)	0 (0.0)
History of CVA	13 (1.2)	0 (0.0)	0 (0.0)
Neoplasm	42 (3.9)	0 (0.0)	0 (0.0)
Hypothyroidism	26 (2.4)	0 (0.0)	0 (0.0)
Hyperthyroidism	6 (0.6)	0 (0.0)	0 (0.0)
Duration of steroid use (days)	11.6 ± 2.5	12.4 ± 1.9	11.3 ± 0.5
Total steroid dose * (mg)	364.0 ± 96.9	399.4 ± 82.7	394.7 ± 72.0
Use of herbal medicine			
<i>Yupung-dan</i>	1021 (94.9)	29 (100.0)	3 (100.0)
<i>Boigyangwi-tang</i>	216 (20.1)	8 (27.6)	0 (0.0)
<i>Gyeontongdodam-tang</i>	186 (17.3)	3 (10.3)	0 (0.0)
<i>Gamiigieopung-san</i>	151 (14.0)	6 (20.7)	0 (0.0)
<i>Hwangnyeonhaedok-tang</i>	145 (13.5)	0 (0.0)	0 (0.0)
<i>Gwiinansim-tang</i>	121 (11.2)	2 (6.9)	0 (0.0)
<i>Naesohwajung-tang</i>	110 (10.2)	2 (6.9)	1 (33.3)
<i>Hyeongbangpaedok-san</i>	97 (9.0)	3 (10.3)	0 (0.0)
<i>Socheongnyong-tang</i>	76 (7.1)	1 (3.4)	0 (0.0)
<i>Banhasasim-tang</i>	71 (6.6)	0 (0.0)	0 (0.0)
<i>Daehwang agent</i>	61 (5.7)	7 (24.1)	2 (66.7)
<i>Hyeongbangsabaek-san</i>	60 (5.6)	1 (3.4)	0 (0.0)

Note: *Conversion to Methylprednisolone.

Abbreviations: DILI, drug-induced liver injury; CVA, cerebrovascular accident.

However, ten patients took herbal medicines for ten days or more (0.9% of the entire patient population), and 3 of 32 (9.4%) patients in the possible DILI group took the medicine for ten days or longer.

A total of 29 patients were determined to have possible DILI based on the significance of the timing of medication use (began taking steroids and herbal medicine simultaneously), reduced symptoms or lack of information after completion of the prescribed drug therapy, alcohol exposure, age, alternative causes of liver injury, and concomitant use of drugs. Three patients developed liver dysfunction, which was considered probable DILI. The characteristics of the entire study population and the possible and probable DILI groups are presented in Table 2.

Table 2 Characteristics of the Patients with Liver Injury

Sex/ Age	Dx	Type of Steroid	Total Dosage	Antiviral Agents	Days from Onset	Peak value					Type of Injury	RUCAM
						AST	ALT	ALP	γGT	TB		
F/53	BP	MPD	496mg	Y	22	71	127	148	101	1.5	Hepatocellular	Probable (6)
M/74	BP	MPD	336mg	N	14	135	202	81	13	0.8	Hepatocellular	Probable (7)
F/60	BP	MPD	352mg	Y	20	87	125	166	15	0.9	Mixed	Probable (7)

Abbreviations: Dx, diagnosis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γGT, gamma-glutamyl transferase; TB, total bilirubin; RUCAM, Roussel Uclaf Causality Assessment Method; BP, Bell's palsy; MPD, methylprednisolone.

Herbal Medicines

All herbal medicines were provided in the form of capsules, powders, and water decoctions. *Daehwang* agents were provided as *Rhei Rhizoma* capsules or combined *Rhei Rhizoma* or *Rhei Rhizoma-Erigeron canadensis* capsules. Most herbal prescriptions, including *Boigyangwi-tang*, *Gamiigigeopung-san*, *Hwangnyeonhaedok-tang*, *Sihogayonggolmoryeo-tang*, were provided in powder form. All patients took herbal medicines at least once. Details of the number of patients who took each herbal medicine and the compositions of the most frequently prescribed herbal medicines are provided in [Supplementary Table 1](#).

Assessment of DILI

Forty-eight patients had normal blood test results between the time of facial nerve palsy diagnosis and initiation of steroid therapy. However, they showed elevated liver enzyme levels after taking steroids alone or in combination with herbal medicine. Of these, six patients who showed elevated liver enzyme levels did not meet the criteria for DILI, and ten patients who had normal liver function test results at the time of concomitant use of herbal medicine and steroids but showed elevated enzyme levels subsequently due to another suspected cause were excluded from the analysis.

Of the remaining 32 patients, 29 were considered to have possible DILI based on their RUCAM scores, which were determined in consideration of significant timing of medication use (began taking steroids and herbal medicine simultaneously), recovery of liver function during medication use, alcohol exposure, age, other causes of liver injury, and concomitant use of other drugs. Three patients began taking herbal medicines sequentially after starting steroid therapy and developed liver dysfunction while taking the herbal medicines. These patients had significant timing of medication use (2 points) and had no information or showed a reduction in symptoms 30 days after completing the prescription (0 points). One patient was younger than 55 years, and two were 55 years or older (1 point), and the patients had no alcohol exposure. Potential causes of liver injury other than the drugs were ruled out (2 points). Steroids or herbal medicines were associated with a risk of hepatotoxicity (2 points). However, the drugs were not restarted for the patients; thus, 0 points were assigned for rechallenge. Therefore, one patient scored 6 points, and two scored 7 points, indicating probable causality. Two patients had the hepatocellular type of injury, whereas one patient had the mixed type of injury.

Assessment of AKI

None of the patients developed drug-induced AKI. Of the 1076 patients, six had a class III estimated glomerular filtration rate or more severe kidney function impairment, whereas 1070 had normal kidney test results throughout the test period.

Discussion

Bell's palsy is a peripheral neuropathy affecting the seventh cranial nerve, with an annual incidence estimated at 20–40 cases per 100,000 individuals.¹⁸ The incidence increases with advancing age and is most commonly observed in individuals in their 40s; it is also notably higher among patients with diabetes mellitus.¹⁹ In recent years, machine learning techniques have been increasingly employed to enhance prognostic prediction and inform clinical decision-making in the diagnosis and management of Bell's palsy. Notably, predictive models based on early clinical data have demonstrated the potential to guide individualized treatment strategies. Early administration of high-dose corticosteroids remains a cornerstone of treatment, with evidence supporting its significant impact on improving clinical outcomes.²⁰

Assessing the risk of herb-induced liver or renal injury in patients receiving corticosteroids is essential to ensure treatment safety and optimize therapeutic benefit. We used the RUCAM scores to investigate whether the concomitant use of herbal medicines and steroids is associated with a risk of liver injury in patients with facial nerve palsy. The RUCAM score is a globally recognized, structured, and validated tool designed to quantitatively assess the likelihood that liver injury is attributable to a specific drug. It is widely used in cases of suspected DILI or HILI.²¹ We selected patients with facial nerve palsy because, compared with other internal medical diseases, their characteristics do not differ significantly from those of the general population. Additionally, patients with facial nerve palsy exhibit characteristics that make them a homogeneous group suitable for evaluating causality. Moreover, drug interactions in facial nerve palsy require further research.

The patients included in this study were treated using a comprehensive clinical pathway. They started using herbal medicine after using steroids for 5 to 7 days. As a result, it was possible to exclude the increase in liver enzyme levels caused by steroids and clearly understand only the safety of the concomitant use of herbal medicine and steroids. In particular, treating the patients according to a uniform clinical pathway enhanced the data quality by ensuring the homogeneity of the study population regarding the duration of steroid and herbal medicine use.

Causality in herb-induced liver injury (HILI) is generally more difficult to evaluate than that in other types of DILI. Herbal medicines are prescribed much less frequently than other drugs, and patients take herbal extracts without medical supervision.²² In addition, it is often difficult to evaluate the exact times patients take herbal medicines and the amount of the medicine they take. Furthermore, some herbal ingredients are also used as food ingredients and are taken for prolonged periods, such as food. Thus, determining causality in these scenarios is challenging owing to the lack of monitoring by healthcare professionals.

Safety data for herbal medicines, including data on the risk of HILI, are inconsistent across studies. Compared to the assessment of DILI, where the injury is assessed as an outcome of the inherent hepatotoxicity of the drug ingredient or an idiopathic liver injury specific to the organism, the assessment of HILI features several distinctive characteristics. First, the reporting rate varies markedly according to study design. In an 11-year prospective study conducted in China, 26 of the 21,470 (0.12%) analyzed patients developed DILI.²³ Similarly, the incidence of HILI in a nationwide study conducted in Korea was 0.6%.²⁴ Multiple cohort studies in Taiwan indicated that 49% of patients with chronic hepatitis concomitantly took herbal medicine for two years or more and that this group had a significantly lower rate of acute exacerbation of hepatitis, risk for liver cirrhosis, and hepatocellular carcinoma, and mortality rate than the group of patients who did not use herbal medicine. The results of this abovementioned study indicate that herbal medicines have hepatoprotective effects.²⁵ In a study of patients with liver cancer conducted in China, the use of herbal medicines significantly increased survival rate, specifically the 3-year survival rate, in patients with huge hepatocellular carcinoma, a finding that supports the reports of the hepatoprotective effects of herbal medicine.²⁶ In contrast, a Korean study reported that herbal medicine is responsible for 27.5% of all DILI cases. These inconsistent results demonstrate that the risks associated with the use of herbal medicines remain controversial.²⁷

These disparities in the results of previous studies could be attributed to the fact that herbal medicines have a combination of ingredients that vary widely in terms of their effects, toxicity, and therapeutic ranges but are all categorized under the umbrella term “herbal medicine.” Additionally, even in herbal medicines with the same common name, the concentrations of the ingredients may vary widely depending on factors such as the scientific name of the drug, quality, timing of harvest, processing method, and dose. For example, *Mahuang* is an herbal prescription with varying ephedrine concentrations. Although the clinical standards for the appropriate dose of ephedrine have been established, the ephedrine content per gram of *Mahuang* ranges from 0.7–1.0% depending on the measurement method, heating time, and region of harvest.^{28,29}

In the present study, none of the patients (men and women who were not of childbearing age or pregnant) had liver-related symptoms such as chronic liver disease or hepatic encephalopathy. However, six patients already had elevated liver enzyme levels at the time the first blood test was performed upon diagnosis of facial nerve palsy before the initiation of steroid therapy. These patients and patients who continued to show normal liver function were excluded. Twenty-nine patients were determined to have possible DILI caused by steroids or herbal medicines, and three patients were determined to have probable DILI caused by concomitant use of herbal medicines and steroids. This translates to an incidence rate of 2.97%, which is relatively high compared to the rates reported in previous studies on the safety of

herbal medicine as well as in prospective randomized clinical trials on steroids that did not include data in specific parameters for liver dysfunction. None of the patients in the present study had elevated serum creatinine levels, indicating kidney injury, while taking steroids and herbal medicines.

Information in drug databases and foundational literature indicate that steroids are potentially hepatotoxic; however, the specific types or rates of hepatic injuries caused by steroids have not been reported. The use of herbs often induces hepatocellular liver injury. It is associated with relatively unchanged ALP levels compared to AST/ALT levels, a finding consistent with the results of the present study.

Rhei Rhizoma is a herb traditionally used as a laxative. It has hepatoprotective activities and therapeutic mechanisms and is reported to have the potential to treat liver failure in animals.^{30–32} However, its active ingredients—sennoside A, aloe-emodin, rhein, emodin, chrysophanol, and physcion—are known for their low bioavailability and potential hepatotoxicity.³³ In the present study, the proportion of patients in the potential DILI group who took *Rhei Rhizoma* was markedly higher than that in the entire study population. This result highlights the need to be cautious when prescribing this herb to patients taking steroids.

This study has a few limitations. First, this was a retrospective analysis; therefore, the findings should be verified in large cohorts or other prospective studies. Second, the study population was not ethnically diverse and consisted of only patients from a single healthcare facility in one country. Third, considering the high prevalence of chronic viral hepatitis in Korea, whether the findings of Korean studies on liver function are generalizable to other regions or populations remains unclear. Lastly, there are different combinations of herbal medicines that have not been explored yet.

Despite these limitations, this study is significant in providing valuable information on the safety of herbal medicines, especially the safety of concomitant use of herbal medicines and steroids without the influence of other drugs, in a relatively homogeneous population.

Conclusion

This study, which used data from more than 1000 cases, indicated that *Yupung-dan* seems to be a relatively safe drug that could be taken concomitantly with steroids. Further prospective studies on the efficacy and safety of *Yupung-dan* will validate this finding. The results of this study also indicate that concomitant use of *Rhei Rhizoma* agents and high-dose steroids should be done with caution. The results of this study suggest that concomitant use of steroids and herbal medicine was safe for renal function but may be associated with hepatotoxicity in rare cases. Thus, proper monitoring is required when prescribing steroids and herbal medicines concurrently.

Ethics Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital at Gangdong (approval number and date: KHNMC0H 2021-02-005, March 12, 2021). This study was a retrospective analysis of medical records from patients who have completed treatment. No additional intervention or interaction with patients was conducted, and researchers collected only the data necessary for the study through a review of medical records. All information in the case report form was recorded in a manner that did not disclose the patients' personal information. Additionally, it was practically impossible to obtain consent from the participants, and even if consent were waived, the risk to the participants would still be extremely low. For the reasons stated above, the Institutional Review Board approved a waiver of informed consent.

Author Contributions

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

Funding

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health and Welfare through the Korea Health Industry Development Institute (KHIDI) (RS-2020-KH087887).

Disclosure

The authors report no conflicts of interest in this work.

References

- Reyes-Vallejo L. Current use and abuse of anabolic steroids | Uso y abuso de agentes anabolizantes en la actualidad. *Actas Urol Esp.* 2020;44(5):309–313. doi:10.1016/j.acuro.2019.10.011
- Vanderbeke L, Van mol P, Van Herck Y, et al. Monocyte-driven atypical cytokine storm and aberrant neutrophil activation as key mediators of COVID-19 disease severity. *Nat Commun.* 2021;12(1):4117. doi:10.1038/s41467-021-24360-w
- Wang J, Yang W, Chen P, et al. The proportion and effect of corticosteroid therapy in patients with COVID-19 infection: a systematic review and meta-analysis. *PLoS One.* 2021;16:e0249481. doi:10.1371/journal.pone.0249481
- Thakur M, Datusalia AK, Kumar A. Use of steroids in COVID-19 patients: a meta-analysis. *Eur J Pharmacol.* 2022;914:174579. doi:10.1016/j.ejphar.2021.174579
- Kumar A, Weber MH, Gokaslan Z, et al. Metastatic spinal cord compression and steroid treatment. *Clin Spine Surg.* 2017;30(4):156–163. doi:10.1097/BSD.0000000000000528
- Sullivan FM, Swan IRC, Donnan PT, et al. Early treatment with prednisolone or Acyclovir in Bell's palsy. *N Engl J Med.* 2007;357(16):1598–1607. doi:10.1056/NEJMoa072006
- Doron S, Snyderman DR. Risk and safety of probiotics. *Clin Infect Dis.* 2015;60:S129–S134. doi:10.1093/cid/civ085
- Tan CSS, Lee SWH. Warfarin and food, herbal or dietary supplement interactions: a systematic review. *Br J Clin Pharmacol.* 2021;87(2):352–374. doi:10.1111/bcp.14404
- Roe AL, Venkataraman A. The safety and efficacy of botanicals with nootropic effects. *Curr Neuropsychopharmacol.* 2021;19(9):1442–1467. doi:10.2174/1570159X19666210726150432
- Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis.* 2009;68(7):1119–1124. doi:10.1136/ard.2008.092163
- Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med.* 1994;96(2):115–123. doi:10.1016/0002-9343(94)90131-7
- Hill LW. Certain aspects of allergy in children. A critical review of the recent literature. *N Engl J Med.* 1961;265:1298–1304. doi:10.1056/NEJM196112142652406
- Jones JP, Engleman EP, Najarian JS. Systemic fat embolism after renal homotransplantation and treatment with corticosteroids. *N Engl J Med.* 1965;273(27):1453–1458. doi:10.1056/NEJM196512302732703
- Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol.* 2017;112(1):18–35. doi:10.1038/ajg.2016.517
- Oh RC, Hustead TR, Ali SM, Pantsari MW. Mildly elevated liver transaminase levels: causes and evaluation. *Am Fam Physician.* 2017;96(11):709–715.
- Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs-II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol.* 1993;46(11):1331–1336. doi:10.1016/0895-4356(93)90102-7
- Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012;2(1):1–138. doi:10.1038/kisup.2012.1
- Monini S, Lazzarino AI, Iacolucci C, Buffoni A, Barbara M. Epidemiology of Bell's palsy in an Italian Health District: incidence and case-control study. *Acta Otorhinolaryngol Ital.* 2010;30(4):198.
- Adour KK, Wingerd J. Idiopathic facial paralysis (Bell's palsy): factors affecting severity and outcome in 446 patients. *Neurology.* 1974;24(12):1112–1116. doi:10.1212/wnl.24.12.1112
- Luo JT, Hung YC, Chen GJ, Lin YS. Predicting early treatment effectiveness in Bell's palsy using machine learning: a focus on corticosteroids and antivirals. *Int J Gen Med.* 2024;17:5163–5174. doi:10.2147/IJGM.S488418
- Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci.* 2015;17(1):14. doi:10.3390/ijms17010014
- Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults – results of a systematic review. *Regul Toxicol Pharmacol.* 2018;95:412–433. doi:10.1016/j.yrtph.2018.03.019
- Melchart D, Hager S, Albrecht S, Dai J, Weidenhammer W, Teschke R. Herbal Traditional Chinese Medicine and suspected liver injury: a prospective study. *World J Hepatol.* 2017;9(29):1141–1157. doi:10.4254/wjh.v9.i29.1141
- Cho JH, Oh DS, Hong SH, et al. A nationwide study of the incidence rate of herb-induced liver injury in Korea. *Arch Toxicol.* 2017;91(12):4009–4015. doi:10.1007/s00204-017-2007-9
- Tsai DS, Huang MH, Chang YS, Li TC, Peng WH. The use of Chinese herbal medicines associated with reduced mortality in chronic hepatitis B patients receiving lamivudine treatment. *J Ethnopharmacol.* 2015;174:161–167. doi:10.1016/j.jep.2015.08.002
- Chen SL, Ho CY, Lin WC, et al. The characteristics and mortality of Chinese herbal medicine users among newly diagnosed inoperable huge hepatocellular carcinoma (≥ 10 cm) patients: a retrospective cohort study with exploration of core herbs. *Int J Environ Res Public Health.* 2022;19(19):12480. doi:10.3390/ijerph191912480
- Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. *Am J Gastroenterol.* 2012;107(9):1380–1387. doi:10.1038/ajg.2012.138

28. Jang IS, Yang CS, Hwang EH. The need for clinical practice guidelines in usage of Mahuang in weight loss. *J Korean Med Obes Res.* 2007;7(1):23–29.
29. Kim H, Han CH, Lee EJ, Song YK, Shin BC, Kim YK. A clinical practice guideline for Ma-huang(*Ephedra sinica*) prescription in obesity. *J Korean Med Obes Res.* 2007;7(2):27–37.
30. Baek SY, Lee EH, Oh TW, et al. Network pharmacology-based approaches of *Rheum undulatum* Linne and *Glycyrriza uralensis* Fischer imply their regulation of liver failure with hepatic encephalopathy in mice. *Biomolecules.* 2020;10(3):437. doi:10.3390/biom10030437
31. Dong GZ, Lee YI, Jeong JH, et al. Stilbenoids from *Rheum undulatum* protect hepatocytes against oxidative stress through AMPK activation. *Phytother Res.* 2015;29(10):1605–1609. doi:10.1002/ptr.5442
32. Semwal RB, Semwal DK, Combrinck S, Viljoen A. Emodin - A natural anthraquinone derivative with diverse pharmacological activities. *Phytochemistry.* 2021;190:112854. doi:10.1016/j.phytochem.2021.112854
33. Dong X, Zeng Y, Liu Y, et al. Aloe-emodin: a review of its pharmacology, toxicity, and pharmacokinetics. *Phytother Res.* 2020;34(2):270–281. doi:10.1002/ptr.6532

Journal of Multidisciplinary Healthcare

Publish your work in this journal

The Journal of Multidisciplinary Healthcare is an international, peer-reviewed open-access journal that aims to represent and publish research in healthcare areas delivered by practitioners of different disciplines. This includes studies and reviews conducted by multidisciplinary teams as well as research which evaluates the results or conduct of such teams or healthcare processes in general. The journal covers a very wide range of areas and welcomes submissions from practitioners at all levels, from all over the world. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-multidisciplinary-healthcare-journal>

Dovepress
Taylor & Francis Group