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Liver enzyme abnormalities in taking traditional herbal medicine in Korea: A retrospective large sample cohort study of musculoskeletal disorder patients



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ABSTRACT

Ethnopharmacological relevance: The objective of this study is to report the incidence of liver injury from herbal medicine in musculoskeletal disease patients as large-scale studies are scarce. Considering that herbal medicine is frequently used in patients irrespective of liver function in Korea, we investigated the prevalence of liver injury by liver function test results in musculoskeletal disease patients.

Materials and methods: Of 32675 inpatients taking herbal medicine at 7 locations of a Korean medicine hospital between 2005 and 2013, we screened for liver injury in 6894 patients with liver function tests (LFTs) at admission and discharge. LFTs included t-bilirubin, AST, ALT, and ALP. Liver injury at discharge was assessed by LFT result classifications at admission (liver injury, liver function abnormality, and normal liver function). In analyses for risk factors of liver injury at discharge, we adjusted for age, sex, length of stay, conventional medicine intake, HBs antigen/antibody, and liver function at admission.

Results: A total 354 patients (prevalence 5.1%) had liver injury at admission, and 217 (3.1%) at discharge. Of the 354 patients with liver injury at admission, only 9 showed a clinically significant increase after herbal medicine intake, and 225 returned to within normal range or showed significant liver function recovery. Out of 4769 patients with normal liver function at admission, 27 (0.6%) had liver injury at discharge. In multivariate analyses for risk factors, younger age, liver function abnormality at admission, and HBs antigen positive were associated with injury at discharge.

Conclusions: The prevalence of liver injury in patients with normal liver function taking herbal medicine for musculoskeletal disease was low, and herbal medicine did not exacerbate liver injury in most patients with injury prior to intake.

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1. Introduction

Complementary and Alternative Medicine (CAM) treatments are most frequently used for musculoskeletal diseases in Korea. The 1st–5th most frequent diseases in inpatient care in National

Health Insurance reimbursements for Korean medicine in 2013 were all musculoskeletal related (1st–5th most frequent Korean standard classification of diseases: M54 Dorsalgia, M17 Gonarthrosis [arthrosis of knee], S33 Dislocation, sprain and strain of joints and ligaments of lumbar spine and pelvis, M51 Other intervertebral disc disorders, M79 Other and unspecified soft tissue disorders, not elsewhere classified) (Kim and Son, 2014). As CAM use increases worldwide, interest in liver toxicity from herbal medicine is also rising (Wolsko et al., 2003).

However, herb-induced liver injury is usually more difficult to detect than drug-induced liver injury (DILI) and incidence of cases is highly variable due to various reasons, such as the fact that many users of herbal products do not discuss them with their physician (Eisenberg et al., 1993, 1998), many herbal preparations are regulated by less stringent standards than conventional drugs

Abbreviations: CAM, Complementary and Alternative Medicine; DILI, drug-induced liver injury; LFT, liver function test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TB, total bilirubin; γ -GTP, γ -glutamyl transpeptidase; HBs, Hepatitis B surface; CIOMS, Council for International Organization of Medical Sciences; Ag, antigen; Ab, antibody; KCD, Korean standard classification of diseases; ICD, International Statistical Classification of Diseases and Related Health Problems

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(Licata et al., 2013), many herbal products are available as “over-the-counter” drugs or food supplements (Singh et al., 2012), and medical use can be both regular or episodic (Tovar and Petzel, 2009). Chalasani et al. (2008) reported in a retrospective U.S. study that herbal and dietary supplements were implicated in 10% of DILI cases, a prospective study on 22 participants conducted in Singapore reported that 68% were related to DILI (Wai et al., 2007), and data from a Chinese medical center on 30 DILI patients indicates that 40% were herb related causes (Wang et al., 2009). On the other hand, many studies report the incidence rate of herb-induced liver injury at less than 1% and clinical symptoms to be mild (Al-Khafaji, 2000).

The discrepancy in previous evidence may be partly attributable to cultural differences regarding herbal products, indiscriminate prescription of herbal medicine, folk medicine, and dietary supplements of uncertain composition and consistency, disparity in research methodology and environment, and small sample sizes. Therefore, to assess the prevalence of liver injury due to herbal medicine, a more specific, standard definition of herbal medicine is called for, and due to relatively low prevalence rates, more large-scale studies are needed.

As many herbal medicine practitioners construe herbal medicine to be natural and therefore “safe” (Ye and He, 2010), herbal medicine is frequently used in patients with abnormal liver function test (LFT) results.

In order to investigate changes in liver enzymes in inpatients taking herbal medicine prescribed by trained medical professionals for musculoskeletal disease, we retrospectively assessed liver injury at discharge by LFT results at admission and its risk factors.

2. Material and methods

2.1. Subjects

We retrospectively reviewed the electronic medical records of 32675 patients who stayed at 7 locations of a musculoskeletal disease-specialty Korean medicine hospital in Korea from December 2005 to December 2013. The total number of patients with blood test results during admission was 29229 and 24% ($n=7003$) received multiple tests at admission and before discharge. Of these patients, we analyzed the results of 6894 patients for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TB).

Inclusion criteria – patients admitted for at least one day who took herbal medicine and at least 2 LFTs during admittance. There were no exclusion criteria.

2.2. Classification of liver enzyme abnormalities

LFTs were measured after a 6 h overnight fast. All inpatients received blood tests at admission except those who refused, and follow-up tests were conducted as deemed necessary. The LFTs included in this study were ALT, AST, ALP, TB, γ -glutamyl transpeptidase (γ -GTP), Hepatitis B surface (HBs) antigen, and HBs antibody.

The normal range for LFTs was ALT \leq 40 U/L; AST \leq 40 U/L; ALP \leq 338 U/L; and TB \leq 1.2 mg/dL. According to the modified Council for International Organization of Medical Sciences (CIOMS) criteria, the term “liver injury” was used to describe an increase of over 2 N (upper limit of the normal range) in ALT, or a combined increase in TB, AST, and ALP, provided one of them was above 2 N. Patients with all 4 enzymes within normal range were defined as having “normal liver function”, and those neither in the “normal” nor “liver injury” group as “liver function abnormality”.

2.3. Statistical analysis

Patients were categorized into 3 groups – “liver injury”, “liver function abnormality”, and “normal liver function” – by LFT results at admission and discharge. Age and γ -GTP results were continuous variables, and sex (male/female), HBs antigen (positive/negative), HBs antibody (positive/negative), and use of conventional medicine (yes/no) were categorical variables. HBs antigen and antibody results were classified into 4 groups; Ag(+)/Ab(+), Ag(+)/Ab(-), Ag(-)/Ab(+), and Ag(-)/Ab(-). Length of stay was assessed as both continuous and categorical variables (\leq 20 days, 20–30 days, and $>$ 30 days).

Simple logistic regression modeling was used to assess influence of age, sex, length of hospital stay, conventional medicine intake, liver function classification at admission, HBs antigen/antibody, and γ -GTP on liver function classification at discharge. Multiple logistic regression modeling was used for factors with a p -value of \leq 0.2. Factors included in the final model were determined in a stepwise manner (included if p -value \leq 0.05, excluded if p -value \geq 0.10). We used stratification of patient characteristics to further assess the association between age and liver function. The statistical package for Social Science for Windows™, version 11.0 (SPSS Inc., Chicago, IL, U.S.A.) was used.

2.4. Ethics statement

Ethical approval was obtained from the institutional review board of Jaseng Hospital of Korean medicine in Seoul, Korea (SIRB2013-37), and all patients provided informed written consent to use of data for academic means prior to hospitalization. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and Tokyo.

3. Results

The average length of hospital stay was 26.17 ± 12.31 days, 45% ($n=3111$) were male, and average age was 44.31 ± 14.49 years.

We classified the patients into 3 groups (liver injury, liver function abnormality, and normal liver function) according to liver function test results at admission, and subcategorized the groups by liver function test results at discharge to better illustrate the change in distribution of liver function state (total 9 groups).

Of 4769 patients with normal liver function at admission, 27 (0.6%) had liver injury at discharge, and out of 354 patients with liver injury at admission, 225 (64%) no longer had liver injury at

Table 1
Classification of patients by liver function test results at admission and discharge^a.

Liver function state at admission	N	Liver function state at discharge	N
Liver injury	354	Liver injury	129 (9)
		Liver function abnormality	143 (0)
		Normal liver function	82 (1)
Liver function abnormality	1771	Liver injury	61 (23)
		Liver function abnormality	763 (28)
		Normal liver function	947 (23)
Normal liver function	4769	Liver injury	27 (27)
		Liver function abnormality	284 (117)
		Normal liver function	4458 (259)

(): No. of patients with a twofold increase in at least one blood index of ATP, AST, ALT, or total bilirubin at discharge compared to admission.

^a The normal range for liver function tests was alanine aminotransferase (ALT) \leq 40 U/L; aspartate aminotransferase (AST) \leq 40 U/L; alkaline phosphatase (ALP) \leq 338 U/L; and total bilirubin \leq 1.2 mg/dL, and the term “liver injury” was used to describe an increase of over 2 N (upper limit of the normal range) in ALT, or a combined increase in total bilirubin, AST, and ALP, provided one of them was above 2 N.

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