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Comparative Study on the Effects of Herbal Medicine and Western Medicine on the Liver Function Based on Cross-Sectional Design

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Abstract

Objective : The purpose of this study is to examine safety of herbal medicine on liver function and compare with western medicine.

Method : 303 subjects of skin disease(vitiligo and psoriasis) were chosen at a local oriental medical clinic, and tested with a spot liver function test from Sept 1, 2006 to Dec 31, 2006. Subjects were grouped into untreated, herbal medicine, western medicine, and combination group by treatment record. Total bilirubin, AST, ALT and LDH was compared in each group, odds ratio and regression coefficient was calculated.

Results : Subjects comprised of 116 individuals receiving western medication(38.28%), 54 receiving herbal medication(17.82%), 107 receiving combined forms of medication(35.31%), and 26 individuals without any types of medication(8.58%). With the mean age of 37.0 yr. 204 were male(67.3%), 99 were female(32.7%). Comparing variables of liver functions, there was no significant difference between the control and experiment groups. After adjusting potential confounders, monthly β(SE) of multiple regression -0.009~0.000 for the herbal group, -0.005~0.000 for the western group, and -0.001~0.001 for the combination group. No significant difference between the groups. OR of T-bilirubin were 1.02, 1.05, and 1.04. AST were 0.92, 0.94, and 0.98. ALT were 0.85, 0.99, and 0.97. LDH were 0.96, 1.06, 1.00 for the herbal, western, and combination group, respectively.

Conclusion : Comparing with western medication, herbal medication did not cause special ill-effect on the liver function based on liver function tests.

Key words : Liver function, Herbal medicine, Western medicine, Safety, Complementary and alternative medicine

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I. Introduction

According to WHO report, 65~85% of the world populations rely on alternative medicine as the primary medical service,[1] and 34% of Americans experienced at least one form of non-conventional medicine in the previous year.[2] Traditional medicine still contributes heavily in their respective countries and this trend will continue for quite some time.

Forms of traditional medicine include herbal medicine, acupuncture, moxibustion, and others.[3] Herbal medicine is most frequently used in Korea and China and is also most effective. Various herbal prescriptions are popularly used in oriental medical clinics and these prescriptions comprise anywhere from a single herb to 20~30 herbs. Composite herbal prescriptions taken orally are in forms of decoction, pill, and powder which are metabolized in the liver. Substances that can damage the liver are carbon tetrachloride, yellow phosphorus, mushroom, and other pharmacological substances including herbal medicine.[4]

Few studies were conducted overseas regarding effects of herbal medicine and the outcomes weren't favorable.[5-7] Other studies from Korea resulted in very opposite results as short or long term intake actually provides protection to the liver.[8-11] Contradicting results are causing confusion to the general public and more concrete results are needed to verify either outcome. Very few studies were aimed at long-term intake of herbal medicine and research procedures had some flaws in few cases. Cross-sectional survey was conducted on patients with mid to long-term intake of herbal medicine at oriental medical clinics to verify effects of herbal medicine in serum liver functions. Study groups were classified into control and experiment groups(herbal medicine, western medicine, and combination).

II. Materials and Methods

1. Materials

1) Subjects

Study subjects were chosen from one Oriental medical clinic in Seoul, Korea for treating skin disease of vitiligo and psoriasis. Total of 303 subjects whom have consented the study were chosen. Duration of study ranged from September 1, 2006 to December 31, 2006. Average month of medicine intake was 5.9(month) in western medicine group, 2.3(month) in oriental medicine group.

Patients were explained the purpose of research and questionnaire was completed before the liver function test. The questionnaire was completed on own in most cases and for incomprehensive questions, trained assistant aided in completion. Items in the questionnaire included gender, age, marriage, drinking, smoking, occupation, BMI(Body mass index), and duration of herbal and western medications.

2) Blood sampling and analysis

Under permission from patients and guardians, 1㎖ spot sampling was collected

from a vein in the elbow area using a sterile syringe. Collected sample was centrifuged for 5 minutes and then analyzed through Auto dry Chemistry Analyzer(Spotchem TM SP-4410, Kyoto Daichi Kagaku Co. Ltd.) for T-bilirubin(Total bilirubin), ALT(Alanine amino-transferase), AST(Aspartate aminotransferase), and LDH(Lactic dehydrogense) for liver functions.

2. Manufacturing and prescription of herbal and western medicines

1) Herbal medicine

Chronic relapsing skin disease such as vitiligo and psoriasis are approached with fixed treatment for all patients but individualized in Oriental medicine according to one's symptoms and constitution. Therefore, different herbal prescription is given for each patient with some basic herbs. Prescribed herbs are categorized into oral administration, external application, or combination. This experiment was focused on herbs for oral administration. Total of 155 herbs were used and commonly prescribed herbs were *Rx. Sophorae Flavescentis, Rx. Glycyrrhizae Uralensis, Rx. Salviae Miltiorrhizae, Rx. Codonopsis Pilosulae, Hb. Lemnae seu Spirodelae, Rx. Iedebouriellae Sesloidis, Fr. Lugustri Lucidi, Fr. Xanthii, Se. Sesami Indici, Rx. Astragali, Rz. Polygonati, Rz. Gusuibu, Rx. Angelicae Sinensis, Fr. Psoraleae Corylifoliae, Rz. Zingiberis Officinalis*, and others.

(1) Decoction

Based on the doctor's prescription, set of herbs for 15 days worth of volume were inserted into a sanitized polypropylene bag. To make an extract, herbs were cooked in an electric herb extractor for 3 hours at 100℃ with 5,500cc of water. Then the extract is sealed in a retort pouch : 50cc for children and 100cc for adults. Vacuum packed pouches were either picked up directly or sent via courier service to patients. Patients were instructed to keep pouches refrigerated.

(2) Pill

According to the prescription, dried herbs are gathered and powdered. Powder is then mixed with rice starch, wheat starch, and/or honey to make into a pill weighing 1 to 10g using a pill generator. Pills were normally taken three times a day before or after a meal but depending on the illness, dosage was adjusted to once a day to up to five times a day.

2) Western medicine

Patients diagnosed under western dermatologist and given only oral medications were surveyed for total duration of treatment.

3. Statistical analysis

For statistical analysis, Stata(2001) statistical package[12] was used for mean(SD)%, ANOVA, multiple regression, and odds ratio (OR).

Ⅲ. Results

Socio-economic characters of the subjects are listed in Table 1. Among 303 subjects, 204 were male(67.3%), 99 were female(32.7%) with the mean age of 37.0±9.5. 198 subjects with normal marriage(65.6%). For the occupation, white-color workers comprised of 152 subjects (50.2%), and blue-color workers were numbered at 85(28.1%). 172 subjects were under habitual alcohol consumption(56.8%), and 116 subjects were smokers(38.3%). 116 subjects were only taking western medications(38.3%), 54 subjects with only herbal medicine(17.9%), and 107 responded with taking both western and herbal medicines concurrently(35.3%). 26 subjects had neither western nor herbal medicine for the treatment(8.9%).

Among the total participants in the study, minimum, maximum, arithmetic mean and SD, and % exceeding upper limit range of liver functions in blood are listed in Table 2.

The range of minimum and maximum values were increased in the order of 0.5 (0.2)㎎/dℓ for T-bilirubin, 27.5(24.3)U/L(male) and 16.7(6.1)U/L(female) for AST, 40.8(44.6) U/L(male) and 19.3(11.3)U/L(female) for ALT, and 251.3±73.4㎎/dℓ for LDH. In the analysis

Table 1. General characteristics of study populations

Variables	Responses	Subjects (n=303)	% or Mean(SD)
Age		303	37.0(9.5)
Gender	Male	204	67.3
	Female	99	32.7
Marriage	Married	198	65.4
	Divorced or separated	10	3.3
	Single	95	31.4
Occupation	White-color	152	50.2
	Blue-color	85	28.1
	Others	66	21.8
Alcohol	Drinker	172	56.8
	Non-drinker	131	43.2
Smoking	Smoker	116	38.3
	Non-smoker	187	61.7
BMI		303	23.5(3.0)
Treatment type	Western med. only	116	38.3
	Oriental med. only	54	17.8
	Combination*	107	35.3
	Untreated	26	8.6

*Combination : Western medicine and oriental medicine

Table 2. Minimum, maximum, arithmetic mean(SD), and percent exceeding upper limit reference range of liver functions in blood

Variables	Min	Max	AM(SD)	% exceeding upper limit reference range	reference value[a]
Tbil	0.2	1.8	0.5(0.2)	1.7%	0.3~1.0
AST	10.0[m]	282.0[m]	27.5(24.3)[m]	5.9%[m]	m : <39
	10.0[f]	36.0[f]	16.7(6.1)[f]	0.0%[f]	f : <29
ALT	10.0[m]	559.0[m]	40.8(44.6)[m]	32.4%[m]	m : <47
	10.0[f]	106.0[f]	19.3(11.3)[f]	3.0%[f]	f : <32
LDH	116.0	672.0	251.3(73.4)	3.0%	106~211

[a] Reference value : Reference provided by (Kyoto Daichi Kaguku Co. Ltd), the manufacturer of auto drug chemistry analyzer

[m] male, [f] female

Tbil : Total bilirubin (unit : mg/dℓ)

AST : Aspartate aminotransferase(unit : U/L)

ALT : Alanine aminotransferase(unit : U/L)

LDH : Lactic dehydrogense)for liver functions(mg/dℓ)

of percent exceeding upper limit reference range, 1.7% for T-bilirubin, 5.9%(male) and 0.0%(female) for AST, 32.4%(male) and 3.0% (female) for ALT, and 3.0% for LDH.

Liver function levels in blood among the experiment groups are listed in Table 3.

T-bilirubin was in the range of 0.51(0.07) ㎎/dℓ for the control group and 0.46(0.03)-0.52(0.02)㎎/dℓ for the experiment groups. AST was in the range of 24.65(2.91)U/L for the control group and 20.04(0.92)-25.02(2.47) U/L for the experiment groups. ALT was in the range of 31.35(3.83)U/L for the control group and 25.09(1.84)-38.00(5.12)U/L for the experiment groups. Finally, LDH was in the range of 249.65(14.13)㎎/dℓ for the control group and 234.61(11.69)-262.88(6.64)㎎/dℓ for the experiment groups. For all variables, no statistical significance was shown(Table 3).

Multiple regression of liver functions in the blood of the control group and experiment groups are shown in Table 4. after adjusting potential confounders. Monthly β(SE) of Monthly β(SE) of T-bilirubin were -0.006(0.004), 0.001 (0.001), and 0.001(0.000) for the Oriental medicine group, western medicine group, and

Table 3. Arithmetic mean(SE) of liver function test values in each groups

Variables	Control (N=26)	Oriental (N=54)	Western (N=116)	Combination (N=107)	p-value
Tbil	0.51(0.07)	0.46(0.03)	0.52(0.02)	0.50(0.02)	0.44
AST	24.65(2.91)	20.04(0.92)	25.02(2.47)	24.73(1.94)	0.50
ALT	31.35(3.83)	25.09(1.84)	38.00(5.12)	34.20(2.60)	0.24
LDH	249.65(14.13)	234.61(11.69)	262.88(6.64)	247.68(6.54)	0.11

Table 4. Regression coefficient (SE) of monthly liver functions in the herbal intake groups adjusted for potential confounders*

Dependent Variables^	Oriental Medicine (month) Beta(SE)	Western Medicine (month) Beta(SE)	Combination (month) Beta(SE)
Tbil	-0.006(0.004)	0.001(0.001)	0.001(0.000)
AST	-0.009(0.006)	-0.004(0.002)	-0.001(0.002)
ALT	-0.001(0.009)	-0.005(0.002)	0.001(0.002)
LDH	0.000(0.008)	-0.001(0.001)	0.001(0.001)

* Adjusted for Age, Sex, Smoking, Drinking and Occupation

^ Dependent Variables are natural logarithm of each liver function level plus one, for example, log(1+AST)

combination group, respectively. Monthly β (SE) of AST were -0.009(0.006), -0.004(0.002), and -0.001(0.002) for the Oriental medicine group, western medicine group, and combination group, respectively. Monthly β(SE) of ALT were -0.001(0.009), -0.005(0.002), and 0.001 (0.002) for the Oriental medicine group, western medicine group, and combination group, respectively. Monthly β(SE) of LDH were 0.000(0.008), -0.001(0.001), and 0.001 (0.001) for the Oriental medicine group, western medicine group, and combination group, respectively.

OR(odds ratio)of the control and experiment groups were compared in table 5, after adjusting confounding factors, the control group being as the denominator(1 as denominator).

OR of T-bilirubin were 1.02, 1.05, and 1.04, for the Oriental medicine, western medicine, and combination group, respectively. OR of AST were 0.92, 0.94, and 0.98, for the Oriental medicine, western medicine, and combination group, respectively. OR of ALT were 0.85, 0.99, and 0.97, for the Oriental medicine, western medicine, and combination

Table 5. Odds ratios* for exceeding reference values of liver function tests adjusted for potential confounders^(N=303)

	Oriental Medicine		Western Medicine		Combination	
	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p
Tbil	1.05(0.99-1.11)	0.092	1.02(0.95-1.09)	0.591	1.04(0.98-1.10)	0.205
AST	0.94(0.80-1.11)	0.489	0.92(0.76-1.10)	0.345	0.98(0.83-1.16)	0.830
ALT	0.99(0.80-1.22)	0.911	0.85(0.67-1.08)	0.185	0.97(0.78-1.21)	0.816
LDH	1.06(0.94-1.18)	0.348	0.96(0.85-1.09)	0.536	1.00(0.89-1.12)	0.991

* Reference group is the control group(untreated).

^ Adjusted for age, sex, smoking, drinking, occupation, and residence.

group, respectively. OR of LDH were 0.96, 1.06, and 1.00, for the Oriental medicine, western medicine, and combination group, respectively. There was no statistical significance from the control group, but OR values differed from the means of intake.

IV. Discussion

Liver is closely related to the metabolism of herbs, and oral administration of herbs directly affect the functions of liver. Liver toxicity normally occurs from toxic chemical substances, metabolites, and naturally existing plant alkaloid, mycotoxin, and other substances. Liver toxicity due to chemicals is classified into categories of metabolite and directly affecting on the liver cells.[13] Internal absorption from these exposures is closely related to absorption rate and target organs as well exposure route of lungs, skin, and gastrointestinal tract. But even the route is made of bio-barrier and one must understand the mechanism of bio-barrier. Bio-barrier is important in terms of toxicology as the barrier itself plays role as the receptor for toxins and hormones, and drastically alters receptive functions by reacting with proteins and lipid substances to change integrity of cells. From western medicine's perspective, liver disorders from liver damage are divided into two categories of toxic liver disorder from chemical metabolism and from hypersensitivity reaction in small number of cases.[4]

Measuring liver enzymes in the serum can effectively analyze liver damage. Disorders accompanying symptoms such as inflammation, necrosis, and biliary obstruction eventually cause the release of liver enzymes into the serum. Measuring blood enzyme is an index to the progression of illness. ALT and AST are the types of transferase which transfer amino groups into α-keto acids. These enzymes are released into blood when liver cell membrane is damaged.[4]

This study was conducted on patients receiving treatments for their intractable skin disorders of vitiligo and psoriasis at an oriental medicine clinic in Seoul, Korea based on cross-sectional design. Unlikely animal laboratory tests, study environments and other factors were beyond control. Potential confounding factors that might contribute to liver functions such as environment pollution, diet, residence, drinks, and others must be either eliminated or adjusted for accurate data.

Participants out of the reference range were 1.7-4.0% for T-bilirubin, AST and LDH, but 22.8% for ALT(Table 2). ALT is an mitochondria enzyme which can affect the heart, liver, muscles, and kidneys. ALT is released from abrupt rupturing of the cells and further studies on the cause of high ALT value must be followed.[13] Table 3. compares the liver functions of the control group and experiment groups. No statistical significance was witnessed in any of herbal medicine(decoction and pills), western medicine, and combined groups. Data suggests that neither herbal nor western medicines affect liver functions and these findings coincide with studies conducted in Korea[8-11] as even combined intake group didn't alter the outcome. But since some of the studies were done

with small number of subjects and other shortcomings such as statistical error and without adjusting confounding factors, it is difficult to concur with those studies. Except for one study done in Korea which reported increase in the liver function values after one week's herbal medication, all others reported no effect or even provided protection for the liver. However, overseas studies[14-16] suggest harmful effects of herbal medicine and recommend not taking the herbal medicine, leading to a controversial debate.

In order to verify effects on the liver functions in relation to the duration of herbal intake, regression coefficient β(SE)values were calculated through multiple regression analysis after adjusting confounding factors (Table 4). Most of the β(SE) values were between -0.009~0.001 per month, suggesting no significant effects on the liver functions. Table 5. shows OR(odds ratios) between exceeding reference values samples of the control and experiment groups after adjusting confounding factors. Only 57 out of range subjects were calculated since the subjects within the reference range weren't the focus of this study. For OR, control group values are regarded as denominator and experiment group values are regarded as numerator. Calculated value greater than 1 is interpreted as causing risk and the value less than 1 is interpreted as yielding protective effects. OR were around 1 or less than 1 in most of the experiment groups with no statistical significance. We can carefully deduce that herbal medicine alone, as well as western medicine alone, does not cause any ill-effects on the liver functions. OR of ASP and ALT actually suggest protective effects. But OR values were calculated from 57 subjects from the total of 303 participants, small number of subjects could have led to incidental results. Previos study indicated significant increase in OR for T-bilirubin in the combined group, calling for further studies in the field.[17] Thus physician needs to pay specific attention when the patient is undergoing dual treatments. For example, effects on children[18] or other organs[19, 20] are possible outcomes. Factors which may cause these ill-effects are toxins within the herbs, misusage, metal contamination, pesticides, mishandled herbs, and lack of standard in herbal production and distribution, and the public's misconception that herbal medicine is natural and safe. There were some limits in this study. First of all, selection bias might influence the results. Second, numbers of subjects in each groups had shortcomings for validity of this study. Third, more intensive study on the duration for herbal medication of subjects were needed. Despite these limits, findings from this study might heavily influence the direction of debate. From the toxicology's notion that every matter in the universe contains some sort of toxin suggests that one can never be too cautious before proper using for a medicinal purpose.[21] More detailed studies on the liver toxicity when herbal and western medicines are taken respectively or simultaneously are needed in the future.

V. Summary

303 patients admitted to one Oriental medical

clinic in Seoul, Korea from September 1, 2006 to December 31, 2006 were chosen for the study. Questionnaire and liver functions in blood were analyzed. Study groups were categorized into the control, herbal, western, and combined group. Effects of herbal and western medications on the liver functions are listed below.

1. Subjects of the study comprised of 116 individuals receiving western medication (38.28%), 54 receiving herbal medication (17.82%), 107 receiving combined forms of medication (35.31%), and 26 individuals without any types of medication(8.58%).

2. Comparing variables of liver functions in blood, there was no significant difference between the control and experiment groups.

3. After adjusting potential confounders, monthly β(SE) of multiple regression -0.009~0.0 for the herbal group, -0.005~0.0 for the western group, and -0.001~0.001 for the combination group. No significant difference between the groups.

4. OR of T-bilirubin were 1.02, 1.05, and 1.04. OR of AST were 0.92, 0.94, and 0.98. OR of ALT were 0.85, 0.99, and 0.97. OR of LDH were 0.96, 1.06, 1.00 for the herbal, western, and combination group, respectively. OR values varied depending on the means of intake.

In summary, herbal medication did not cause any ill-effect on the liver function based on liver function tests. On the other hand, odds ratios for each group showed potential protective effects on 57 subjects exceeding reference values of AST and ALT. Even though T-bilirubin increased in all experiment groups and LDH also increased in western group only, but, there were no significant differences between groups.

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