Clinical Case Report

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Effectiveness and safety of Injinoryung-San-Gagambang (Yinchen Wuling powder) decoction on stroke patients with elevated serum liver enzymes

Three case reports

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Abstract

Rationale: Injinoryung-San-Gagambang (IJORS) effectively improves hepatic dysfunction caused by polypharmacy in stroke patients.

Patient concerns: We present 3 cases of hepatic dysfunction caused by polypharmacy, one of which was a 51-year-old man with cerebellum infarction and pneumonia as a complication of stroke. He took multiple medications because of baseline diseases. After recurrence of pneumonia, his laboratory tests showed abnormal aminotransferase levels. Another patient was an 81-year-old woman with cerebral infarction at the right-middle cerebral artery. She was also taking >5 medications. Her laboratory tests conducted on admission showed abnormally elevated aminotransferase levels. The last patient was 77-year-old man with cerebral infarction at the left-middle cerebral artery. He also had an abdominal aneurysm, a thoracic aortic aneurysm, and a myocardial infarction. After taking multiple medications including healthy functional foods, his laboratory tests showed abnormally elevated aminotransferase levels.

Diagnosis: Diagnosis is conducted with the result of laboratory test including blood count, chemistry test.

Interventions: All 3 patients received the same herbal treatment (IJORS decoction) for 1 to 3 weeks.

Outcomes: All 3 patients' abnormal serum aminotransferase level were significantly improved by IJORS decoction treatment while keeping other medicines.

Lessons: IJORS can be considered as an effective treatment for hepatic dysfunction induced by numerous medications in stroke patients.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BID = bis in die, same as twice a day, BP = blood pressure, BT = body temperature, BUN = blood urea nitrogen, CARE guidelines = case report guidelines, Cr = creatinine, DDB = biphenyl dimethyl dicarboxylate, DM = diabetes mellitus, HBeAg = hepatitis B e-antigen, HBsAg = hepatitis B Surface antigen, hs = Hora somni, same as before sleep, HTN = hypertension, IJORS = Injinoryung-San-Gagambang, LFT = liver function test, P.O. Med = Per os medication, QD = Quaque die, same as once a day, RFT = renal function test, r-GTP = gamma-glutamyl transferase, TID = ter in die, same as three times a day, WKUGH = Wonkwang University Gwangju Korean Medical Hospital.

Keywords: case report, herbal medicine, Injinoryung-San-Gagambang, liver function, Yinchen Wuling powder

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1. Introduction

According to nationwide representative research conducted in the Scotland, 12.6% of stroke patients had ≥11 repeat prescriptions as compared with only 1.5% of healthy controls.[1] This burden of medication is commonly defined as polypharmacy, which is linked with a heightened risk of drug-related problems,[2] hepatic disorders.[3] A side effect of clopidogrel, which is commonly used for secondary prevention of ischemic stroke, is increasing liver function levels.[4] The findings of the aforementioned studies suggest that stroke patients may be vulnerable to liver damage because of polypharmacy.

Conventional approaches to hepatic dysfunction in stroke patients are using biphenyl dimethyl dicarboxylate (DDB),[5,6] silymarin.[7] These medcation normalize elevated blood alanine aminotransferase (ALT) levels in patients with various disorders, such as viral hepatitis and a fatty liver. Previous research reported that DDB lowered blood ALT, whereas it had no effect on aspartate aminotransferase (AST) and gamma-glutamyl transferase (r-GTP).[6] According to a double-blind, randomized, multicenter trial in Korea on the efficacy of DDB, ALT levels were normalized after >4 weeks, and AST levels were unchanged after 12 weeks.[8]

Most stroke patients are prescribed numerous drugs because of underlying disease and secondary stroke prevention.[1] Medication adherence can be a burden for these patients.

We describe the cases of 3 stroke patients with abnormal aminotransferase levels who had positive liver outcomes, as assessed by a liver function test (LFT) following treatment with Injinoryung-San-Gagambang (IJORS) for 1 to 3 weeks. This study followed the Case Report guidelines (CARE guidelines).

2. Case presentation

Three stroke patients with abnormal levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (r-GTP) in a liver function test (LFT) received hospital care from January to June 2018 at Wonkwang University Gwangju Korean Medical Hospital (WKUGH, Gwangju, South Korea).

This study was approved by the WKUGH's Institutional Review Board (WKIRB 2018–15) and the patients have provided informed consent for publication of the case.

The serum aminotransferase level was considered normal in accordance with that used in previous studies.[9,10]

The IJORS decoction was prepared by boiling in 500 mL of distilled water for approximately 2 hours until the volume of the solution was concentrated to 100 to 120 mL. The IJORS decoction was administered 3 times daily after meals. The components of IJORS are presented in Table 1.

Table 1

Components and 1 day dose of Injinoryung-San-Gagambang (IJORS).

Medical plants	Weight (g) divide(#) 3 times
Artemisiae capillaris herba	60g#3
Alismatis rhizoma	24g#3
Atractylodis rhizoma alba	24g#3
Polyporus umbellatus	24g#3
Poria (Hoelen)	24g#3
Aurantii immaturus fructus	18g#3
Lonicerae flos	12g#3
Forsythiae fructus	12g#3
Coptidis rhizoma	6g#3

3. Case 1

A 51-year-old man with dizziness who had been diagnosed with cerebellum infarction on December 24, 2017 was admitted to the WKUGH on January 9, 2018. Based on the patient medical records, he had received treatment for pneumonia as a complication of stroke. He had also been diagnosed with hypertension (HTN) and diabetes mellitus (DM). The patient had a history of tuberculosis treatment in 2000 and had made a complete recovery.

From the date of admission, the patient had been taking multiple medications, such as anti-hypertensive drug, hypoglycemic agent, and aspirin, because of baseline disease. The patient's medication list is shown in Table 2.

On January 18, 2018, he had fever, chills, sputum, cough, and anorexia. The vital signs were as follows: blood pressure (BP) of 150/90 mmHg, body temperature (BT) of 38.5 °C, and a pulse rate of 130/min. The results of a chest x-ray pointed to recurrence of pneumonia. The patient was treated with ceftriaxone sodium hydrate (Cefaxone Injection, Shinpoong pharm, Seoul, Korea), 15 mg/2 mL ambroxol hydrochloride (Huons Ambroxol HCl Injection, Huons, Seoul, Korea), 10% aminoacetic acid (Zentalamin Injection, Samsung Pharm, Seoul, Korea), 375 mg L-carbocysteine (Rhinathiol Capsule, Hyundai Pharm, Seoul, Korea), 8 mg bromhexine hydrochloride (Bisolvon Tablet, Sanofi-aventis Korea, Seoul, Korea), and 325 mg acetaminopen (Setopain Tablet, Sama Pharm, Wonju city, Korea). For the per os medication's (P.O. Med) loading dose, 3 times for a day.

Table 2

Composition of per os medication.

Patient	Product name (ingredients label)	Dose
Patient 1	Twynsta Tab. 80/5 mg (amlodipine besylate 6.935 mg, telmisartan 80 mg)	1T QD
	Januvia Tab. 100 mg (sitagliptin phosphate hydrate 128.5 mg)	1T QD
	Diabex Tab. 500 mg (metformin hydrochloride 500 mg)	1T QD
	Astrix Cap. 100 mg (aspirin enteric Gr. 120.98 mg)	1C QD
	Radin-Q Tab. (ranitidine hydrochloride 84 mg)	2T BID
	Mucosta Tab. (rebamipide 100 mg)	2T BID
	Gliatilin soft cap. (choline alfoscerate 400 mg)	2T BID
Patient 2	Amlodipine Tab. (amlodipine besylate 6.944 mg)	1T QD
	Aspirin enteric coated Tab. 100 mg (Aspirin 100 mg)	1T QD
	Chrorel Tab. (clopidogrel bisulfate 97.875 mg)	1T QD
	Mucotra Tab. 100 mg (rebamipide 100 mg)	2T BID
	Gliatilin soft cap. (choline alfoscerate 400 mg)	2T BID
Patient 3	Isotril ER Tab. 60 mg (isosorbide-5-mononitrate 90% 66.7 mg)	1T QD
	Sigmart Tab. 5 mg (nicorandil 5 mg)	1T BID
	Platless Tab. (clopidogrel bisulfate 97.875 mg)	1T QD
	Crestor Tab. 10 mg (rosuvastatin calcium10.4 mg)	1T QD
	Concor Tab. 2.5 mg (isoprolol fumarate 2.5 mg)	1T QD
	Aricept Tab. 10 mg (donepezil hydrochloride 10 mg)	1T QD
	Keppra Tab. 500 mg (levetiracetam 500 mg)	1T BID
	P.K-Merz Tab. (amantadine sulfate 100 mg)	1T BID
	Alfoatirin soft cap. (choline alfoscerate 400 mg)	3T TID
	Folic acid Tab. 1 mg (folic acid 1 mg)	1T QD
	Harnal-D cap. 0.2 mg (tamsulosin hydrochloride 0.2 mg)	1T hs

BID = bis in die, same as twice a day, Cap. = Capsule, hs = Hora somni, same as before sleep, QD = quaque die, same as once a day, Tab. = Tablet, TID = ter in die, same as 3 times a day.

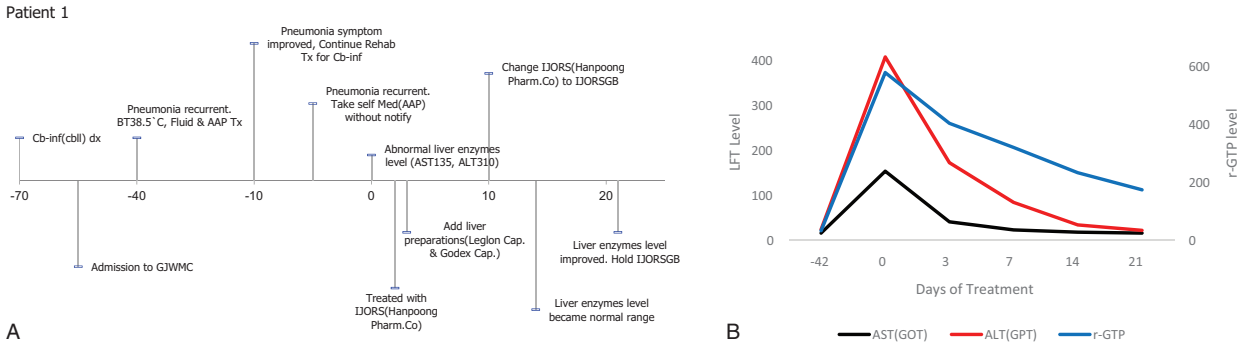

Figure 1. (A) A timeline of the patient 1 treatment. (B) Changes in aminotransferase levels of patient 1.

Thereafter, his vital signs stabilized after 1 week. But pneumonia relapsed again on 2 March.

Subsequently, the patient was prescribed P.O. Med (Acetaminopen 325 mg TID, Acetaminopen ER 650 mg TID, Bromhexine Hydrochloride, L-Carbocysteine for Antitussives agents TID).

But the patient had been taking another drug for several days included acetaminophen 300 mg, Pan Cold-S Oral Solution (Dongwha Pharm. CO., Seoul, Republic of Korea), without notifying doctors. As a result, he had an abnormal range of aminotransferase level in a lab test on March 3, 2018.

The patient was prescribed 3 g IJORS prescription (Plus Granule, Hanpoong Pharm, Jeonju city, Korea) for 10 days from 5 March combined with 70 mg silymarin (Legalon Capsule, Bukwang Pharm, Seoul, Korea) and DDB 25 mg (Godex Capsule, CELLTRION Pharm., Seoul, Korea). As the results of the first LFT follow up after treatment revealed no improvement in aminotransferase levels, we changed the IJORS prescription (Plus Granule, Hanpoong Pharm, Jeonju city, Korea) to IJORS decoction (Table 1). Three weeks after starting the treatment, the patient abnormal aminotransferase levels returned to normal. Figure 1(A) shows a timeline of the patient treatment, and the aminotransferase levels are shown in Fig. 1(B).

4. Case 2

An 81-year-old woman with left hemiparesis and dysarthria who had been diagnosed with cerebral infarction at right middle cerebral artery on April 14, 2017 was admitted to the WKUGH on January 9, 2018. The patient was taking aspirin, antihypertensive drugs, and anti-arteriosclerotic agents. The patient reported that she took medication for pruritus and tinea pedis. However, as did not bring the medication with her on the day of admission, we could not confirm the names of the medications or classify the type of drugs. The patient's medication list is shown in Table 2.

Based on the results of a LFT performed on May 3, 2018, the date of her admission, the patient aminotransferase levels were abnormal. The patient was prescribed IJORS decoction combined with 70 mg silymarin (Legalon Capsule, Bukwang Pharm, Seoul, Korea) and DDB 25 mg (Godex Capsule, CELLTRION Pharm, Seoul, Korea). The same IJORS decoction was prescribed as for Patient 1. After 1 week of the herbal treatment, the patient aminotransferase levels returned to normal. Although the patient r-GTP level was still high, the patient daughter refused continued treatment due to the cost, so the herbal medicine was discontinued. The patient was discharged on 26 May. Thus, it was not possible to follow up the r-GTP level. A timeline of the treatment is given in Fig. 2(A), and the aminotransferase levels are shown in Fig. 2(B).

5. Case 3

A 77-year-old man presented with complaints of right hemiplegia, aphasia, and a history of HTN, DM, and gout diagnosed in 2007.

The patient history included an abdominal aneurysm, a thoracic aortic aneurysm, and surgery on October 31, 2015 following a myocardial infarction. According to the patient wife,

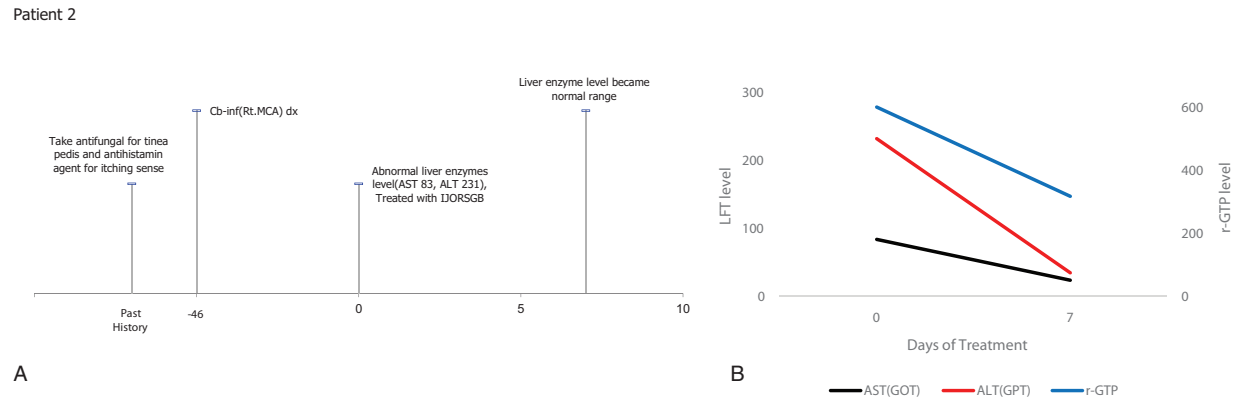

Figure 2. (A) A timeline of the patient 2 treatment. (B) Changes in aminotransferase levels of patient 2.

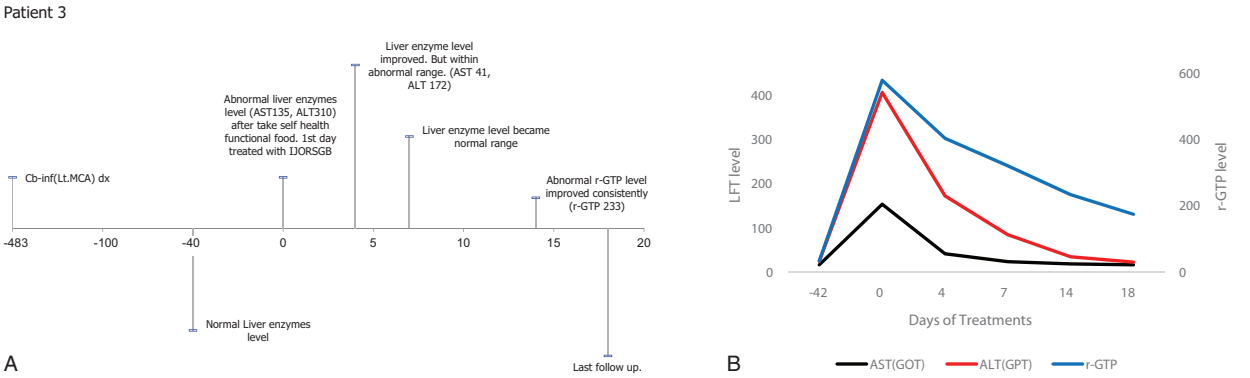

Figure 3. (A) A timeline of the patient 3 treatment. (B) Changes in aminotransferase levels of patient 3.

the patient had abnormal aminotransferases levels and renal function test (RFT) levels in the past and had recovered.

At the time of admission to the WKUGH from July 20, 2017 to November 6, 2017, the patient had a normal aminotransferases level. At the time of his second admission on February 21, 2018, he still had a normal LFT results. The patient reported that he was taking 11 different medications for underlying disease (HTN, DM, epilepsy, and a myocardial infarction, anticoagulant) at that time. The patient was prescribed the same herbal medication prescribed during his first admission period.

On May 11, 2018, the follow up of the patient LFT revealed an extremely abnormal level of aminotransferase. As there was no particular reason for the abnormal aminotransferases level, we consulted the patient wife. His wife reported that the patient consumed a large amount of healthy functional foods, such as Huttuynia cordata, Ginseng, and sockeye salmon.

We instructed the patient to cease consumption of these functional foods and prescribed the same IJORS decoction as in case 1 and 2. After 3 weeks of the herbal treatment, the patient's aminotransferase level returned to normal. The patient r-GTP level remained high. However, due to the insurance coverage period, the patient was discharged on 7 June, and no further data were obtained on his r-GTP level. A timeline of the patient treatment is presented in Fig. 3(A), and the aminotransferase levels are shown in Fig. 3(B).

6. Discussion

We described 3 cases of stroke patients with abnormal aminotransferase levels who were treated using IJORS. All the patients were treated with IJORS 3 times daily for 18.33 ± 7.41 (mean ± standard deviation) days. Blood urea nitrogen (BUN), creatinine clearance (Cr), and bilirubin (total/direct) values were within the normal range before and after treatment (Table 3). All 3 stroke patients had lower aminotransferase levels after treatment. During the follow-up period, no specific adverse effects of the IJORS were reported.

Previous studies of IJORS focused on chronic hepatitis,[11–13] alcoholic liver disease,[14] liver cirrhosis,[15] postoperative liver dysfunction,[16] cardiovascular system diseases,[17] and hyperlipidemia.[18] To the best of our knowledge, there are no studies on liver dysfunction in stroke patients or in patients taking multiple drugs. It may be difficult to reduce the number of drugs in patients prescribed multiple drugs for underlying diseases like stroke patients who had HTN or DM. In such cases, an alternative approach is needed that can improve the function of the liver faster and more effectively than conventional liver preparations, such as DDB.

Previous studies reported that each of the herbs used in IJORS have been shown to improve liver function and to have hepatoprotective and hypolipidemic effects.[19–21] For example, research showed that Artemisia capillaris contained effective constituents, such as scoparone, scopoletin, isochlorogenic acid, and pumilaside, for the treatment of hepatitis.[19] Scoparone reduced ALT levels, and isochlorogenic acids markedly inhibited the expression of hepatitis B Surface Antigen (HBsAg), hepatitis B e-antigen (HBeAg), and cccDNA. *Poria cocos* was effective against acetaminophen-induced liver injury by suppressing NF-κB pathway-based apoptosis and inflammatory stress in liver cells.[20] *Alismatis rhizoma* exhibited hypolipidemic effects and decreased ALT activity.[21]

Table 3

Results of bilirubin and renal function test.

Patient 1	**Before IJORS administration**	**After 21 day IJORS administration**	**Normal range**
Bilirubin (total/direct), mg/dL	1.13/0.29	1.05/0.27	0.22–1.2/0.05–0.3
BUN/Cr, mg/dL	14.42/0.65	13.81/0.77	8–20/0.5–1.3
Patient 2	**Before IJORS administration**	**After 7 day IJORS administration**	**Normal range**
Bilirubin (total/direct), mg/dL	0.83/0.23	0.35/0.17	0.22–1.2/0.05–0.3
BUN/Cr, mg/dL	17.91/0.76	14.48/0.77	8–20/0.5–1.3
Patient 3	**Before IJORS administration**	**After 21 days IJORS administration**	**Normal range**
Bilirubin (total/direct), mg/dL	1.39/0.6	0.77/0.22	0.22–1.2/0.05–0.3
BUN/Cr, mg/dL	11.07/0.93	10.01/0.93 (after 3 d)	8–20/0.5–1.3

BUN = blood urea nitrogen, Cr = creatinine, IJORS = Injinoryung-San-Gagambang.

But also the present study has some limitations. First, the study included only 3 case reports. Therefore, more cases are needed to confirm the effect of IJORS. Second, in 2 cases, the effects of IJORS alone could not be determined, as it was combined with liver preparations. Moreover, this study had a retrospective case series study design. Given the study design and absence of a control group. Therefore, multiple errors and biases may have occurred.

In spite of these limitations, IJORS will be beneficial to the clinical field and physicians who prescribe medicine to stroke patients with liver disease. Furthermore, the stroke patients in the present study with abnormal serum aminotransferase levels due to polypharmacy showed improvements in LFT after IJORS treatment, without any major side effects. These findings point to the potential effectiveness of IJORS, which is generally accepted as safe, as an intervention for liver dysfunction in patients taking multiple drugs. Further studies are needed to confirm the ability of IJORS to improve the liver function of stroke patients taking multiple drugs for the prevention of a second attack or underlying diseases.

Author contributions

Conceptualization: Hongmin Chu, Sangkwan Lee.
Supervision: Sangkwan Lee.
Writing – original draft: Hongmin Chu, Chanran Park.
Writing – review & editing: Cheolhyun Kim, Kang-Keyng Sung, Sangkwan Lee.
All authors have read and approved the final manuscript.

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