

Original Article

Clinical Assessment of Usefulness, Effectiveness and Safety of *Kyejibokryung-hwan* on Various Neuropathies

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We were to assess clinical effectiveness, safety and usefulness of *Kyejibokryung-hwan* (KBH), which has been used for *Er-hyul* similar with vascular or neurologic disorders causing sensory or motor abnormalities. This study is a retrospective single case series. Two hundred ninety five patients were treated with KBH for various neuropathies in our hospital. Of them, 120 cases were excluded because of insufficient medical records or failure to follow up; the remaining 175 were included in the analysis. There were 18 patients with sensory abnormalities and 28 with motor abnormalities after stroke. Of peripheral type, there were 14 with diabetic neuropathy, 12 with carpal tunnel syndrome, 41 with spinal radiculopathies, and 62 with idiopathic neuropathies, for which the effectiveness was assessed as 55.6%, 21.4%, 64.3%, 83.3%, 45.0%, and 56.5%, respectively. Adverse effects including indigestion or diarrhea were seen in 3.4% of the total patients. Taking the effectiveness and the safety together into consideration, the usefulness was assessed as 55.6%, 21.4%, 64.3%, 83.3%, 45.0%, and 54.8% for treating post-stroke sensory and motor abnormalities, diabetic neuropathy, carpal tunnel syndrome, spinal radiculopathies, and idiopathic neuropathies, respectively. In conclusion, we suggest that KBH is a useful herbal medicine for various neuropathies, especially of sensory type.

Key Words : *Kyejibokryung-hwan*, neuropathy

Introduction

Kyejibokryung-hwan (KJH) is a traditional herbal formulation created by Zhang-Ji in Jin-Gui-Yao-Lue (金櫃要略), about 200 BC, and used clinically for "*Er-hyul*" (blood stagnation, *Oketsu* in Japanese and *Yu-xie* in Chinese) syndrome in Asian countries since then. The

clinical condition of *Er-hyul* syndrome is similar to vascular or neurologic disorders causing sensory or motor abnormalities. Some experimental and clinical studies on KJH have been reported previously (1-4). However, clinical evaluation of KJH on vascular or neurologic disorders is rare. Therefore, we aimed to assess clinical effectiveness, safety and usefulness of KBH by examining the cases we experienced at our hospital.

Methods

This is a retrospective cohort study. We reviewed the medical records of outpatients who were treated with KBH (composed of *Cinnamomi*

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Table 1. Case Summary of Central and Peripheral Neuropathies

	Central Type		Peripheral Type			
	Sensory type (n=18)	Motor type (n=28)	Diabetic neuropathy (n=14)	Carpal tunnel syndrome (n=12)	Spinal radiculopathy (n=41)	Idiopathic neuropathies (n=62)
Age	60.7±9.1	61.4±8.2	64.6±13.0	55.4±5.5	52.9±9.6	50.7±14.1
Sex, male (%)	7 (38.9)	16 (57.1)	6 (42.9)	0	7 (17.1)	11 (17.7)
Onset, month	11.6±12.9	10.4±14.1	30.7±66.6	11.2±21.3	50.0±108.3	5.2±7.3
Months of treatment	1.6±1.3	1.0±0.8	2.5±3.1	0.7±0.5	1.0±1.1	1.2±0.9
History (%)						
Hypertension	9 (50.0)	11 (39.3)	8 (57.1)	0	6 (14.6)	10 (16.1)
Diabetes Mellitus	3 (16.7)	4 (14.3)	14 (100.0)	0	3 (7.3)	1 (1.6)
Heart disease	0	0	0	1 (8.3)	1 (2.4)	1 (1.6)
Hyperlipidemia	1 (5.6)	2 (7.1)	0	0	2 (4.9)	3 (4.8)
Others	0	0	1 (7.1)	1 (8.3)	3 (7.3)	3 (4.8)
Improvement on VAS	48.3±41.6	11.4±45.8	40.0±38.0	59.2±35.8	24.1±43.4	41.5±40.0
Adverse effects	0	4 ¹⁾ (14.3)	0	0	0	2 ²⁾ (3.2)

¹⁾ Mild indigestion was in two cases, and severe abdominal discomfort in the others.

²⁾ Mild indigestion was in one case, and diarrhea in another.

ramulus 1.25g, *Paeoniae Radix* 1.25g, *Persicae semen* 1.25g, *Poria* 1.25g, and *Moutan cortex* 1.25g and now being manufactured as TJ-25 by Tsumura & Co. of Japan) at the Department of Cardiovascular & Neurologic Diseases (Stroke Center), Kyung Hee Oriental Medical Center, Seoul, Korea, from May 1, 2003 to November 1, 2005. We excluded patients whose medical records were insufficient to confirm their diagnosis or assess the effect of KBH.

The effectiveness of KBH was evaluated into 5 categories based on the improvement of visual analog system (VAS): 1) supremely efficacious (more than 75% of improvement on VAS), 2) more than efficacious (from 50% to 75%), 3) efficacious (from 25% to 50%), 4) non-effective (under 25%), and 5) aggravating.

The safety of KBH was evaluated into 3 categories based on the severity of clinical adverse effects: 1) none, 2) mild adverse effects, and 3) severe adverse effects which resulted in medicine change, unbalance of serum electrolytes

(sodium, potassium and chloride ion), or severe edema (weight gain over 2kg per a week).

The usefulness of KBH was estimated as 5 categories taking effectiveness and safety into consideration: 1) supremely useful (supremely efficacious and no adverse effects, 2) more than useful (supremely efficacious and mild adverse effects, more efficacious and non adverse effects, or efficacious and no adverse effects), 3) useful (more than efficacious and mild adverse effects, or efficacious and mild adverse effects), 4) non-useful (more than efficacious and severe adverse effects, or non-effective and no adverse effects), and 5) detrimental (non-effective and any adverse effects, or aggravating regardless of adverse effects).

Results

KBH was prescribed to 295 patients with various neuropathies accompanied by sensory or motor abnormalities in their extremities. After excluding 120 cases with poor medical records,

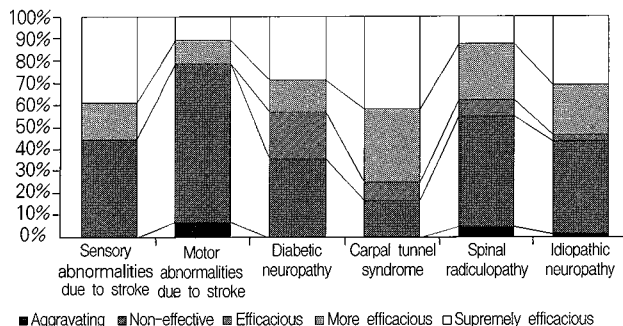


Fig. 1. Effectiveness of Kyejibokryung hwan on various neuropathies.

175 cases remained. The causes of their symptoms were evaluated as cerebrovascular diseases in 46 cases and peripheral neuropathies in 129 cases.

The central type was classified by their main symptoms: sensory abnormalities (n=18) or motor abnormalities (n=28). The peripheral type was classified by diagnosis: diabetic neuropathy (n=14), carpal tunnel syndrome (n=12), spinal radiculopathies (n=41), or idiopathic neuropathies (n=62) (Table 1).

Central type was confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI). Diabetic neuropathy was diagnosed when a patient experienced numbness, pain, or tingling in the feet which seemed to be caused by diabetic mellitus. Carpal tunnel syndrome was diagnosed

when palm numbness and pain was due to median nerve neuropathy, which was supported by electromyogram (EMG). Spinal radiculopathy was confirmed when symptoms such as back pain or abnormal sensation of their extremities correlated well with cervical or lumbar spine X-ray.

1. Effectiveness assessment

In central type, the percentage of more than efficacious was 55.6% and 21.4% in sensory and motor abnormalities induced by stroke, respectively. In peripheral type, the percentage of more than efficacious was 64.3%, 83.3%, 45.0%, and 56.5% in diabetic neuropathy, carpal tunnel syndrome, spinal radiculopathy, and idiopathic neuropathies, respectively (Fig. 1).

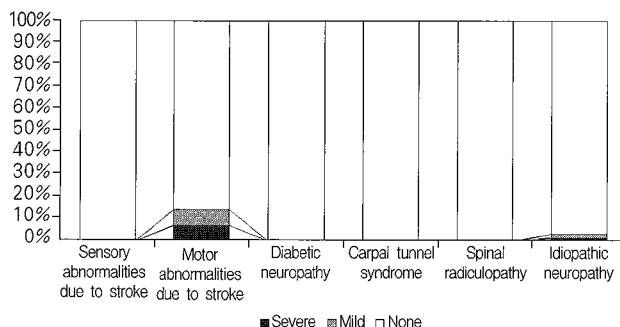


Fig. 2. Adverse effects of Kyejibokryung hwan on various neuropathies.

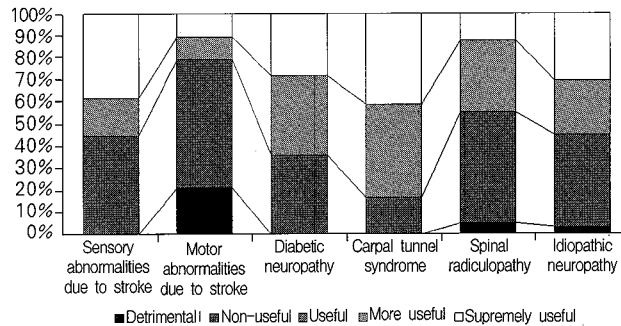


Fig. 3. Usefulness of Kyejibokryung hwan on various neuropathies.

2. Safety assessment

The percentage of adverse events was 14.3% and 3.2% in post-stroke motor abnormalities and idiopathic neuropathies. There was no adverse effect in the other groups (Fig. 2).

3. Usefulness assessment

In central type, the percentage of more than useful was 55.6% and 21.4% in sensory and motor abnormalities induced by stroke respectively. In peripheral type, the percentage of more than useful was 64.3%, 83.3%, 45.0%, and 54.8% in diabetic neuropathy, carpal tunnel syndrome, spinal radiculopathy, and idiopathic neuropathies, respectively (Fig. 3).

Discussion

The previous studies of KBH were mainly focused on gynecological problems in Japan⁵⁻⁹). However, in Korea, KBH is frequently used to treat various neuropathies due to vascular or neurologic disorders, so we aimed to assess the clinical usefulness of KBH by a review of our cases.

Cerebrovascular attack leaves neurologic deficits such as sensory or abnormal abnormalities. Some medications and physical exercise were applied

to stroke patients for aiding recovery from their symptoms. For sensory abnormalities, mainly composed of so-called thalamic pain (central post stroke pain), some amitriptyline as an adrenergic reuptake inhibitor and the sodium channel blockers are the drugs of first choice¹⁰). Motor cortex stimulation or anticonvulsants such as lamotrigine were reported to be effective in relieving pain^{11,12}). However, these treatments are difficult to perform and responses are often unsatisfactory¹³). We observed that 55.6% of the KBH-treated patients were substantially relieved of pain and abnormal sensation, and there were 55.6% of more than usefulness. These results may be caused by the protective effect of KBH against NO-mediated neuronal death¹⁴) and vascular injury¹). KBH is also known to have antioxidative effect and by inhibiting the release of free radicals after post-ischemic brain injury¹⁵⁻¹⁷), and prevents the progression of atherosclerosis^{2,15}). However, KBH seemed to have a little therapeutic effect on the recovery of motor function. The more than usefulness was assessed only 21.4%.

Diabetic neuropathy is one of the chronic complications approaches 50% in most diabetic patients¹⁸) affecting their quality of life by bring about sensory abnormality such as numbness,

pain, or tingling in the feet. Alpha-lipoic acid, aldose reductase inhibitors, and some prostaglandins are reported to be effective¹⁹⁻²¹⁾, but much controversy remains because of their limited effects. In our results, more than efficacious was 64.3%, and more than useful was 64.3%. These results are in accordance with the previous report which showed a beneficial effect of KBH on diabetic nephropathy by improving metabolic abnormalities associated with diabetes³⁾.

Carpal tunnel syndrome (CTS) is caused by pressure on the median nerve in the carpal canal. Symptoms include numbness of the thumb and fingers, hand pain, particularly at night, and handicap of the hand efficiency²²⁾. Electromyography is the best evaluation test to confirm the disease²³⁾. There are some methods such as non-steroidal anti-inflammatory drugs (NSAIDs), rehabilitation modalities, and surgical procedure^{4,24-26)}. However, there is no consensus on the most effective method of treatment. In this study, KBH showed high effectiveness on improving the symptoms with no adverse effect. Anti-inflammatory effects of KBH may explain these results²⁷⁾. Furthermore, *Cinnamomi ramulus*, a major component of KBH, had therapeutic effect on numbness and pain in the limbs²⁸⁾, and *Paeoniae Radix*, another component of KBH, inhibits the secretions of inflammatory cytokines²⁹⁻³¹⁾, and activates the GABA receptor (Sugiyama et al., 1996).

Back pain and abnormal sensation of the upper or the lower limbs are the most common complaints of patients with spinal radiculopathy. Osteophytectomy is a common surgical treatment³²⁾. Conservative care such as physical therapy, spinal manipulation, medications, collars, and traction is the most appropriate first step, but their effectiveness is limited³³⁾. Our data shows that KBH was 45.0% more than efficacious and

45.0% more than useful. These results suggest that it could be considered an effective non-surgical treatment for spinal radiculopathy.

In idiopathic neuropathies, the more than efficacious was 56.5%, and more than useful were 54.8%. We think that anti-inflammatory effect and the therapeutic effect of KBH on stagnation of peripheral blood flow might play a role³⁴⁾.

There were 6 cases (3.4%) with adverse effects. The symptoms were gastrointestinal problems such as indigestion or diarrhea. Of them, three cases were severe, so the medicine had to be changed. These might be due to the inhibition of gastric acid by *Paeoniae Radix*³⁵⁾.

When we consider various neuropathies caused by vascular and neurologic disorders as *Er-hyul* syndrome, our findings seem to stand with the view of traditional oriental medicine that KBH has therapeutic effect on *Er-hyul*.

We confess this study has insufficient persuasive power to allow firm conclusions to be drawn: it is not an RCT but only a retrospective cohort study. However, we could suggest that KBH is a useful herbal medicine for various neuropathies especially in sensory types based on our findings.

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