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Systematic Review: Effects of the Kampo Formula Yokukan-San-Ka-Chimpi-Hange on Behavioral and Psychological Symptoms of Dementia

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Abstract

Introduction: Randomized usual-case controlled studies on Japanese dementia patients with behavioral and psychological symptoms were conducted to examine the effects of Kampo medicine Yokukan-San (YKS) on the behavioral and psychological symptoms of dementia (BPSD). These studies showed that YKS is effective in treating BPSD. Yokukan-San-Ka-Chimpi-Hange is a Kampo medicine made by adding dried citrus peel and pinellia tuber to YKS. In Japan, we usually administer Yokukan-San-Ka-Chimpi-Hange as Kracie Yokukan-San-Ka-Chimpi-Hange extract granules (KB-83), produced by Kracie Pharma, Ltd. (Tokyo, Japan).

Methods: We investigated 3 trials carried out on the use of KB-83 for the treatment of severe dementia in elderly.

Results: KB-83 showed no change in core symptoms after administration in cases of dementia, but significant improvements in BPSD were reported. KB-83 was particularly effective in treating aggressive symptoms such as restlessness or abusive language.

Conclusion: In the treatment of dementia, we think that the administration of KB-83 is effective in mitigating the BPSD, and that further studies are need to investigate the effects of KB-83.

Keywords: Kampo medicine; Dementia; Behavioral and Psychological Symptoms of Dementia; Yokukan-San-Ka-Chimpi-Hange

Abbreviations: YKS: Yokukan-San; BPSD: Behavioral and Psychological Symptoms of Dementia; KB-83: Yokukan-San-Ka-Chimpi-Hange Extract Granules; 5-HT: 5-Hydroxy Tryptamine; AD: Alzheimer's Disease; HDS-R: Revised Hasegawa's Dementia Scale; Behave-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; Kono's DBC: Kono's Dementia Balance Check; UC: Usual Care

Introduction

In 2005, the Food and Drug Administration reported a 1.6 to 1.7-fold increase in mortality in a group of elderly dementia patients who were administered an atypical antipsychotic drug compared to the placebo group [1,2]. A position paper on the principles of care for Alzheimer's disease (AD) written in 2006 and published by the American Association for Geriatric Psychiatry stressed the fact that there is no medication available that can dramatically improve the behavioral and psychological symptoms of dementia (BPSD), and that medication should only be used upon thorough consideration of both the risks and benefits entailed, and with the understanding that the benefits to be had are modest [3].

Randomized usual-case controlled trials in Japanese dementia patients with behavioral and psychological symptoms were conducted by Iwasaki et al. [4], Mizukami et al. [5], Monji et al. [6], and Okahara et al. [7] on the effectiveness of Kampo medicine Yokukan-San (YKS) in treating BPSD. These studies showed that YKS is effective in treating BPSD.

Yokukan-San-Ka-Chimpi-Hange is a Kampo medicine made by adding dried citrus peel and pinellia tuber to YKS (Table 1). In Japan, we usually administer Yokukan-San-Ka-Chimpi-Hange as Kracie Yokukan-San-Ka-Chimpi-Hange extract granules (KB-83), produced by Kracie Pharma, Ltd. (Tokyo, Japan).

Takeda et al. [8] have shown that several types of flavonoids contained in dried citrus peel can relieve loss of appetite due to decreased ghrelin via 5-HT2 receptor antagonism. Accordingly, it is assumed that KB-83 may be better suited than YKS for the treatment of elderly patients whose digestive tract function has deteriorated.

Also, Ito et al. have suggested that dried citrus peel extract, hesperidin (one of dried citrus peel's main components) and its metabolite hesperetin may have an anxiolytic-like effect [9]. Accordingly, it is possible that KB-83 is effective in treating anxiety and irritability found among BPSD. Recently, reports have emerged on the use of KB-83 in the elderly with dementia.

Composition		Weight
Hange	Pinellia tuber	5.0 g
Byakujyutsu	Atractylodes rhizome	4.0 g
Bukuryo	Poria sclerotium	4.0 g
Senkyu	Cnidium rhizome	3.0 g
Chimpi	Citrus unshiu peel	3.0 g
Toki	Japanese angelica root	3.0 g
Saiko	Bupleurum root	2.0 g
Kanzo	Glycyrrhiza	1.5 g
Chotoko	Uncaria hook	3.0 g

Table 1: Composition of herbal medicines.

Methods

We investigated three studies on the efficacy of KB-83 in elderly patients with severe dementia (Table 2) [10-12]. In one of the severe dementia studies, Miyazawa et al. administered KB-83 (7.5 g/day) for eight weeks to 18 subjects diagnosed with AD (80.1 ± 7.4 years old; eleven males, seven females) [10]. For the diagnosis of AD, the authors used the Diagnostic and Statistical Manual of Mental Disorders- IV [13] as well as the Alzheimer's Criteria proposed in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association [14].

Core symptoms and peripheral symptoms were evaluated before administering KB-83 and at 4 and 8 weeks after administration. As evaluation scales, the authors used the Revised Hasegawa's Dementia Scale (HDS-R), a question style assessment, for core symptoms [15], and the Behavioral Pathology in AD Rating Scale (Behave-AD), an observation style assessment for BPSD [16].

	Total	Age	Duration of administration	Time point	Core symptoms	BPSD
Miyazawa et al. [10]	18	80.1 ± 7.4	8W	4W, 8W	HDS-R	Behave-AD
Magome et al. [11]	18	79.6 ± 6.8	4W	4W	HDS-R	Kono's DBC
Suzuki et al. [12]	16	84.6 ± 5.0	4W	2W, 4W	HDS-R	Behave-AD

Table 2: Study, patients, and treatment characteristics of included trials in dementia patients with behavioral and psychological symptoms.

Magome et al. administered KB-83 (7.5 g/day) for 4 weeks to 18 patients diagnosed with AD based on HDS-R (79.6 ± 6.8 years old; 11 males, 7 females) [11]. Before and after the administration of KB-83, core symptoms were evaluated based on HDS-R, while peripheral symptoms were evaluated based on the ten positive symptom items in Kono's Dementia balance check (Kono's DBC) [17]. Suzuki et al. [12] administered KB-83 (7.5 g/day) for four weeks to 16 patients diagnosed with dementia and exhibiting BPSD (84.6 ± 5.0 years old; 6 males, 10 females) [12]. Core symptoms were evaluated in the form of study items by using HDS-R before administration and at four weeks. BPSDs were evaluated before administration, at 2 weeks and at 4 weeks by using Behave-AD.

With the exception of specially mentioned cases, Wilcoxon signed rank tests were conducted in the above studies for statistical analysis (before administration *vs.* at 2 weeks, before administration *vs.* at 4 weeks, and before administration *vs.* at 8 weeks).

Results

Below are summary of results of the three studies on severe dementia. We evaluated core symptoms based on HDS-R. Across the studies by Miyazawa et al. [10], Magome et al. [11] and Suzuki et al. [12], no significant changes were observed before and after administration (Table 3).

Significant improvements were found by Miyazawa et al. in BPSD when using Behave-AD, at 14.3 ± 8.8 points before administration, 9.2 ± 6.5 points 4 weeks after administration, and 7.6 ± 5.6 points 8 weeks after administration (before administration *vs.* 4 weeks after administration: p=0.0037; before administration *vs.* 8 weeks after administration: p= 0.0038; Friedman test: p=0.0016) (Table 4) [10].

	Before administration		After administration		
Miyazawa et al. [10]	12.4	± 6.5	12.9	± 7.9	n.s.
Magome et al. [11]	10.6	± 7.4	10.8	± 7.8	n.s.
Suzuki et al. [12]	8.4	± 6.7	8.4	± 5.6	n.s.

Table 3: Changes in HDS-R before and after the administration of KB-83 in dementia.

	Suzuki et al. [12]		Miyazawa et al. [10]	
Evaluation	2w	4w	4w	8w
Delusional ideas	p=0.023	p=0.016	p<0.01	p<0.05
Hallucinations	n.s.	n.s.	n.s.	n.s.
Behavioral disorders	n.s.	n.s.	n.s.	p<0.05
Aggressiveness	n.s.	p=0.078	p<0.01	p<0.01
Diurnal rhythm	n.s.	n.s.	p<0.05	n.s.
Emotional disorders	n.s.	p=0.059	n.s.	n.s.
Anxiety and fears	p=0.056	p=0.010	p<0.05	n.s.
Total	p=0.018	p=0.002	p<0.01	p<0.01

Table 4: Changes in Behave AD upon administration of KB-83 in dementia.

By item, significant improvements were observed in delusional ideas, behavioral disorders, aggressiveness, diurnal rhythm disorders,

anxiety and fears; especially significant improvements to aggressiveness such as, abusive language, intimidation, violence, and restlessness, was recognized (before administration *vs.* 4 weeks after administration: p=0.0066; p=0.0048 8 weeks after administration; Friedman test: p=0.0012) [10].

With Behave-AD, Suzuki et al. found significant improvements from the second week onwards, with 14.4 ± 9.5 before administration, 10.6 ± 9.1 points at 2 weeks, and 9.9 ± 8.3 at 4 weeks (before administration *vs.* 2 weeks after administration: p=0.018; before administration *vs.* 4 weeks after administration: p=0.002) [12].

By item, the study found a significant improvement of delusional ideas, anxiety and fears; the improvement of delusional ideas from the 2 weeks onwards was particularly significant (p=0.023 at 2 weeks and p=0.016 at 4 weeks after administration for hallucinatory ideas; p=0.056 at 2 weeks and p=0.010 at 4 weeks after administration for anxiety and fears). Trends for improvement were found for aggressiveness and emotional disorders (p=0.078 at 4 weeks for aggressiveness; p=0.059 at 4 weeks for emotional disorders) [12].

Magome et al. [11] studied the 10 positive symptom items in Kono's DBC. A significant decrease in the overall score was observed, at 10.7 ± 6.4 before administration and 3.3 ± 3.5 after the administration of KB-83 (p<0.01) (Table 5).

	Magome et al. [11]
Evaluation	4w
Irritability/anger/shouting/violence	p<0.01
Resistance to nursing/bathing	p<0.01
Desire to return home/go out	p<0.05
Insomnia	p<0.01
Wandering	p<0.01
Frequent nurse calls/ attention-seeking	p<0.05
Impatience	p<0.05
Delusions/hallucinations/soliloquy	p<0.01
Nervousness	n.s.
Theft/theft of food/overeating/allotriophagy	n.s.
Total	p<0.01

Table 5: Changes in BPSD in Kono's DBC upon administration of KB-83 in dementia.

In terms of individual item scores, significant improvements were found in 8 items: irritability/anger/shouting/violence, resistance to nursing/bathing, desire to return home/go out, insomnia, wandering, frequent nurse calls/attention-seeking, impatience, and delusions/hallucinations/soliloquy [11].

Discussion

Mastuda et al. summarized the results of the randomized usual-case controlled trials in Japanese dementia patients with behavioral and psychological symptoms carried out by Iwasaki et al. [4], Mizukami et al. [5], Monji et al. [6], and Okahara et al. [7] on the administration of YKS for BPSD [18].

Standardized mean difference and weighted mean difference were calculated. All studies used the Neuropsychiatric Inventory (NPI) for the evaluation of behavioral and psychological symptoms of dementia.

They identified 4 relevant studies (total n=236). YKS was superior to usual care (UC, i.e., controls) in the reduction of total NPI scores (p=0.0009. weighted mean difference =-7.20, I2=0%). In addition, YKS was more efficacious in reducing scores on the NPI subscale (delusions, hallucinations, and agitation/aggression) than UC (p<0.00001-0.0009). Mini-mental state examination scores did not differ between the YKS and UC treatment groups. They suggest that YKS has a beneficial effect on NPI and that YKS seems to be a well-tolerated treatment.

Overall effect of the prescription of YKS is speculated to be effective on the 5-HT nervous system and the glutamic acid nervous system. With regard to the 5-HT nervous system, a partial antagonist effect on 5-HT1A receptors [19] and a down regulation effect on 5-HT2A receptors [20] is currently being clarified; with regard to the glutamic acid nervous system, an inhibiting effect on the release of glutamic acid [21], a stimulating effect on glutamic acid transporters [22], and a protective effect on nerve cells [23] are being clarified. KB-83 is obtained by adding dried citrus peel and pinellia tuber to YKS, and is speculated to produce effects that are due to this addition. In severe cases of dementia, just as with YKS, the administration of KB-83 resulted in no significant differences in core symptoms. However, improvements were observed to aggressive BPSD such as abusive language and restlessness.

Considering these three studies, we suspect that KB-83 has effects for delusional idea or anxiety and fears at the early in the therapy as 2 weeks. For aggressiveness as irritability, anger, or resistance to nursing, the effect of KB-83 appears from 4 weeks. About diurnal rhythm like insomnia, the effect of KB-83 was found at only 4 weeks.

Yamakuni et al. reported nobiletin - a component of dried citrus peel contained in KB-83 - to be effective in improving memory disorders, inhibiting brain cholinergic neurodegeneration, and inhibiting amyloid β accumulation and neurotoxicity in the brain [24]. Additionally, Sato et al. [25] have made it clear that dried citrus peel components hesperidin and narirutin are effective in aiding recovery from age-induced demyelination.

The effects of dried citrus peel seen in these reports suggest that the administration of KB-83 was not only effective in improving BPSD as seen with YKS, but also had possibility to lead to the improvement of core dementia symptoms by cerebral blood flow analysis of variation in oxygenated hemoglobin with monitoring hemoglobin in the frontal lobe at rest and during task execution [26].

Conclusion

KB-83 showed no change in core symptoms after administration to dementia patients, but significant improvements in BPSD were reported. We think that KB-83 was thought to be particularly effective in treating restlessness and other aggressive symptoms, and that as YKS further studies are need to investigate the effects of KB-83 because there not so many studies about KB-83 against BPSD.

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