

Xiong-gui-tiao-xue-yin (Kyuki-chouketsu-in), a Traditional Herbal Medicine, Stimulates Lactation with Increase in Secretion of Prolactin but not Oxytocin in the Postpartum Period

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Abstract: The aim of the present investigation was to evaluate the clinical efficacy of Xiong-gui-tiao-xue-yin, a traditional Japanese herbal medicine, in stimulating lactation in the postpartum period. We enrolled 82 women who had a normal delivery in Osaka Medical College Hospital, and randomly assigned them to the following two groups: a group of 41 women who received Xiong-gui-tiao-xue-yin at a dose of 6.0 g/day (Group X), and a group of 41 women who received ergometrine (methylergometrine maleate) at a dose of 0.375 mg/day (Group E). Volume of lactation was determined daily until Day 6 postpartum. Plasma prolactin and oxytocin concentration were measured at Days 1 and 6 postpartum. The results showed that volume of lactation was significantly higher in Group X than in Group E at Days 4 ($p = 0.042$), 5 ($p = 0.038$), and 6 ($p = 0.046$). Significant differences between Groups X and E were noted in plasma prolactin concentration at Days 1 (157.9 ± 78.2 ng/ml and 129.1 ± 64.8 ng/ml; $p = 0.037$) and 6 (167.5 ± 95.4 ng/ml and 117.1 ± 53.6 ng/ml; $p = 0.0042$) postpartum. On the other hand, at Day 1, oxytocin concentration was significantly higher in Group E than in Group X ($p = 0.0024$). No adverse effects were observed in this study. The results of our study demonstrate the beneficial effects of Xiong-gui-tiao-xue-yin on lactation, with increase in prolactin level without increase in oxytocin level in the postpartum period. Therefore, Xiong-gui-tiao-xue-yin can be expected to improve lactation in women in the postpartum period. Further detailed bio-pharmacological studies and clinical trials to investigate the properties of this drug are warranted.

Keywords: Xiong-gui-tiao-xue-yin (Kyuki-choketsu-in); Herbal Medicine; Postpartum; Lactation; Prolactin; Oxytocin.

Introduction

Traditional herbal medicines are highly valued by the Japanese people because of their safety, absence of side-effects, wide range of applicable diseases/conditions, favorable outcome of treatment, and the fact that all of their ingredients are extracts of natural plants. In “*Wan bing hui chun*” (Returning Spring to the Tens of Thousands of Diseases), a famous textbook on treatments and remedies in Chinese natural medicine, Gong Ting-xian notes that Xiong-gui-tiao-xue-yin, a traditional regimen consisting of 13 different herbs, enhances postpartum recovery and thereby, hastens restoration of psycho-physical condition before pregnancy. In our recent studies, Xiong-gui-tiao-xue-yin was found to have sufficient efficacy in treating the psycho-physical disorders commonly experienced by women in the postpartum period, such as subinvolution of the uterus, anemia (Ushiroyama *et al.*, 2003), and maternity blues (Ushiroyama *et al.*, 2005). The effect of the regimen described for Xiong-gui-tiao-xue-yin includes not only reduction of lochia, improvement of anemia, maternity blues and postpartum depression, but also enhancement of lactation. To our knowledge, however, enhancement of lactation by this agent has not been demonstrated scientifically.

We conducted the present study to establish the clinical efficacy of Xiong-gui-tiao-xue-yin in puerperal women by evaluating enhancement of lactation and changes in the plasma concentrations of prolactin and oxytocin.

Materials and Methods

Patients

The subjects were a total of 82 women who had spontaneous labor pain followed by a normal delivery in Osaka Medical College Hospital. None had conditions requiring special management during pregnancy such as breech presentation, gestational toxicosis, diabetes mellitus, multiple conception, or premature rupture of membranes. Using the envelope method, the women were randomly assigned to a group of 41 women receiving Xiong-gui-tiao-xue-yin (Kanebo Pharmaceutical Co., Ltd., Tokyo, Japan) at a dose of 6.0 g/day (Group X), or a group of 41 women receiving ergometrine (methylethergometrine maleate) at a dose of 0.375 mg/day (Group E). There were no significant differences between the two groups in age, number of deliveries, gestational age at delivery, body mass index, intrapartum blood loss, duration of labor, and neonatal birth weight (Table 1).

Trial Drug

Xiong-gui-tiao-xue-yin is an extract of 13 different herbal drugs (Table 2). The daily dose of Xiong-gui-tiao-xue-yin is a mixture of 2 g each of Japanese angelica root (*dang gui*), cnidium rhizome (*chuan xiong*), rehmannia root (*di huang*), atractylodes rhizome (*bai shu*), hoelen (*fu ling*), Citrus unshiu peel (*chen pi*), cyperus rhizome (*xian fu zi*), moutan bark (*mu dan pi*) and lindera root (*wu yao*); 1.5 g each of jujube fruit (*da zao*)

Table 1. Baseline Characteristics of the Subjects

	Xiong-gui-tiao-xue-yin	Ergometrine	Significance
No. of subjects	41	41	
Age (year) (SD)	30.8 (3.9)	30.9 (4.0)	n.s.
Number of Deliveries (SD)	1.43 (0.52)	1.46 (0.51)	n.s.
Gestational Day of Delivery (SD)	276.5 (7.0)	275.6 (9.1)	n.s.
Duration of Delivery (hour) (SD)	7.34 (2.6)	7.66 (3.5)	n.s.
Blood Loss During Delivery (g) (SD)	211.3 (115.0)	231.0 (125.5)	n.s.
Infant's Birth Weight (g) (SD)	3,033.4 (261.8)	3,058.6 (272.4)	n.s.
Apgar Score (SD)	9.55 (0.7)	9.47 (0.7)	n.s.
Plasma Biochemical Values Before Delivery (SD)			
Hb (g/dl)	11.3 (0.11)	11.4 (0.12)	n.s.
TP (g/dl)	5.87 (0.42)	5.90 (0.41)	n.s.
Albumin (g/dl)	3.53 (0.50)	3.42 (0.41)	n.s.
T-CHO (mg/dl)	251.6 (41.4)	250.4 (43.3)	n.s.
TG (mg/dl)	233.6 (83.1)	237.4 (75.7)	n.s.

Hb: Hemoglobin, TP: total protein, T-CHO: total cholesterol, TG: triglyceride.

Table 2. Components of Herbal Drugs in Xiong-gui-tiao-xue-yin (Kyuki-chouketsu-in)

Japanese angelica root (<i>dang gui</i>)	2.0 g	Jujube fruit (<i>da zao</i>)	1.5 g
Cnidium rhizome (<i>chuan xiong</i>)	2.0 g	Siberian motherwort herb (<i>yi mu cao</i>)	1.5 g
Rehmannia root (<i>di huang</i>)	2.0 g	Ginger rhizome (<i>gan jian</i>)	1.5 g
Atractylodes rhizome (<i>bai shu</i>)	2.0 g	Glycyrrhiza root (<i>gan cao</i>)	1.5 g
Hoelen (<i>fu ling</i>)	2.0 g		
Citrus unshiu peel (<i>chen pi</i>)	2.0 g		
Cyperus rhizome (<i>xian fu zi</i>)	2.0 g		
Moutan bark (<i>mu dan pi</i>)	2.0 g		
Lindera root (<i>wu yao</i>)	2.0 g		

and siberian motherwort herb (*yi mu cao*); and 1 g each of ginger rhizome (*sheng jiang*) and glycyrrhiza root (*gan cao*). The above ingredients are chopped and extracted with hot water, and the extract is filtered and lyophilized to prepare lyophilized powder (daily dose of 4.58 g). The lyophilized powder, which must be stored at 4°C, is processed to obtain granules for a commercial preparation (daily dose of 6.0 g). The subjects took 2.0 g of the commercial preparation dissolved in 100 ml of hot water about 30 min before every meal.

Protocol

The women received full explanations of the trial and gave informed consent before enrolment. The women, who were randomly assigned to either Group X or E, began to take the trial drug on the day of delivery. Evaluation was performed between Days 1 and 6 postpartum to determine daily lactation volume (measurement of weight of

the baby before and after nursing). On Days 1 and 6 postpartum, blood samples were obtained to determine plasma prolactin and oxytocin concentrations. Plasma prolactin and oxytocin levels were measured using a commercially available enzyme immunoassay kit (bioMerieux-Vitek, Ltd., Tokyo, Japan). All women enrolled in the trial received cefditoren pivoxil, an antimicrobial agent commonly administered to puerperal women, at a dose of 300 mg/day, and serrapeptase, an anti-inflammatory enzyme preparation, at a dose of 30 mg/day.

Data Analysis

Results are expressed as mean \pm SD. Inter-group comparisons were performed using the Wilcoxon signed-rank test and Mann-Whitney U test. Computerized statistical data analysis was performed using Stat View J5.0 (Abacus Concepts, Inc., Berkeley, California, USA). In all comparisons, differences were considered significant when $p < 0.05$.

Results

Between Days 4 and 6 postpartum, the women in Group X had significantly larger volume of lactation than those in Group E (Day 4: 276.5 ± 21.4 vs 155.3 ± 61.2 g; $p = 0.042$, Day 5: 342.6 ± 43.6 vs 245.5 ± 59.4 g; $p = 0.038$, Day 6: 413.7 ± 68.1 g vs 293.3 ± 98.5 g; $p = 0.046$, Fig. 1). On Days 1 and 6 postpartum, plasma prolactin concentrations were significantly higher in Group X than in Group E (Day 1: 157.9 ± 78.2 ng/ml and 129.1 ± 64.8 ng/ml; $p = 0.037$, Day 6 (167.5 ± 95.4 ng/ml and 117.1 ± 53.6 ng/ml; $p = 0.0042$, Fig. 2). At Day 1, plasma oxytocin concentration was significantly higher in Group E than in Group X ($p = 0.0024$), although there was no significant difference in plasma oxytocin concentration between Groups X and E at Day 6 postpartum (Fig. 3). No adverse effects were observed in the women of either groups.

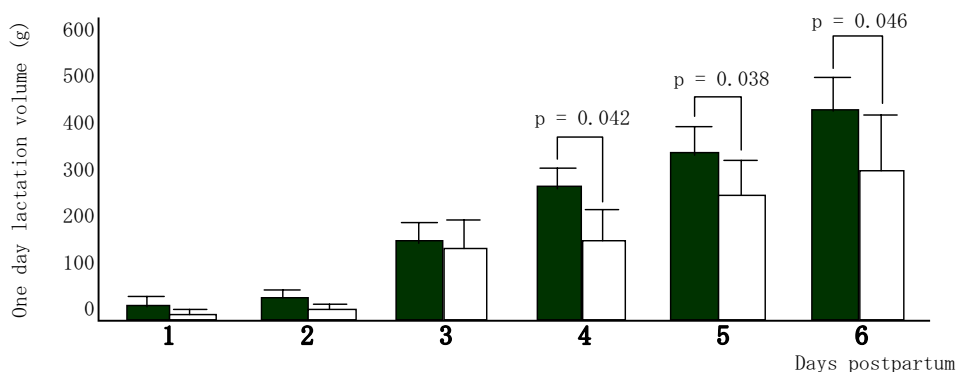


Figure 1. Comparison of daily lactation volume in the postpartum period between women receiving Xiong-gui-tiao-xue-yin and those receiving ergometrine. Closed columns: Xiong-gui-tiao-xue-yin, open columns: ergometrine.

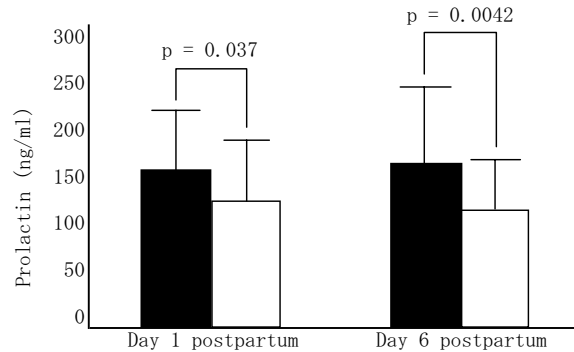


Figure 2. Comparison of plasma prolactin concentration at Days 1 and 6 postpartum between women receiving Xiong-gui-tiao-xue-yin and those receiving ergometrine. Closed columns: Xiong-gui-tiao-xue-yin, open columns: ergometrine.

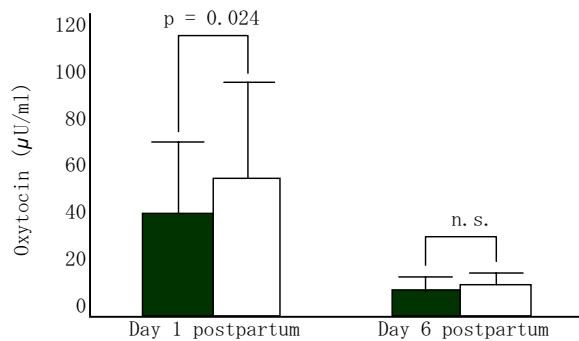


Figure 3. Comparison of plasma oxytocin concentration at Days 1 and 6 postpartum between women receiving Xiong-gui-tiao-xue-yin and those receiving ergometrine. Closed columns: Xiong-gui-tiao-xue-yin, open columns: ergometrine.

Discussion

Kampo medicine attempts to detect biological imbalances in each patient suffering illness and to eliminate them. Therefore, patient information must be collected by determination of signs of pathology appearing in the human body, mind and spirit. This is the core of the process of diagnosis and treatment in Kampo medicine. Traditional Chinese medicine is now called “complementary and alternative medicine (CAM)” in the Western world. CAM has been incorporated into daily common medical practice, and many scientific studies of its mechanisms of action have been aggressively performed.

Various studies have shown that CAM, especially in the form of herbal remedies, is commonly used for young women and pregnant women in Japan and the US (Allaire *et al.*, 2000; Ushiroyama *et al.*, 1995; 2001). Allaire *et al.* (2000) reported in their survey study

of certified nurse-midwives in North Carolina, that the use of herbal remedies to stimulate labor and to treat perineal discomfort, inadequate lactation, postpartum depression, postpartum hemorrhage and malpresentation.

Although very few studies have demonstrated the efficacy of herbal medicines in improving puerperal lactation, use of Yangxueshengru oral liquor, a herbal drug, has been found to improve breast milk secretion significantly and to increase daily amount of lactation (Chen *et al.*, 1995).

Xiong-gui-tiao-xue-yin is typically administered to puerperal women to supplement what are termed “qi” and “ketsu” in traditional herbal medicine; in modern medical terms, its usefulness is in improving systemic circulation to restore normal physical condition. The classic textbook “*Wan bing hui chun*” suggests that Xiong-gui-tiao-xue-yin improves anemia, enhances uterine contraction, prevents severe puerperal fever, stimulates lactation and improve psychological disorders (Matsuda, 1989; Yakazu, 1997). The ingredients of Xiong-gui-tiao-xue -yin used in this trial are essentially identical to those described in *Wan bing hui chun*, although the following changes have been made to establish the regimen currently available in Japan: steamed and dried ginger rhizome (*gan jian*) in the original regimen has been replaced by peeled and dried ginger rhizome; the contents of *da zao* and *yi mu cao* have been increased to 1.5 g/day; and the contents of main ingredients such as *dang gui*, *chuan xiong* and *di huang* have been decreased to 2 g/day.

Although gynecologists commonly administer ergometrine, an ergot alkaloid, to puerperal women, some specialists suggest that use of ergot alkaloids should be avoided because of its adverse reactions such as hypertension, nausea/vomiting, and feeling of chest compression (Peters *et al.*, 1996; Soriano *et al.*, 1996; Fuchi *et al.*, 1997; de Groot *et al.*, 1998). Ergot alkaloids should not be used by the puerperal women with heart disease. In our recent trial, women receiving Xiong-gui-tiao-xue-yin tend to have more favorable uterine retrieval and exhibited significant increase in the hemoglobin concentration during the postpartum period than those receiving ergometrine (Ushiroyama *et al.*, 2003). Furthermore, we have reported that Xiong-gui-tiao-xue-yin should be used to prevent maternity blues and postpartum depression (Ushiroyama *et al.*, 2005).

Aono (1990) reported that the initiation of milk secretion in puerperal women appears to be closely related to the induction of the increase in prolactin levels by adequate suckling, in which oxytocin appears to play an important role. Yoneda *et al.* (1995) reported that administration of recombinant human prolactin was effective in improving the lactational performance of bromocriptine-treated rats, and that recombinant human prolactin might be useful for the treatment of women with poor lactation. Nappi *et al.* (1993) reported that the dopamine agonist, dihydroergocryptine reduced prolactin levels and suppressed puerperal lactation. On the other hand, oxytocin did not stimulate milk secretion in the puerperal women with inadequate lactation (Ylikorkala *et al.*, 1984).

The results of the present trial indicate that Xiong-gui-tiao-xue-yin promotes lactation in postpartum women. Furthermore, plasma prolactin concentration, which was higher in the herbal medicine-treated group, may be related to induction of adequate production and secretion of breast milk in postpartum women. These findings suggest the possibility that this herbal regimen may aid lactation in puerperal women by inducing adequate prolactin

secretion. Although higher oxytocin secretion was observed in women not receiving than in those receiving Xiong-gui-tiao-xue-yin at Day 1 postpartum, the volume of lactation was small in both groups at that time. Adequate lactation may require stimulation of milk production by sufficient prolactin in the mammary glands prior to initiation of oxytocin secretion. Xiong-gui-tiao-xue-yin may promote physiological lactation step by step by regulating secretion of prolactin and oxytocin.

In conclusion, Xiong-gui-tiao-xue-yin was confirmed to enhance lactation in puerperal women after delivery without any adverse drug reactions. Xiong-gui-tiao-xue-yin may improve the quality of life of puerperal women when used as a complement or alternative to ergots, or as a commonly available medication after delivery. Xiong-gui-tiao-xue-yin may be an ideal natural remedy that will contribute to the health of puerperal women throughout the world.

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