

# Hemostatic effects of kyukikyogaito in dienogest treatment

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## Summary

**Purpose of Investigation:** A frequent side effect of treatment with dienogest (DNG) is irregular bleeding. The present study investigated the benefits of adding traditional Japanese Kampo medicine (kyukikyogaito), which has known hemostatic effects, on DNG treatment. **Materials and Methods:** This retrospective study assessed the occurrence of irregular bleeding in 175 patients following oral administration of DNG (2 mg/day) for three months or more. The authors also investigated the clinical hemostatic effects of kyukikyogaito (TJ-77; 9.0 g/day) administered for 30 days in patients with irregular bleeding. **Results:** The frequency of irregular bleeding in patients who received DNG was 80.0%. The continuation rates for DNG treatment were 62.3% in the DNG alone group and 85.0% in the DNG plus kyukikyogaito group ( $p = 0.016$ ). The efficacy of kyukikyogaito among patients with irregular bleeding was 82.6%. **Conclusion:** Administration of kyukikyogaito, which includes Artemisia leaf and donkey glue, was effective and could improve the continuation rate for DNG treatment by reducing irregular bleeding.

**Key words:** Endometriosis; Adenomyosis; Dienogest; Irregular bleeding; Kyukikyogaito.

## Introduction

Dienogest (DNG) is a fourth-generation progestin used to improve pain associated with endometriosis and adenomyosis. Its mechanism of action includes inhibition of ovulation, inhibition of estrogen production, and direct inhibition of cell proliferation in the endometriosis lesion. Since DNG does not have androgen, glucocorticoid or mineralocorticoid actions [1], it can thus be administered for long periods. However, luteinizing hormone (LH)-specific bleeding is a very frequent side effect [2]. The mechanism of irregular bleeding has the effect of suppressing estrogen production. During DNG administration, the endometrium becomes thinner than during a normal menstrual cycle and enters a secretory state due to the progesterone effect of DNG. A thin endometrium in the secretory state is likely to show rogue irregular bleeding during DNG administration [3]. As irregular bleeding continues, anemia occurs and the quality of life reduces, often resulting in discontinuation of DNG administration. It is therefore important to reduce the occurrence of bleeding during DNG treatment.

Kyukikyogaito is a prescription medicine introduced in the Chinese classic medical book *Jin Gui Yao Lue*. Its indications include uterine bleeding, bleeding after abortion, bleeding during pregnancy, abdominal pain during pregnancy, heat with agitation in the hands and feet, anemia, as well as several other conditions. Use is prescribed for people with relatively low physical strength and those who become anemic owing to excessive bleeding, mainly with regard to the medium and deficiency pattern types [4].

The purpose of this study was therefore to evaluate the benefit of adding traditional Japanese Kampo medicine (kyukikyogaito) [5, 6], which has known hemostatic effects, to DNG treatment.

## Materials and Methods

The study included patients examined at Kanazawa Medical University Hospital between January 2008 and December 2018. Retrospective analysis was performed for 175 patients who provided informed consent. Thirty patients with < 3 months of DNG administration or non-indication were excluded (Figure 1). The study was approved by the Kanazawa Medical University Ethics Committee (approval number: I409).

The study assessed the occurrence of irregular bleeding following oral administration of DNG (2 mg/day) for 3 months or more. In addition, the authors investigated the clinical hemostatic effects of kyukikyogaito (TJ-77; 9.0 g/day) administered for 30 days in patients with irregular bleeding. The data evaluated included bleeding onset time, bleeding volume, pathological diagnosis (endometriosis, uterine adenomyosis, uterine fibroid with endometriosis and/or adenomyosis), presence or absence of pretreatment (GnRH agonist), smoking status, female blood hormone levels (estradiol [E2] at the third month of treatment), and hemoglobin levels around kyukikyogaito treatment.

The irregular bleeding pattern was systematically assessed according to the reference period method. Clinical diagnosis was performed using ultrasonography and magnetic resonance imaging.

The extent of uterine bleeding was assessed as follows: no bleeding, spotting, light bleeding, medium bleeding, and heavy bleeding. With regards to the hemostatic effects of kyukikyogaito administration, this agent was considered ineffective when the extent of bleeding was unchanged and effective when bleeding decreased or disappeared.

Fisher's exact test and the Mann-Whitney  $U$  test were

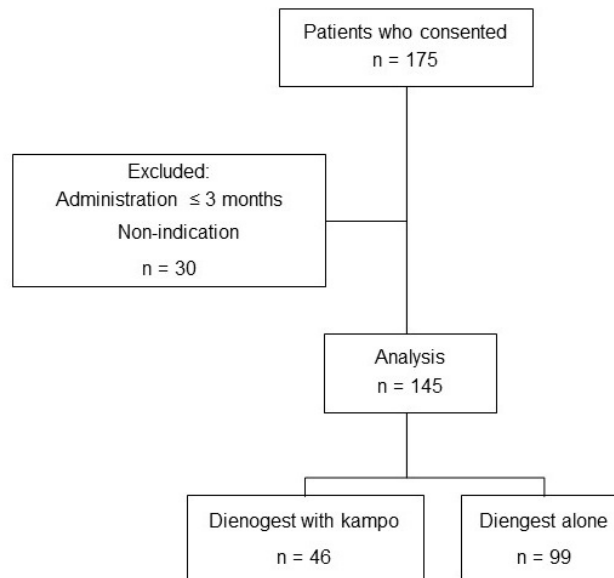


Figure 1. — Flowchart for patients treated with dienogest.

used for statistical analyses. All statistical analyses were performed using GraphPad Prism 6 version 6.05. The significance level was set at 5%.

## Results

The study included 145 patients treated with DNG. The clinical characteristics of these patients are shown in Table 1. Of the 145 patients treated with DNG, 116 (80.0%) had irregular bleeding. The clinical characteristics of patients with irregular bleeding in terms of their diagnosis, treatment and smoking status are shown in Table 2. No significant differences in the occurrence of irregular bleeding were observed according to the diagnosis, pretreatment with a GnRH agonist, or smoking status.

Table 3 shows the comparison between patients treated with DNG alone versus DNG plus kyukikyogaito in terms of their age, BMI, initial bleeding time, pretreatment with GnRH agonist and smoking status. No significant differences were observed between the two groups for any of these parameters.

The DNG treatment continuation rates (excluding pre-operative treatment patients, fertility treatment patients and menopause patients) were 62.3% (43/69) in the DNG alone group and 85.0% (34/40) in the DNG plus kyukikyogaito group. This difference was statistically significant ( $p = 0.016$ ).

Table 1. — Characteristics of patients with DNG treatment.

Demographics	n (%)
<b>Number of Patients</b>	145
Age *	39.8 ± 6.8 (20–54)
BMI *	22.2 ± 4.0 (15.1–35.9)
<b>Diagnosis</b>	
Endometriosis	78 (53.8)
Adenomyosis	16 (11.0)
Uterine fibroid with endometriosis and/or adenomyosis	51 (35.2)
<b>Initial bleeding time</b>	
1–3 months	92 (79.3)
≥ 4 months	24 (20.7)
<b>Extent of Bleeding</b>	
None	29 (20.0)
Spotting	13 (9.0)
Light	46 (31.7)
Medium	49 (33.8)
Heavy	8 (5.5)
<b>Treatment</b>	
Dienogest alone	110 (75.9)
GnRH agonist pre-treatment	35 (24.1)
<b>Smoking status</b>	
Non-smoker	116 (80.0)
Smoker	29 (20.0)
<b>Kampo medicine</b>	
No prescription	99 (68.3)
Kyukikyogaito prescription	46 (31.7)

\* Age in years and BMI in kg/m<sup>2</sup> are shown as mean ± SD (range).

Table 2. — Characteristics of patients with irregular bleeding.

Characteristics	Irregular bleeding n (%)	Odds ratio (95% CI)	p value
<b>Patients treated with dienogest</b>			
Total	116/145 (80.0)		
<b>Diagnosis</b>			
Endometriosis	59/78 (75.6)	1	
Adenomyosis	15/16 (93.8)	1.24 (0.57-2.71)	
Uterine fibroid with endometriosis and/or adenomyosis	42/51 (82.4)	1.09 (0.64-1.85)	
<b>Treatment</b>			
Dienogest	89/111 (80.2)	1.05 (0.59-1.88)	0.88
GnRH agonist pre-treatment	26/34 (76.5)		
<b>Smoking status</b>			
Non-smoker	91/116 (78.4)	0.95 (0.52-1.74)	0.88
Smoker	24/29 (82.8)		

Table 3. — Comparison between patients treated with dienogest alone or dienogest plus kyukikyogaito.

Demographics	Dienogest alone	Dienogest plus kyukikyogaito	p value
<b>Patients (n)</b>	99	46	
<b>Age *</b>	39.3 ± 7.0 (20–54)	40.7 ± 6.3 (24–50)	0.2
<b>BMI *</b>	22.3 ± 3.8 (16.2–35.9)	22.0 ± 4.6 (15.1–35.2)	0.28
<b>Initial bleeding time, n (%)</b>			
1–3 months	56 (80.0)	36 (78.3)	0.43
≥ 4 months	14 (20.0)	10 (21.7)	
<b>Treatment</b>			
Dienogest alone	72 (72.7)	38 (82.6)	0.22
GnRH agonist pre-treatment	27 (27.3)	8 (17.4)	
<b>Smoking status</b>			
Non-smoker	76 (76.8)	40 (87.0)	0.18
Smoker	23 (23.2)	6 (13.0)	

\* Age in years and BMI in kg/m<sup>2</sup> are shown as mean ± SD (range).

Table 4. — Effectiveness of kyukikyogaito among patients with irregular bleeding.

Demographics	Effective rate of kyukikyogaito, n (%)	Odds ratio (95% CI)
<b>Dienogest patients</b>		
Total	38/46 (82.6)	
<b>Diagnosis</b>		
Endometriosis	18/19 (94.7)	1
Adenomyosis	4/5 (80.0)	0.84 (0.20 to 3.65)
Uterine fibroid with endometriosis and/or adenomyosis	16/22 (72.7)	0.77 (0.31 to 1.91)
<b>Bleeding volume</b>		
Spotting	0	
Light	10/11 (90.9)	1
Medium	25/31 (80.6)	0.89 (0.32 to 2.43)
Heavy	3/4 (75.0)	0.83 (0.15 to 4.63)

The E2 levels at the third month of DNG treatment were 62.3 ± 70.3 pg/mL for patients without irregular bleeding and 66.5 ± 63.6 pg/mL for those with irregular bleeding ( $p = 0.39$ ). Furthermore, there were no significant differences in mean E2 levels between patients with different extents of bleeding, although it was difficult to elucidate whether the E2 level was a risk factor for heavy bleeding.

Overall, kyukikyogaito was effective in 82.6% (38/46) of patients with irregular bleeding. The effectiveness of kyukikyogaito according to diagnosis and extent of bleeding is shown in Table 4. No significant differences were observed between different diagnosis or bleeding groups, although sample sizes are small.

With regard to the change in hemoglobin level with ad-

ministration of kyukikyogaito, the ineffective group ( $n = 8$ ) had a pretreatment hemoglobin level of 13.2 g/dL and a post-treatment level of 13.0 g/dL ( $p = 0.62$ ). The effective group ( $n = 38$ ) had a pretreatment hemoglobin level of 12.9 g/dL and post-treatment level of 12.9 g/dL ( $p = 0.93$ ). Thus, no significant differences were observed between pre- and post-treatment hemoglobin levels in both the ineffective and effective kyukikyogaito groups.

## Discussion

The incidence of irregular bleeding in patients receiving DNG treatment was found here to be 80.0%, while initial bleeding occurred within 3 months from the first dose of DNG in 79.3% of patients. Genital bleeding with DNG is thought to arise from breakthrough bleeding in the pseudodecidua due to the pro-gestational effects of DNG [3]. Therefore, if irregular bleeding can be suppressed within 3 months of the first dose of DNG, it rarely occurs after that period.

With regard to the clinical diagnosis, irregular bleeding is more common in cases of endometriosis/uterine fibroids with adenomyosis and adenomyosis. Therefore, the authors believe that diseases associated with adenomyosis tend to cause irregular bleeding [7]. The reason why irregular bleeding occurs frequently in patients with adenomyosis has not yet been clarified. Several hypotheses have been put forward to explain the heavy menstrual flow associated with adenomyosis, including increased endometrial surface, altered PGE/PGF $2\alpha$  balance and hampered myometrial contractility [8].

With regard to treatment, no significant difference was noted in the frequency of irregular bleeding between patients who received DNG alone (80.2%) and those who received pretreatment with a GnRH agonist (76.5%). Kitawaki *et al.* [9] reported that pretreatment with a GnRH agonist decreased irregular bleeding during DNG administration. However, in the present study pre-treatment with a GnRH agonist appeared to have no effect on irregular bleeding.

The DNG treatment continuation rate was significantly higher in the DNG with kyukikyogaito group than in the DNG alone group. Irregular bleeding was suppressed by the administration of kyukikyogaito, thereby improving the DNG treatment continuation rate.

The overall efficacy of kyukikyogaito administration was 82.6%, indicating that it is beneficial during DNG treatment. Furthermore, kyukikyogaito showed the highest efficacy in patients with endometriosis (94.7%), followed by those with adenomyosis (80.1%) and uterine fibroid with endometriosis and/or adenomyosis (72.7%). Furthermore, kyukikyogaito showed higher efficacy in hemostasis as the extent of irregular bleeding was lower. Since kyukikyogaito can reduce irregular bleeding, it could help to improve the quality of life for women with endometriosis.

Kyukikyogaito is composed of JP Japanese Angelica root (4.0 g), JP Peony root (4.0 g), JP Rehmannia root

(5.0 g), and JP Cnidium rhizome (3.0 g), all of which have blood-enriching actions. In addition it contains JP Glycyrrhiza (3.0 g), which has harmonic actions, as well as JP Artemisia leaf (3.0 g) and donkey glue (3.0 g) that have hemostatic actions [10]. Artemisia leaf contains essential oils such as tannin, cineol, thujone, borneol, camphor, enzymes, polysaccharides, vitamins A, B1, B2, C, and K, as well as other components. Its medicinal effects include the promotion of blood circulation and hemostasis. It can also help improve poor blood circulation, irregular bleeding, menstrual abnormality and constipation. Artemisia leaf has been used for the hemostatic treatment of conditions such as incisional wounds since ancient times. The folk medical manual of the Edo period states that wormwood should be used for bleeding and trauma. In the scientific literature, the mechanism for the local hemostatic effect of Artemisia leaf is thought to be the contraction of tissues and blood vessels associated with the action of tannins [11, 12].

The components of donkey glue [13] include proteins in which collagen has been hydrolyzed into mixtures of various amino acids, as well as 27 kinds of minerals such as calcium, magnesium, iron and chondroitin. Its medicinal effects include the relief of menstrual pain, menstrual irregularity, and massive bleeding from the uterus. Gelatin itself has no intrinsic hemostatic effect and the primary hemostatic effect of collagen contained in gelatin is associated with local hemostasis [14]. In addition, gelatin has been used previously as a plasma substitute for blood transfusion. In 1894, Czerny *et al.* were the first to succeed with intravenous injection of gelatin in animals [15]. The adoption of gelatin for transfusion purposes in humans began in 1915 when Hogan used gelatin for the treatment of shock during World War I [16]. However, gelatin has the side effect of causing erythrocyte aggregation and hence its practical use was stopped. It has been reported that Artemisia leaf was used as a topical hemostatic agent and that donkey glue was used as a local hemostatic agent or substitute plasma preparation. However, the mechanism for hemostasis associated with oral kyukikyogaito that includes Artemisia leaf and donkey glue has not yet been clearly demonstrated. The authors expect that studies on the mechanisms relating to hemostasis of kyukikyogaito will be reported in the future.

The present study showed the benefits and effectiveness of kyukikyogaito, which is expected to have a high therapeutic effect as a hemostatic medicine. A limitation of this study was the sample size, with further large studies required to confirm the present results. Unlike Western medicine which involves a single component, Japanese herbal medicine is multicomponent and hence this limits the identification of active ingredients.

## Conclusion

Administration of kyukikyogaito, which includes *Artemisia* leaf and donkey glue, was effective in improving the DNG treatment continuation rate and reducing irregular bleeding associated with DNG administration. In future

work the authors plan to investigate other agents with hemostatic effects such as orengedokuto for the treatment of patients in whom kyukikyogaito was not effective.

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### Conflict of Interest

The authors declare no competing interests.

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