Original Article

Efficacy and safety of *daikenchuto* (TJ-100) in pregnant women with constipation

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**A R T I C L E   I N F O**

Keywords:
- constipation
- constipation assessment scale
- *daikenchuto*
- pregnancy
- trimester

**A B S T R A C T**

**Objective:** Constipation is common and a significant problem in pregnant women. The purpose of this study was to examine the efficacy and safety of *daikenchuto* in pregnant women with constipation.

**Material and methods:** This was a prospective study, and a total of 20 patients were registered between February 2010 and August 2012. The patients received 7.5 g/d of *daikenchuto* for 28 days from the day of registration. All enrolled patients were asked to complete the constipation assessment scale (CAS) every day. In addition, we measured the aspartate transaminase, alanine transaminase, blood urea nitrogen, and creatinine levels to assess the adverse effects of *daikenchuto*.

**Results:** The CAS scores were significantly lower at 28 days after *daikenchuto* treatment (*p* = 0.019), with a significant effect achieved on Day 1. The impact of the therapy was greatest in the second trimester (*p* = 0.043). No significant adverse effects of *daikenchuto* were observed, and the rates of preterm birth and pregnancy-induced hypertension were 10% and 5%, respectively, which are similar to previously reported values.

**Conclusion:** We herein demonstrated the efficacy and safety of *daikenchuto* in pregnant women with constipation. We hope that our findings will aid in the management of constipation in pregnant women.

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**Introduction**

Constipation is a significant problem in pregnant women and is often managed with a combination of stool softeners, laxatives, and dietary modifications (e.g. increased fiber intake) [1]. Although the frequency of stools is often improved with the above therapies, uncomfortable abdominal symptoms, such as abdominal distension and pain, often persist [2].

*Daikenchuto* (TJ-100), a traditional Japanese herbal medicine, is commonly used to treat adhesive bowel obstruction and chronic constipation [2,3]. This compound is composed of extract granules of Japanese pepper, processed ginger, ginseng radix, and maltose powder derived from rice. *Daikenchuto* extract powder (Tsumura & Co., Tokyo, Japan) is manufactured as an aqueous extract containing 2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng, and 88.9% maltose syrup powder. The main ingredients of *daikenchuto* are hydroxy-alpha-sanshool (Japanese pepper), 6-shogaol (processed ginger), and ginsenoside Rb1 (ginseng radix). Contamination studies have certified *daikenchuto* to be free of unexpected pharmaceutical ingredients, toxins, pesticides, microbes, and heavy metals.

Treatment with *daikenchuto* has been reported to be effective for postoperative ileus [4], irritable bowel syndrome [5], and constipation in both children and Parkinson's patients [6,7]. Recently, evidence has accumulated regarding the following mechanisms of action of *daikenchuto*: the activation of endogenous adrenomedullin in patients with Crohn's disease [8], anti-inflammatory effects [9], increased gastrointestinal motility [10], and the upregulation of the blood flow in the colon [11]. The clinical efficacy of *daikenchuto* is now well established; however, there are no reports regarding its efficacy or safety in pregnant women with constipation.

The purpose of this study was to examine the efficacy of *daikenchuto* in pregnant women with constipation. In addition, we performed maternal blood tests focused on the liver and renal functions during treatment and assessed the outcomes of pregnancy in order to evaluate the safety of *daikenchuto*.
Materials and methods

Patients

This was a prospective interventional one-arm study conducted with the aim of determining the efficacy and safety of daikenchuto in pregnant women between February 2010 and August 2012 at Nagoya University Hospital, Nagoya, Japan. We excluded the patients with previous abdominal or pelvic surgery and finally registered a total of 20 healthy pregnant women suffering with constipation during this period. The patients received 7.5 g/day of daikenchuto for 28 days from the day of registration. In addition, we measured the aspartate transaminase (ALT), alanine transaminase (AST), blood urea nitrogen (BUN), and creatinine levels before and after treatment in order to assess the adverse effects of daikenchuto. All patients provided their written informed consent to participate in this study, which was approved by the Ethics Committee of Nagoya University Hospital.

Maternal and neonatal data were extracted from the patients’ records, including maternal age, body mass index, gestational age at delivery, neonatal birth weight and sex, and umbilical pH at birth. Preterm delivery was defined as delivery at < 37 weeks of gestation. Pregnancy-induced hypertension was defined as the occurrence of gestational hypertension and proteinuria during pregnancy, with the reversal of these conditions after delivery. Gestational hypertension was defined as a systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg after 20 weeks of gestation in previously normotensive patients. Proteinuria was defined as a protein level above 300 mg on 24-hour urine collection.

Constipation assessment scale

The patients enrolled in this study were asked to complete the constipation assessment scale (CAS) every day. The CAS was introduced to determine whether an individual is experiencing constipation and assess the severity of the problem [12]. The scale consists of eight descriptors of constipation: (1) abdominal distension or bloating; (2) a change in the amount of gas passed rectally; (3) a reduced frequency of bowel movements; (4) liquid stools; (5) rectal fullness or pressure; (6) rectal pain during bowel movements; (7) small stools; (8) the inability to pass stool [12]. The patients were asked to rate whether the item is no problem, some problem, or a severe problem. No problem is scored as 0, some problem as 1, and severe problem is scored as 2. The patient was then asked to respond to each item, and the ratings are summed to obtain a total score, which ranges from 0, representing no problems with constipation, to 16, indicating severe constipation. Completing this scale takes less than 2 minutes on average.

Statistics

The data were entered into a spreadsheet (Excel; Microsoft Japan Co., Ltd., Tokyo, Japan), and SPSS was used for the data analysis (V.19.0; SPSS Japan Inc., Tokyo, Japan). The Wilcoxon signed-rank test was used to compare the CAS scores. In the box and whisker plot, the data are presented as the mean ± quartile deviation. A p-value of < 0.05 was considered to be significant.

Results

Maternal characteristics

The background characteristics of the patients are shown in Table 1. Aside from having constipation, all participants were healthy pregnant women. A total of six patients were in the first trimester (<14 weeks of gestation), eight patients were in the second trimester (14–27 weeks of gestation) and six patients were in the third trimester (> 28 weeks of gestation) at the time of registration. The rates of preterm birth and pregnancy-induced hypertension were 10% and 5%, respectively, which are similar to those reported [22] in pregnant Japanese women.

Effects of daikenchuto based on the CAS scores

We examined the CAS scores at before and after daikenchuto therapy (Figure 1). The CAS scores were significantly lower at 28 days after daikenchuto treatment (p = 0.019), indicating that daikenchuto significantly improves constipation in pregnant women. We then examined the CAS scores in each of the eight categories and found that abdominal distension or bloating, a reduced frequency of bowel movements and small stools each significantly improved after daikenchuto treatment (p = 0.013, 0.022, and 0.046, respectively).

Effects of daikenchuto based on the CAS scores in each trimester

We examined the CAS scores before and after daikenchuto therapy in each trimester (Figure 2). The CAS scores were significantly lower in the second trimester (p = 0.043); however, no significant differences were observed in the first and third trimesters (p = 0.357 and 0.273, respectively). Therefore, we concluded that daikenchuto is useful for treating constipation in pregnant women in the second trimester in particular.

Time course of the CAS scores

We examined the time course of the CAS scores, as shown in Figure 3. On Day 1 after the initiation of daikenchuto treatment, the CAS scores significantly improved (p = 0.002). Thereafter, the CAS scores did not differ significantly from those observed on Day 1. These results indicate that the effects of daikenchuto are noticed by patients the day after the start of treatment.

Evaluation of the safety of daikenchuto

We examined the AST, ALT, BUN, and creatinine levels before and after treatment. The mean levels of these parameters were as follows (before vs. after treatment): 16 IU/L versus 17 IU/L for ALT, 11 IU/L versus 12 IU/L for AST, 8.0 mg/dL versus 8.0 mg/dL for BUN, and 0.45 mg/dL versus 0.46 mg/dL for creatinine. No significant

Table 1

Maternal characteristics and outcomes of pregnancy.

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal background</td>
<td></td>
</tr>
<tr>
<td>Maternal age (y)</td>
<td>35.0 (21–41)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Maternal body mass index</td>
<td>21.6 (17.9–26.7)</td>
</tr>
<tr>
<td>Pregnancy outcomes</td>
<td></td>
</tr>
<tr>
<td>GA at delivery, weeks</td>
<td>38.0 (33–41)</td>
</tr>
<tr>
<td>Neonatal birth weight (g)</td>
<td>2730 (1906–3762)</td>
</tr>
<tr>
<td>Fetal growth SD</td>
<td>-0.1 (-1.8 to 1.4)</td>
</tr>
<tr>
<td>Male neonate</td>
<td>90 (45%)</td>
</tr>
<tr>
<td>Umbilical artery pH</td>
<td>7.33 (7.20–7.44)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Low birth weight infant (&lt; 2500 g)</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>

Data are presented as the mean (range) or n (%). BMI = body mass index; GA = gestational age; SD = standard deviation.
adverse effects of daikenchuto were observed, and no patients exhibited abnormal values of the above parameters. During the treatment period, the clinical courses of both the mothers and fetuses were uneventful in all cases.

Discussion

This is the first study of the efficacy of daikenchuto in pregnant women with constipation. Our results showed that daikenchuto significantly improves the symptoms of constipation, including abdominal distension or bloating, a reduced frequency of bowel movements and small stools among the eight categories included in the CAS. Daikenchuto has been reported to decrease the volume of bowel gas in both male and nonpregnant female patients\[2,13\], similar to the effect observed among pregnant women in the present study. Therefore, we recommend treatment with daikenchuto in pregnant women suffering from constipation, primarily that complicated with abdominal distension. We also examined the period from the initiation of daikenchuto therapy with respect to improvements in constipation and found that the CAS scores significantly improved on Day 1 after the initiation of daikenchuto treatment. These results indicate that the effects of daikenchuto are noticeable to patients within one day after the start of treatment. We believe that this information provides useful advice for patients.

Furthermore, we examined the efficacy of daikenchuto in each trimester and observed a significant in the second trimester only. Although the CAS scores had a tendency to improve in the third trimester, the difference was not significant. We speculate that the following reasons may account for this phenomenon. First, the progesterone levels in pregnant women increase slowly during the first and second trimesters and rapidly during the third trimester. The level of progesterone has been reported to be a possible etiological factor for constipation \[14\textendash16\]; therefore, the particular hormonal environment in the third trimester may explain the present results. Second, the uterus is largest in size in the third trimester, and bowel movements appear to be impaired due to compression of the uterus during this time. Lastly, the sample size was small in the present study. Among the six third trimester patients registered in this study, five exhibited improved CAS scores, while one showed disease exacerbation, with a decrease in the CAS score of 4\textendash9. This may explain the lack of power to demonstrate a statistically significant difference. Therefore, a larger study is warranted to elucidate this issue. Similarly, no significant effects were noted in the first trimester. In the first trimester, some patients suffer from hyperemesis and symptoms such as nausea, vomiting and decreased food intake. In such circumstances, as well as under conditions of a hypovolemic state, the effects of daikenchuto on constipation may be limited.

Figure 1. Constipation assessment scale (CAS) scores at before and after daikenchuto therapy. The CAS scores were significantly lower after daikenchuto treatment \((p = 0.019)\), indicating that daikenchuto significantly improves constipation in pregnant women. The mean CAS score before and after treatment was 10.0 and 5.0, respectively.

Figure 2. Constipation assessment scale (CAS) scores before and after daikenchuto therapy in each trimester. (A) First trimester, (B) second trimester and (C) third trimester. The CAS scores were significantly lower in the second trimester \((p = 0.043)\); however, no significant differences were observed in the first or third trimester \((p = 0.357 \text{ and } 0.273, \text{ respectively})\). The mean CAS scores before and after treatment were 10.0 and 8.0 in the first trimester, 10.0 and 3.0 in the second trimester, and 7.0 and 5.0 in the third trimester, respectively.
Therefore, we can conclude that there are no significant effects of *daikenchuto* therapy on the ALT, AST, BUN, or creatinine levels, and no patients exhibited any abnormal values of these parameters. We also examined the safety of *daikenchuto* in pregnant women in this study. In Japan, *daikenchuto* is used in pregnant women in Japan to treat constipation, and is covered by public insurance. According to the animal reproductive toxicology studies, *daikenchuto* has failed to demonstrate a risk to the fetus. Therefore we consider that *daikenchuto* can be regarded as safe for the first trimester of pregnancy. Moreover, *daikenchuto* has been reported to have no effect on either spontaneous contractions or the contractile response of the uterus [17] and is therefore considered to be safe for pregnant patients. In the present study, among the total 20 patients, the incidence of preterm birth and pregnancy-induced hypertension was 10% (2 patients) and 5% (1 patient), respectively. The prevalence of preterm birth and pregnancy-induced hypertension have been reported to be approximately 11% [18] and 7% [19,20], respectively, which are similar to our findings in this study. Furthermore, the clinical courses of both the mothers and fetuses during *daikenchuto* treatment were uneventful in this study. There were no significant effects on the ALT, AST, BUN, or creatinine levels, and no patients exhibited any abnormal values of these parameters. Therefore, we can conclude that there are no significant adverse effects of *daikenchuto* in pregnant women, despite the small number of cases in this analysis.

There are several limitations associated with this study. First, the number of cases was small. A larger study is thus required to overcome this limitation. Second, the CAS, which was employed in the present study to evaluate the symptoms of constipation, consists of a questionnaire, and the results are therefore subjective. However, the diagnosis of constipation is frequently made by the patient, and a symptom-based diagnosis of constipation is acceptable for most clinicians. Hence, the CAS method exhibits sufficient evidence of validity and reliability [12] and is potentially useful as a quick assessment tool for evaluating constipation. Third, we have no data regarding food intake and dietary patterns of the patients in this study. Intake of rice and pulses was negatively and that of confectioneries and bread positively associated with functional constipation among a population of young Japanese women [21]. Therefore the further study is required about this issue. In conclusion, this study is the first to assess the efficacy and safety of *daikenchuto* in pregnant women with constipation. Our findings demonstrated that the efficacy of *daikenchuto* therapy is greatest in the second trimester and that a significant effect is achieved the first day after the start of treatment. Although the present data may have some limitations, we hope that our findings will aid in the management of constipation in pregnant women.

**Conflicts of interest**

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**


