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Original Article

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

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ABSTRACT

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

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*.

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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 was 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.

	$n = 20$
Maternal background	
Maternal age (y)	35.0 (21–41)
Nulliparity	5 (25%)
Maternal body mass index	21.6 (17.9–26.7)
Pregnancy outcomes	
GA at delivery, weeks	38.0 (33–41)
Neonatal birth weight (g)	2730 (1906–3762)
Fetal growth SD	−0.1 (−1.8 to1.4)
Male neonate	90 (45%)
Umbilical artery pH	7.33 (7.20–7.44)
Preterm birth	2 (10%)
Pregnancy-induced hypertension	1 (5%)
Low birth weight infant (< 2500 g)	3 (15%)

Data are presented as the mean (range) or n (%).
BMI = body mass index; GA = gestational age; SD = standard deviation.