Comparison of the Effectiveness of Ginger and Vitamin B6 for Treatment of Nausea and Vomiting in Early Pregnancy: A Randomized Double-Blind Controlled Trial

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Objective: *To compare the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in pregnancy.*
Design: *Randomized double-blind controlled trial.*
Setting: *Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital.*
Material and Method: *One hundred and twenty-six pregnant women, with a gestational age of ≤ 16 weeks who had nausea and vomiting, required anti-emetics, had no medical complication, and were not hospitalized. Pregnant women were randomly allocated to receive either 650 mg of ginger or 25 mg of vitamin B6. They were given three times per day for 4 days. The degree of nausea and vomiting were assessed by three physical symptoms of Rhode's score (episodes of nausea, duration of nausea and number of vomits). These were recorded 24 hours before treatment for baseline and each subsequent day of treatment. Difference of baseline and post-treatment nausea vomiting scores were calculated for both groups during 4 days of treatment.*
Results: *One hundred and twenty-three women returned to follow-up. Ginger and vitamin B6 significantly reduced nausea and vomiting scores from 8.7 ± 2.2 to 5.4 ± 2.0 and 8.3 ± 2.5 to 5.7 ± 2.3 respectively, ($p < 0.05$). The mean score change after treatment with ginger was greater than with vitamin B6 (3.3 ± 1.5 versus 2.6 ± 1.3), ($p < 0.05$). There were some minor side effects in both groups 25.4% and 23.8% ($p = 0.795$) respectively, such as sedation, heartburn, arrhythmia.*
Conclusion: *Both ginger and vitamin B6 were effective for treatment of nausea and vomiting in pregnancy. Moreover, ginger was more effective than vitamin B6. Side effects from ginger were reported to be minor and did not need any treatment.*

Keywords: *Nausea, Vomiting, Pregnancy, Ginger, Vitamin B6*

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Nausea and vomiting are very common in early pregnancy[1], and frequently interfere with their family and routine work. The cause of nausea and vomiting in pregnant is still unknown. Therefore, wide varieties of treatment have been used empirically[2]. Prescription drugs are usually avoided in early pregnancy due to concern for potential teratogenic effect. There is increasing interest in alternative therapies. Vitamin B6 is frequently used as a first line treatment for pregnant women experiencing nausea and vomiting[3]. However, a large number of pregnant women require additional drugs, such as dimenhydrinate, promethazine[4,5]. These drugs may cause side effects such as sedation, mouth dryness, motor weakness, visual disturbance. Ginger has been used for thousands of years as Chinese traditional medicine for anti-emetic effect. Five trials[6-10] consistently showed that there are no significant adverse effects on pregnancy outcomes such as abor-

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tion, birth weight, gestational age, Apgar scores and congenital abnormalities. In one study[9], allocation of 125 mg ginger extracts (EV. EXT 35; equivalent to 1.5 gm for dried ginger) given 4 times daily for 4 days did not find any adverse effects of pregnancy outcomes including antenatal and post-partum hemorrhage. Ginger appeared to be more effective in reducing nausea and vomiting than placebo. Smith et al[10] showed that 1.05 g of ginger was equivalent to 75 mg of vitamin B6 daily in treating nausea and vomiting in pregnancy. The effectiveness of ginger may increase with the dose.

The purpose of the present study was to compare the effectiveness of 2 gm daily of ginger and the recommended dose (25 mg three times a day) of vitamin B6 to treat nausea and vomiting in early pregnancy.

Material and Method

The trial took place at the antenatal clinic in Bangkok Metropolitan Administration Medical College and Vajira Hospital (BMAMC&VH), between May 2005 and August 2005. The study was approved by the Ethics Committee for Research involving Human Subjects, BMAMC&VH. The target population was pregnant women at or before 16 weeks of gestation who had nausea with or without vomiting and required treatment. Subjects were excluded if they: 1) were hospitalized for hyperemesis gravidarum; 2) had taken other medications in the past week that might aggravate or alleviate nausea and vomiting such as iron tablets or anti-emetics; 3) were unable to take the medication as prescribed; 4) had other medical disorders such as hepatitis or gastrointestinal diseases that might manifest with nausea and vomiting; 5) had language or geographic barriers; 6) refused to participate in the trial.

All patients gave written informed consent before enrolling in the trial. Patients were randomly allocated to receive two 325 mg capsules of ginger or two 12.5 mg identical-looking capsules of vitamin B6 three times daily before meals for 4 days. Both groups did not take any other medication outside the trial. Patients were requested to take two randomized capsules immediately to confirm their ability to swallow the capsules. Patients were advised to divide their meals into frequent smaller meals with high carbohydrate and low fat. Patients were requested to record their symptoms at first enrollment 24 hours before treatment for the baseline score, then at noon of each subsequent day of treatment. Patients were requested to return the day after completing their medication to assess their responses to treatment. Those who did not return would be contacted by telephone.

Ginger and identical-looking vitamin B6 capsules were prepared by a pharmacist in a registered herbal factory. Briefly, fresh ginger root was chopped into small pieces, dried in sunlight and ground into powder. The powdered ginger was weighed and packed into a 325 mg capsule by a capsule machine. Ginger capsules were sterilized by Cobalt 60 gamma ray. Vitamin B6 tablets 25 mg were divided in half and packed into 12.5 mg per capsule, identical to the ginger capsules. Both ginger and vitamin B6 capsules were similarly packed in an envelope containing 24 capsules. The randomization of patients was done by using a table of random numbers with block of four to receive ginger or vitamin B6. The treatment code was concealed by placing the patient's assignments in sequence in sealed opaque envelopes that were drawn in ascending consecutive order. The codes were kept strictly confidential for blinding the physician and subjects and were broken at the end of the study.

The primary outcome was the change of nausea vomiting scores (mean of post treatment scores minus baseline scores). Nausea vomiting scores were assessed by three physical symptoms (episodes of nausea, duration of nausea and numbers of vomits) modified from full Rhode's score[11]. These scores could be used clinically to evaluate severity and change of nausea and vomiting in pregnancy. Lowest score was 3 and the highest score was 15 indicating severe nausea and vomiting. Data were analyzed by statistical program SPSS, stata/SE 7.0. The differences of quantitative data within the same subjects (pre and post-treatment) were analyzed by ANOVA with repeated measurement or paired t-test, and between the two groups by independent t-test. P-value of 0.05 was used to determine statistical significance. Descriptive statistics were summarized as mean with standard deviation and percentage. Other secondary outcome measures included the occurrence of side effects such as heart burn, arrhythmia, headache and sedation. Analysis was performed by excluding those who were lost to follow up.

The sample size was calculated using data from a pilot study of 15 cases treated with vitamin B6. Improvement of nausea vomiting was reported with the mean score change of 3.3 ± 1.89. The author calculated that if the score change of 30% was clinically important, the sample size of 57 subjects per group would be able to detect this difference with probability of two tailed type I error of 5% and type II error of 20%. To allow for a 10% dropout rate, a total sample of 63 per group was calculated.

Results

During the study period, 126 pregnant women who suited the criteria were enrolled in the present study. They were randomly allocated to receive ginger in 63 cases and vitamin B6 in 63 cases. Two cases (3.2%) in the ginger group and one case (1.6%) in the vitamin B6 group did not return to follow up. This left 61 cases in the ginger group and 62 cases in the vitamin B6 group. Baseline characteristics of those who were lost to follow up were similar to the main study cases. There were no differences in the baseline demographics characteristics (age, week of gestation, weight, height, parity, education, occupation, marital status and motion sickness) between the two groups as shown in Table 1.

Baseline nausea vomiting scores and post-treatment scores are shown in Table 2. Baseline of nausea vomiting score in the ginger and vitamin B6 groups was 8.7 ± 2.2 and 8.3 ± 2.5, respectively. In the ginger group, nausea vomiting scores on day1 to day 4 were 6.8 ± 2.3, 5.9 ± 2.4, 4.9 ± 2.1, 3.9 ± 1.2, respectively and average post treatment score was 5.4 ± 2.0. In the vitamin B6 group, nausea vomiting scores on day 1 to day 4 were 6.9 ± 2.8, 5.7 ± 2.5, 5.1 ± 2.4, 4.8 ± 2.2, respectively and average post treatment score was 5.7 ± 2.3. Comparing baseline scores and post treatment scores in the same group, both ginger and vitamin B6 improved nausea vomiting scores from baseline. When comparing the average score change from baseline, the ginger group was 3.3 ± 1.5 and the vitamin B6 group was 2.6 ± 1.3. Both of these were significantly different ($p < 0.05$), as shown in Table 3. Moreover, the average score change in the ginger group was more than in the vitamin B6 group (3.3 ± 1.5 versus 2.6 ± 1.3), and was statistically significant ($p < 0.05$, 95%CI -1.14, -0.17). Each day, there were significant differences in the score change of the ginger group compared to the vitamin B6 group; on day 1 (1.8 ± 1.5 versus 1.3 ± 1.2), day 3 (3.8 ± 1.9 versus 3.2 ± 1.5) and day 4 (4.7 ± 1.8 versus 3.5 ± 1.5) ($p < 0.05$).

Table 1. Baseline characteristics

Characteristics	Ginger (n = 63)	Vitamin B6 (n = 63)
Age		
mean ± SD (year)	23.8±5.1	24.4±5.3
Gestational age		
mean ± SD (week)	12±2	11±2
Weight		
mean ± SD (kg)	51.6±5.4	54.4±11
Height		
mean ± SD (cm)	156.7±5.3	157.1±5.5
Parity (%)		
0	52.4%	57.1%
1	38.1%	34.9%
2	7.9%	6.3%
3	1.6%	1.6%
Education (%)		
No	1.6%	1.6%
Primary school	52.4%	50.8%
Secondary school	38.1%	38.1%
Diploma	6.3%	9.5%
University	1.6%	0%
Occupation (%)		
Housewife	25.4%	23.8%
Employee	65.1%	68.3%
Trade	6.3%	6.3%
Business	3.2%	1.6%
Marital status (%)		
Marriage	96.8%	100%
Widow	3.2%	0%
Motion sickness (%)		
No	81.0%	79.5%
Yes	19.0%	20.6%

Table 2. Baseline and post-treatment of nausea vomiting scores

Ginger (n = 61) Nausea vomiting score (mean ± SD)			Vitamin B6 (n = 62) Nausea vomiting score (mean ± SD)		
Baseline	Post-treatment	p-value*	Baseline	Post -treatment	p-value*
8.7±2.2	Day1: 6.8±2.3	0.008	8.3±2.5	Day1: 6.9±2.8	0.009
	Day2: 5.9±2.4	0.005		Day2: 5.7±2.5	0.006
	Day3: 4.9±2.1	<0.001		Day3: 5.1±2.4	<0.001
	Day4: 3.9±1.2	<0.001		Day4: 4.8±2.2	<0.001
	Average: 5.4±2.0	<0.001		Average: 5.7±2.3	<0.001

* Paired t-tests: $p < 0.05$

Table 3. Change of nausea vomiting scores

	Change of nausea vomiting score (baseline minus post-treatment score ± SD)		
	Ginger	Vitamin B6	p-value*
Day 1	1.8±1.5	1.3±1.2	0.043
Day 2	2.8±1.7	2.6±1.6	0.391
Day 3	3.8±1.9	3.2±1.5	0.043
Day 4	4.7±1.8	3.5±1.5	0.008
Average	3.3±1.5	2.6±1.3	0.042

* Independent t-test: significance $p < 0.05$

Comparing side effects of both groups, the ginger group was 16 of 61 patients (25.4%) and the vitamin B6 group was 15 of 62 patients (23.8%) and was not statistically significant (p value = 0.795). In the ginger group, occurrence of heartburn was 8 of 61 (12.7%), sedation was 7 of 61 (11.1%) and arrhythmia was 1 of 61 (1.6%). In the vitamin B6 group, occurrence of heartburn was 2 of 62 (3.2%), sedation was 11 of 62 (17.5%), and headache was 2 of 62 (3.1%). Side effects were reported to be minor and did not preclude them from taking their prescribed medication.

On follow-up visits, 58 of 61 patients (95.1%) in the ginger group and 60 of 62 patients (96.8%) in the vitamin B6 group had 100% compliance. Four patients (6.3%) in the ginger group correctly identified what they were taking, but none in the vitamin B6 group. One patient (1.6%) in the ginger and four patients (6.3%) in the vitamin B6 group took other medications during this trial because four patients had a common cold and one had headache. Three of 61 patients (4.9%) in the ginger group and 4 of 62 patients (6.5%) in vitamin B6 group took other ginger products.

Discussion

Nausea and vomiting in early pregnancy remain a significant public health problem that has physiological, emotional, social, and economic consequences to women, their families and society. Many medications and alternative therapies are currently available for the treatment of morning sickness. Vitamin B6 is used as a first line treatment for morning sickness. Ginger has been evaluated in many controlled trials for the treatment of morning sickness[6-10]. Ginger is an effective option for treatment of nausea and vomiting in early pregnancy. There are trials that compare the effectiveness of ginger to vitamin B6[8,10].

In the present study, there were no differences among both groups with respect to the patient's demographics data and compliance. Both ginger and vitamin B6 significantly reduced nausea and vomiting. Average score change from baseline in the ginger group (1.95 gm daily) was 3.3 ± 1.5 and in the vitamin B6 group (75 mg daily) was 2.6 ± 1.3. Considering difference in both groups, the average score change in the ginger group was 0.7 more than the vitamin B6 group, with statistical significance ($p < 0.05$, 95%CI -1.14, -0.17). At the end of the trial, the use of other antiemetics was reported by 7 of 12 patients (5.7%).

Sripramote et al[8] showed both ginger (1.5 gm daily) and vitamin B6 (30 mg daily) significantly reduced the degree of nausea and number of vomiting episodes. Comparing the efficacy, there was no significant difference between ginger and vitamin B6 for the treatment of nausea and vomiting during pregnancy. Smith et al[10] showed ginger (1.05 gm daily) was equivalent to vitamin B6 (75 mg daily) in reducing nausea (mean difference 0.2, 90%CI of -0.3, 0.8), vomiting (mean difference 0.5, 90%CI of 0.0, 0.9) in early pregnancy. However, the present study reported the previous use of antiemetics, ginger or vitamin B6 did not exclude entry to the trial. At the end of the intervention, the use of other antiemetics was reported by 51 women (20%).

In the present study, the authors used daily dosage of vitamin B6. This was 75 mg daily and was equal to Smith et al's trial. Currently, this dosage was routinely recommended for treatment of nausea and vomiting in pregnancy[12,13]. Dosage of ginger was increased to 1.95 gm daily that is the proven safety dose[9] and may be more effective than a dose of 1.05 gm daily. The powdered ginger was packed into 325 mg capsule because 650 mg capsule are hard to swallow. The 25 mg vitamin B6 tablets were divided in half and packed into 12.5 mg capsules. Each patient was to receive two identical capsules and equal dose. The authors chose a study period of 4 days because previous studies[6,7,9] showed that the effect of ginger was evident within a few days of treatment and too long a period would result only in a higher rate of subject noncompliance and loss to follow up.

The present study is consistent with other trials showing that ginger is an effective treatment for nausea and vomiting in pregnancy. Moreover, effectiveness of ginger was better than vitamin B6 as it significantly reduced nausea and vomiting symptom during the four days of treatment. The mechanism of the action of ginger on nausea and vomiting has not been fully identified although several hypotheses

have been proposed. It has been reported that symptoms of nausea and vomiting during pregnancy improved in direct correlation to the improvement in pregnancy induced gastric dysrhythmias[14]. Therefore, ginger-induced reduction of pregnancy symptoms may be due to a direct effect of the drug on the gastrointestinal tract.

The occurrence of side effects from ginger was reported to be minor during the four day period of treatment. However, the short duration of treatment periods and small number of patients may have been insufficient to test properly the safety of the ginger with regard to pregnancy outcomes. Further studies should be done in a multicenter, with a large number of patients to produce a definite statement on the safety of ginger in pregnancy and accompanied by long term follow-up to detect uncommon complications such as congenital anomalies.

In conclusion of the present study, both ginger and vitamin B6 were effective for treatment of nausea and vomiting in early pregnancy. Moreover, ginger was more effective than vitamin B6. The side effects from ginger were reported to be minor and did not need any treatment.

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เปรียบเทียบประสิทธิผลระหว่างขิงกับวิตามินบี 6 ในการรักษาอาการคลื่นไส้อาเจียนในสตรีตั้งครรภ์ระยะแรก โดยการทดลองปกปิดแบบสุ่ม

พรดี จิตธรรมมา, เกษม แก้วเกียรติคุณ, บุษบา วิริยะสิริเวช

วัตถุประสงค์: *เปรียบเทียบประสิทธิผลระหว่างขิงกับวิตามินบี 6 ในการรักษาอาการคลื่นไส้อาเจียนในสตรีตั้งครรภ์ระยะแรก*

ชนิดของการวิจัย: *วิจัยเชิงทดลองแบบ Randomized double-blind controlled trial*

สถานที่ทำการวิจัย: *ภาควิชาสูติศาสตร์-นรีเวชวิทยา วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล*

วัสดุและวิธีการ: *สตรีตั้งครรภ์อายุครรภ์น้อยกว่าหรือเท่ากับ 16 สัปดาห์ ที่มีอาการคลื่นไส้อาเจียนมีความต้องการยาแก้คลื่นไส้อาเจียน แต่ไม่รุนแรงจนต้องนอนโรงพยาบาล ไม่มีโรคแทรกซ้อนทางอายุรกรรม แบ่งกลุ่มสตรีตั้งครรภ์เป็น 2 กลุ่ม แต่ละกลุ่มได้รับขิงขนาด 650 มิลลิกรัม หรือวิตามินบี 6 ขนาด 25 มิลลิกรัม ให้รับประทานวันละ 3 ครั้ง ระยะเวลา 4 วัน ระดับความรุนแรงของอาการคลื่นไส้อาเจียนประเมินจาก 3 อาการของ Rhode's score (จำนวนครั้งของอาการคลื่นไส้ ระยะเวลาของอาการคลื่นไส้ และจำนวนครั้งที่อาเจียน) ประเมินช่วง 24 ชั่วโมงก่อนได้รับยาเป็นคะแนนพื้นฐานและคะแนนหลังได้รับยาในแต่ละวัน เปรียบเทียบความแตกต่างคะแนนก่อนและหลังได้รับยาทั้งสองกลุ่ม*

ผลการศึกษา: *สตรีตั้งครรภ์จำนวน 123 คนกลับมาตรวจตามนัด ขิงและวิตามินบี 6 สามารถลดอาการคลื่นไส้อาเจียนได้อย่างมีนัยสำคัญ คะแนนจาก 8.7 $\pm$ 2.2 เหลือ 5.4 $\pm$ 2.0 และ 8.3 $\pm$ 2.5 เหลือ 5.7 $\pm$ 2.3 ตามลำดับ, ($p < 0.05$) สตรีกลุ่มที่ได้รับขิง คะแนนเปลี่ยนแปลงหลังการรักษามากกว่าได้รับวิตามินบี 6 (3.3 $\pm$ 1.5 เปรียบเทียบกับ 2.6 $\pm$ 1.3), ($p < 0.05$) อาการข้างเคียงที่เกิดขึ้นขณะได้รับขิงและวิตามินบี 6 คือ แสบร้อนในอก หัวใจเต้นผิดปกติ ง่วงซึม ซึ่งไม่จำเป็นต้องได้รับการรักษา*

สรุป: *ทั้งขิงและวิตามินบี 6 สามารถลดอาการคลื่นไส้อาเจียนในสตรีตั้งครรภ์ระยะแรกและขิงมีประสิทธิผลมากกว่าวิตามินบี 6 ในการลดอาการคลื่นไส้อาเจียน อย่างมีนัยสำคัญทางสถิติ*