Vitamin B6 Is Effective Therapy for Nausea and Vomiting of Pregnancy: A Randomized, Double-Blind Placebo-Controlled Study

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Fifty-nine women completed a randomized, double-blind placebo-controlled study of pyridoxine hydrochloride (vitamin B6) for the treatment of nausea and vomiting of pregnancy. Thirty-one patients received vitamin B6, 25-mg tablets orally every 8 hours for 72 hours, and 28 patients received placebo in the same regimen. Patients were categorized according to the presence of vomiting: severe nausea (score greater than 7) or mild to moderate nausea (score of 7 or less). The severity of nausea (as graded on a visual analogue scale of 1–10 cm) and the number of patients with vomiting over a 72-hour period were used to evaluate response to therapy. Twelve of 31 patients in the vitamin B6 group had a pre-treatment nausea score greater than 7 (severe) (mean 8.2 ± 0.8), as did ten of 28 patients in the placebo group (mean 8.7 ± 0.9) (not significant). Following therapy, there was a significant difference in the mean "difference in nausea" score (ie, baseline − post-therapy nausea) between patients with severe nausea receiving vitamin B6 (mean 4.3 ± 2.1) and placebo (mean 1.8 ± 2.2) ($P <$ .01). In patients with mild to moderate nausea and in the group as a whole, no significant difference between treatment and placebo was observed. Fifteen of 31 vitamin B6-treated patients had vomiting before therapy, compared with ten of 28 in the placebo group (not significant). At the completion of 3 days of therapy, only eight of 31 patients in the vitamin B6 group had any vomiting, compared with 15 of 28 patients in the placebo group ($P <$ .05). The adjusted odds ratio for emesis in the treatment versus placebo groups, stratified by the presence or absence of pre-treatment emesis, was 0.1156 ($P <$ .005). In conclusion, the mean "difference in nausea" score in patients with severe nausea and the total number of patients with vomiting were significantly reduced following vitamin B6 therapy. *(Obstet Gynecol 78:33, 1991)*

Nausea and vomiting are common and annoying symptoms often observed during the first 16 weeks of pregnancy.[1] Several uncontrolled studies in the 1940s suggested efficacy from the use of pyridoxine (vitamin B6) for the treatment of nausea and vomiting of pregnancy.[2–6] However, in 1979, the American Medical Association Council on Drugs stated that there was no solid evidence that vitamin B6 is effective against nausea.[7]

The purpose of this study was to evaluate in a randomized, double-blind placebo-controlled manner the efficacy of vitamin B6 for the treatment of nausea and vomiting of pregnancy.

Materials and Methods

The study was approved by the Institutional Review Board of The University of Iowa Hospitals and Clinics. Between July 1, 1989 and August 1, 1990, 74 patients consented to participate in a double-blind, randomized placebo-controlled study of vitamin B6 for the treatment of nausea and vomiting of pregnancy.

Patients were recruited from the general obstetric clinic by care-providing physicians and nurses. All participants underwent a general physical examination and routine obstetric evaluation. Screening evaluation included a complete history, urinalysis, hepatitis B surface antigen test, and ultrasonography to establish dates and viability. We excluded any patients with another medical condition that might manifest itself with nausea and vomiting or patients requiring hospitalization. The patients gave written informed consent to be randomized by a table of random numbers into two groups.

Patients in the vitamin B6 group received nine 25-mg tablets of pyridoxine hydrochloride, to be taken orally one every 8 hours starting the following morning. They were given instructions to take the medication between 6–8 AM, 2–4 PM, and 10–12 PM for 72 hours.

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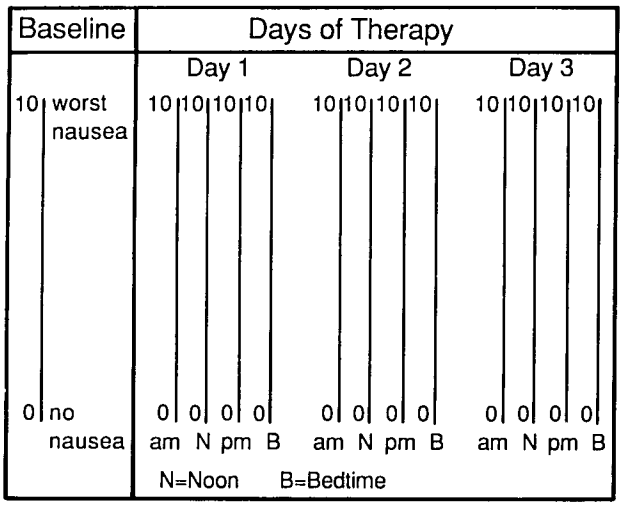

Figure 1. Visual analogue scale for grading nausea.

Patients in the placebo group received identical-appearing tablets to be taken in the same regimen. All individuals involved in the study except for the pharmacist were blinded as to the nature of the medication. The patients were also advised to divide their meals into frequent small ones rich in carbohydrates and low in fat.

We used a 10-cm unmarked visual analogue scale, anchored with 0 = no nausea and 10 = worst possible nausea, to grade the severity of nausea (Figure 1). Patients rated their nausea by marking this linear scale at the corresponding severity four times daily (AM, noon, PM, bedtime). The first documentation, recorded on the initial visit, reflected nausea over the last 24 hours. Along with grading nausea, all patients recorded the number of episodes of emesis for the 24 hours before their initial visit and on each subsequent day.

After the completion of therapy, the markings on each of the analogue scales were measured in centimeters, thus obtaining an objective measurement of the severity of nausea at different times of the day. An average daily nausea score was then calculated and the mean nausea score for the 3 days of therapy obtained. Before data analysis, we arbitrarily divided the patients into two subgroups according to the severity of their nausea. Patients with a nausea score of greater than 7 were in the severe nausea subgroup, and those with scores less than or equal to 7 were categorized in the mild to moderate nausea subgroup. These two subgroups were then compared. The number of patients with vomiting before and after therapy was also compared. Complete absence of emesis was considered a therapeutic success.

Statistical analysis employed the Student t test and χ^2 where applicable. Stratified analysis using the Mantel-Haenszel χ^2 was performed to evaluate the number of patients with vomiting.

Table 1. Group Characteristics

	Vitamin B6	Placebo	P
N	31	28	
Age (y)	29.4 ± 5.6	28.1 ± 5.3	NS
Range	19–42	16–37	
Gestation (wk)	9.3 ± 2.4	9.7 ± 3.0	NS
Range	6.0–15.5	6.0–19.0	
Median	9.0	9.0	
Parous	21 (68%)	13 (46%)	NS

NS = not significant.

Results

Seventy-four patients seen in the regular obstetric outpatient clinic at The University of Iowa Hospitals and Clinics consented to participate in this study. Fifty-nine women completed the protocol, 31 patients in the vitamin B6 group and 28 in the placebo group. Of the 15 who failed to complete the study, seven forgot to take the assigned medication, three decided to decline the protocol once at home, and five were lost to follow-up.

There were no statistical differences in maternal age, gestational age, or parity at entry to the study (Table 1).

There were 12 patients (39%) in the vitamin B6 group and ten (36%) in the placebo group with a mean baseline nausea score of greater than 7 on the scale of 1–10 cm (severe subgroup). All other patients were categorized in the mild to moderate nausea subgroup. Table 2 presents the mean "difference in nausea"

Table 2. Mean Scores for "Difference in Nausea" Between Baseline and Post-Therapy in Various Groups

Nausea	Vitamin B6	Placebo	P
Mean pre-therapy score			
All patients			
N	31	28	
Mean ± SEM	6.4 ± 1.8	6.6 ± 1.9	NS
Severe			
N	12	10	
Mean ± SEM	8.2 ± 0.8	8.7 ± 0.9	NS
Mild to moderate			
N	19	18	
Mean ± SEM	5.2 ± 1.3	5.3 ± 1.6	NS
Mean difference in nausea (baseline − post-therapy)			
All patients	2.9 ± 2.4	1.9 ± 2.0	NS
Mild to moderate	2.0 ± 2.1	2.2 ± 2.0	NS
Severe	4.3 ± 2.1	1.8 ± 2.2	<.01

NS = not significant; SEM = standard error of the mean.

Table 3. Number of Patients With Emesis

	Vitamin B6	Placebo	*P*
All nausea patients (*N*)	31	28	
Emesis			
Baseline	15 (48%)	10 (36%)	NS
Post-therapy	8 (26%)	15 (54%)	<.05
Severe nausea patients (*N*)	12	10	
Emesis			
Baseline	7 (58%)	6 (60%)	NS
Post-therapy	3 (25%)	7 (70%)	<.05

NS = not significant.

score, calculated as the baseline minus the post-therapy nausea score, in all patients and in both the severe nausea and mild to moderate nausea subgroups. A significant improvement ($P < .01$) in the mean "difference in nausea" score was observed after therapy in the severe nausea subgroup on vitamin B6. No significant change in this score was seen in the mild to moderate nausea subgroup or in the group of all patients. Of the 12 patients with severe nausea in the vitamin B6 group, only one continued to have severe nausea after therapy, compared with five of ten in the placebo group ($P < .05$).

Table 3 presents the number of patients with vomiting before and after therapy. We noted a significant improvement in the total group ($P < .05$) and in the severe nausea subgroup ($P < .05$). Table 4 summarizes the stratified analysis given the presence or absence of pre-treatment emesis. The crude odds ratio for emesis versus no emesis in the treatment versus placebo groups was 0.3014, with a 95% confidence interval of 0.1018–0.8926, which is significant at $P < .05$. When the analysis was stratified by pre-treatment emesis status, the adjusted odds ratio was 0.1156, with a 95% confidence interval of 0.0268–0.4993 at $P < .005$. In the severe nausea subgroup, the crude odds ratio for emesis in the treatment versus placebo groups was 0.037, with a 95% confidence interval of 0.0042–0.3238. This is significant at $P < .005$. Stratified analysis in the severe nausea subgroup gave a similar P value, but small numbers in each cell precluded calculation of the adjusted odds ratio.

Table 4. Patients Stratified by Baseline and Final Vomiting Status

Baseline emesis	Final outcome	Vitamin B6	Placebo
All nausea patients*			
Yes	Emesis	8	8
	No emesis	7	2
No	Emesis	0	7
	No emesis	16	11
Severe nausea patients†			
Yes	Emesis	3	6
	No emesis	4	0
No	Emesis	0	3
	No emesis	5	1

* Adjusted odds ratio 0.1156 ($P < .005$).
† $P < .05$.

Discussion

The incidence of nausea and vomiting in pregnancy is high. Koh et al[8] reported an incidence of 45–55%. Other authors[1,9,10] have demonstrated a prevalence of up to 89.4%, although only about 10% of women require medication for this symptom. The etiology of nausea and vomiting of pregnancy is unknown, and it is likely that more than one mechanism is involved.

Pyridoxine (vitamin B6) is a water-soluble B complex vitamin that is an essential coenzyme in the metabolism of amino acids, carbohydrates, and lipids.[11] The requirements for pyridoxine are increased during pregnancy, but low serum concentrations are not normally seen until the second and third trimesters.[12] Pyridoxine deficiency without clinical symptoms is common during pregnancy,[13] and there is no relationship between the biochemical indicators of vitamin B6 status and the incidence or degree of morning sickness in pregnant women.[14]

The first use of pyridoxine for severe nausea and vomiting of pregnancy was reported by Willis et al in 1942.[2] In an uncontrolled study, they used parenteral vitamin B1 and B6 to treat nausea, with almost complete relief. Several other similarly uncontrolled studies in the same decade suggested efficacy from the use of vitamin B6,[3–6,15] but no controlled trials have been published. Pyridoxine was originally included in the formulation of Bendectin (10 mg of doxylamine and 10 mg of pyridoxine) for the control of nausea and vomiting in pregnancy, which was the only preparation approved by the Food and Drug Administration for this indication. In 1959, Geiger et al[16] showed a statistical difference between Bendectin and placebo in a double-blind study of the treatment of nausea and vomiting of pregnancy. The available evidence does not support a teratogenic risk from ingestion of vitamin B6 during pregnancy.[17]

Nausea is a subjective symptom that is difficult to quantify. We elected to use a visual analogue scale from which we extrapolated the severity of nausea in centimeters and thus obtained an objective measurement that we were able to analyze statistically. Our results showed a significant improvement ($P < .01$) in nausea in patients in the severe nausea subgroup, who had nausea scores greater than 7. When we compared the total number of patients with any vomiting before

and after vitamin B6 therapy, there was also a significant improvement ($P < .005$).

The management of pregnant women complaining of nausea and vomiting must include reassurance of a good prognosis, because symptoms nearly always improve as pregnancy advances. Dividing food intake into frequent small meals, rich in carbohydrates and low in fat, may also be helpful in reducing symptoms. Iron tablets are associated with a high incidence of nausea as a side effect and should be avoided in patients with nausea.[18]

In this study, oral vitamin B6 at a dosage of 25 mg every 8 hours did not improve symptoms in patients with mild to moderate nausea. However, it significantly improved nausea in those pregnant women complaining of severe nausea and significantly reduced vomiting in all patients.

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