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Ginger treatment of hyperemesis gravidarum

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Summary

Thirty women participated in a double-blind randomized cross-over trial of the efficacy of a natural product, the powdered root of ginger (*Zingiber officinale*), and placebo in hyperemesis gravidarum. Three patients had to be withdrawn. Each woman swallowed capsules containing either 250 mg ginger or lactose q.i.d. during the first 4 days of the treatment period. Interrupted by a 2 days wash-out period the alternative medication was given in the second 4-day period. The severity and relief of symptoms before and after each period were evaluated by two scoring systems. The scores were used for statistical analyses of possible differences. Subjectively assessed, 19 women (70.4%) stated preference to the period in which ginger, as was later disclosed, had been given ($P = 0.003$). More objectively assessed by relief scores a significantly greater relief of the symptoms was found after ginger treatment compared to placebo ($P = 0.035$). No side effects were observed. The possible mutagenic and antimutagenic characters of ginger reported in a study of *E. coli* have not been evaluated with respect to any significance in humans. Powdered root of ginger in daily doses of 1 g during 4 days was better than placebo in diminishing or eliminating the symptoms of hyperemesis gravidarum.

Ginger; Zingiber officinale; Hyperemesis gravidarum

Introduction

Nausea and vomiting (emesis) are frequent features in pregnancy, complicating up to 50% of normal, singleton pregnancies. The more severe condition, hyperemesis gravidarum, is ill-defined. In this present study hyperemesis was defined as vomiting occurring during pregnancy, appearing for the first time before 20th week of gestation, and of such severity as to require the patient's admission to hospital [1]. The rare, almost intractable condition of pernicious hyperemesis with extreme disturbances of nutrition and electrolyte balance was not seen. Hyperemesis occurs in approximately 0.3% of pregnancies. It may still be accompanied by serious complications [2].

The etiology of hyperemesis gravidarum is unknown. The possible etiologic theories have been of endocrine, metabolic, allergic, psychosomatic or neurotic nature [1]. A wide variety of therapies have been suggested over the years. At present, the therapeutic regime consists mainly of correction for loss of fluids and electrolytes supplied with an

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antiemetic drug. This is often unable to relieve more than morning sickness [1] and alternative treatment is of interest.

There is a resemblance of the gastrointestinal symptoms in motion sickness and hyperemesis. A report demonstrated the effects of ginger, as the powdered rhizome of *Zingiber officinale*, on the symptoms of motion sickness provoked in a revolving chair with a vertical component added [3]. *Z. officinale* was superior not only to placebo but to dimenhydrinate (an antihistamine 'Dramine', U.S.) in reducing motion sickness. This inspired to the present study.

Patients and Methods

Patients

The patients were recruited among 6700 pregnant women delivering in the department over a period of 26 months, ending April 1988. The last patient studied delivered in November 1988. Consecutively, 30 pregnant women admitted to the hospital with hyperemesis before the 20th week of gestation and in whom the symptoms persisted after 2 days participated in the trial giving written informed consent. At this time the severity of the hyperemesis was assessed by a scoring system evaluating the degree of nausea, vomiting, and weight loss. Acetonuria and an eventual disturbance of the hematocrit value were also taken into consideration (Table I).

Besides the scoring system, Table I shows how the patients were distributed according to symptoms after they had been admitted to hospital for 2 days. The severity of the hyperemesis was assessed by the same scoring system prior to the second treatment period. The severity score served the purpose of objectifying the symptoms of hyperemesis. Furthermore, a significant reduction in the second score may indicate a carry-over effect of an active substance in the first treatment period.

The first severity score should mount up 10 points or more for including the patient. Their condition should allow oral intake of capsules. Other antiemetic medication was withdrawn, but parenteral fluids (dextrose, dextrose-saline) were allowed to be continued. Patients No. 22, 27 and 28 had had an antiemetic for a few days before the trial. Patients No. 1, 6, 9, and 15 received some intravenous fluid during the first treatment period. Pregnant women in whom gastrointestinal symp-

TABLE I

Data on the participating women, the scoring system of the severity of hyperemesis [4], and the distribution of the patients on the items of the severity score. Patients No. 1–14 received ginger capsules and patients No. 15–27 a placebo during treatment period I

	Scores	Data and distribution of patients	
		Nos. 1–14	Nos. 15–27
Age, years, mean (range)		27.1 (20–39)	25.6 (18–36)
Gravida, No., mean (range)		2.6 (1–6)	2.5 (1–7)
Gestational week, mean (range)		11.0 (7–17)	10.8 (7–16)
Severity score			
Degree of nausea			
Morning sickness only	1	1	0
More episodes of nausea through the day	2	3	4
Constant nausea	3	10	9
Duration of vomiting (days)			
≤ 5	1	0	1
6–7	2	4	1
> 7	3	10	11
Number of vomiting attacks per day			
2–3	1	1	3
4–6	2	7	7
7–9	5	3	3
≥ 10	7	3	0
Weight loss (kg)			
< 2	2	3	1
2–4	4	6	6
≥ 5	6	5	6
Acetonuria			
Absent	0	10	8
Positive	1	3	3
Strongly positive	2	1	2
Dehydration			
Hematocrit ≤ 0.45	0	13	12
Hematocrit 0.45–0.50	1	1	1
Hematocrit > 0.50	2	0	0

toms might have originated from gallbladder or liver disease, duodenal ulcer, pancreatitis etc. were excluded from the study. The 2 days of observation allowed eventual exclusion from the study.

During the study period, three patients had to be excluded: Two (code No. 7 and 10) did not accomplish the intake of capsules according to the study protocol and one (code No. 20) had a gallstone diagnosed during the trial. Thus the study comprised 27 women.

Methods

The study design was a double-blind randomized cross-over trial. A flow sheet of the trial is given in Table II. All patients received capsules containing ginger as powdered root of *Zingiber officinale* (250 mg) or lactose (250 mg) q.i.d. prepared by the dispensary of the hospital which also randomized the packages. The capsules were swallowed totally. As each woman received either ginger or placebo during the first treatment period and vice versa during the second she became her own control.

For the evaluation of an effect of treatment, a scoring system for symptom relief was applied (Table III). In contrast to the severity score, the relief score included a subjective assessment in the patient's opinion about the treatment after each period. The severity and relief scoring systems were adopted with minor modifications from a report on hyperemesis and ACTH [4].

The code remained sealed until the study had been completed.

TABLE II

Flow sheet of the double-blind randomized cross-over trial in treatment of hyperemesis gravidarum by ginger (the powdered root of *Zingiber officinale*) versus placebo

Day 0	Informed consent Severity score I
Day 1–4: Treatment period I	Intake of capsules containing ginger or placebo (250 mg, q.i.d.)
Day 5: Wash-out period	Relief score I
Day 6: Wash-out period	Severity score II
Day 7–10: Treatment period II	Intake of capsules of ginger or placebo alternative to treatment period I (250 mg, q.i.d.)
Day 11	Relief score II Preference to treatment period I or II

TABLE III

The scoring system for the evaluation of an therapeutic effect of the treatment on day 5 and 11 (relief score) [4]

		Scores
Nausea	Worsened	−3
	No change	0
	Diminished/decreased	2
	Disappeared	3
Vomiting	Worsened	−3
	No change	0
	Diminished/decreased	2
	Disappeared	3
Change in body weight	Decreased	−4
	No change	−1
	Increased ≤ 1.0 kg	1
	Increased $> 1.0- \leq 2.0$ kg	2
	Increased $> 2.0- \leq 3.0$ kg	3
	Increased > 3.0 kg	4
Patient's opinion about the treatment	No relief	0
	Slight relief	1
	Good relief	2
	Excellent relief	3
Total		

Statistical methods

The Mann-Whitney test was applied on non-paired and the Pratt test on paired data. The sign test was used in calculating the preference. $P < 0.05$ was chosen as an indication of a statistically significant difference. Calculations were performed on a personal computer using the MEDSTAT programme [5].

Results

Table IV gives the severity scores for the patients when entering their first and second treatment period, their preference of treatment period, and the relief scores after each period. The code

TABLE IV

The assessment of the hyperemesis symptoms in the patients by severity scores before entering treatment periods I and II, patient's preference of treatment period, and their relief scores after each period *

Patient No.	Code No.	Severity scores		Preference	Relief scores	
		I	II		I	II
1	1	17	7	I	10	−7
2	4	17	9	II	−4	9
3	5	13	7	I	9	−10
4	6	10	9	II	−7	2
5	8	12	7	I	2	2
6	9	18	11	?	8	10
7	14	16	10	?	6	2
8	15	13	7	I	7	−2
9	17	12	6	I	9	−1
10	23	10	6	I	−1	5
11	25	14	9	I	−2	−10
12	26	10	7	I	4	1
13	28	17	6	I	11	−7
14	29	13	15	II	5	4
Mean		13.7	8.2		4.1	−0.1
15	2	15	6	I	8	−7
16	3	14	8	?	−4	1
17	11	13	10	II	7	11
18	12	14	8	II	1	2
19	13	10	8	II	6	11
20	16	12	10	II	−4	10
21	18	11	7	?	1	1
22	19	15	10	II	7	1
23	21	16	14	II	−4	7
24	22	12	10	II	1	5
25	24	15	7	II	4	5
26	27	12	9	II	−7	−1
27	30	14	9	II	−4	2
Mean		13.3	8.9		0.9	3.7

* Patients No. 1–14 had ginger and No. 15–27 placebo during treatment period I.

numbers refer to the order in which they entered the study. In the tables patients are ordered according to the treatment during the first period. Patients No. 1–14 had ginger capsules whereas patients No. 15–27 received placebo.

Randomisation

Analyses revealed no differences between the two groups with regard to age, number of pregnancies, gestational age, and severity scores when entering the study.

Although it may seem that there was a slight skewness in the distribution of the number of vomiting attacks between the groups (Table I), analysis of each item of the severity score did not demonstrate any statistically significant difference between the groups.

Severity score I and II are not directly comparable. The weight loss registered in the first score had occurred during a variable time as patients entered the trial at different gestational ages. The loss in weight was calculated from the weight recorded at the first visit to the antenatal clinic. The second score comprised weight change during the seven days of admission to hospital.

The mean values of the severity scores decreased equally in the two groups from the first to the second period of treatment. This may reflect the beneficial effect of admission to hospital on the hyperemesis. As the mean values of the second severity score were equal there was probably no carry-over effect of ginger to the second period in patients No. 1–14.

Preference

When specifically asked which treatment period they preferred 19 women (70.4%) mentioned the period in which, as was later disclosed, they received ginger. Four women (14.8%) preferred the placebo treatment period while four (14.8%) were unable to state any preference.

The preference to the ginger treatment period was statistically significant ($P = 0.003$). Age, number of pregnancies, parity and week of gestation did not seem to influence the preference to ginger.

Relief scores

Considering the differences in relief scores for all patients after the ginger treatment period and after the placebo treatment period, respectively, a significantly greater relief on the hyperemesis symptoms was demonstrated after ginger compared to placebo ($P = 0.035$).

Analyses of the single items of the relief scores (nausea, vomiting, weight change, individual opinion) indicated that the difference obtained espe-

cially was by a reduced number of attacks of vomiting and of decreased nausea.

Outcome of pregnancy

Patient No. 6 had a spontaneous abortion in the 12th week of gestation, and patient No. 27 asked for a legal abortion in week 11 because of severe marital and social problems.

The remaining 25 women delivered living infants. The mean birth weight was 3585 g (range 2450–5150 g). The mean gestational age at delivery was 39.9 weeks (range 36–41 weeks). All infants were without deformities and discharged in good conditions. All had Apgar scores of 9–10 after 5 min.

Discussion

The main therapeutic concern in hyperemesis should be the correction of fluid and electrolyte status in the patient. The value of drug therapy is doubtful but comes at stage if nausea and vomiting strain the patient extremely. In a prospective study there was no indication that the usual antiemetic drugs prescribed to pregnant women were associated with teratogenicity [6]. However, there is an understandable reluctance to use drugs of any kind during early pregnancy.

A natural product such as ginger would seem more acceptable. There is a tradition that dates back centuries of using the fluid extract of the rhizome of ginger in symptoms of gastrointestinal distress, the recommended daily doses being 1 g. The efficacy of ginger is thought to depend on aromatic, carminative and absorbent properties [7].

Furthermore, the use of ginger is well known in foods (cakes, tarts (amounting 30 g), marmalades) and beverages (ginger ale).

Vomiting results from activity of the emetic centre in the brain stem. This centre receives stimuli from the gastrointestinal tract and from higher centres, and activates the vomiting proces. The emetic centre also receives stimuli from a centre on the surface of the medulla, a chemoreceptor zone, which is directly stimulated by toxic substances and by raised blood levels of urea and ketones [8]. The properties of ginger suggest that it ameliorates the effects on motion sickness in the gastrointestinal tract itself [3]. In hyperemesis ginger may stimulate the motility of the gastrointestinal tract and its absorbent property may reduce stimuli to the chemoreceptor zone. Moreover, ginger may block the gastrointestinal reactions and the subsequent nausea feedback [3]. It is unlikely that the powdered ginger root acts at the level of the central nervous system. At the end of this study the authors got familiar with reports suggesting possible mutagenic as well as antimutagenic components in ginger [9,10]. An investigation of the fluid extract of the rhizome of ginger disclosed gingerol as a mutagen. However, the fluid extract also contained strong antimutagenic components against gingerol. The study was carried out in a culture of a certain strain of *Escherichia coli*. The system was not submitted to any activating or inhibiting enzyme test such as for example the Ames test. Retrieval of the literature has not brought any further information on the subject. In the present study there appeared no deformities of the infants. One spontaneous abortion occurred in 27 pregnancies which was not a suspicious high rate of fetal wastage in early pregnancy.

In this study, 19 of 27 patients experienced the powdered *Rhizoma zingiberis* in daily doses of 1 g during 4 days better than a placebo in diminishing or eliminating the symptoms of hyperemesis gravidarum. The preference to ginger was of statistical significance. The relief seemed to be achieved by reducing the degree of nausea and the number of attacks of vomiting. No side effects were observed. Ginger is a natural product and the amount used did not exceed amounts prescribed in recipes for cakes or tarts. It is unlikely that ginger acts at the CNS level as do the antihistamines. The suggestion is that the effect is carried out directly in the gastrointestinal tract.

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