



Prospective Comparative Study of Ginger versus Combination of Doxylamine plus Pyridoxine in Alleviating Nausea and Vomiting of Pregnancy

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ABSTRACT

Nausea and vomiting of pregnancy are common and bothersome complaints of early pregnancy. Use of currently available medications is restricted due to potential teratogenic effect during embryogenesis. So alternative natural therapies e.g. Ginger are preferred.

Objective: Present study was to compare the safety, effectiveness of ginger versus combination of doxylamine plus pyridoxine in treating nausea and vomiting of pregnancy.

Methods: 250 women having nausea and vomiting of pregnancy up to 12 weeks gestation, fulfilling inclusion criteria were included & divided into 3 groups. (I) Ginger gp 100 women (II) Doxylamine plus Pyridoxine gp 100 women (III) Control 50 women. Each group was further classified into mild, moderate and severe, using the Rhodes Index of Nausea, Vomiting and retching (RINVR). Group I was given half teaspoon of liquid extract of fresh ginger (equivalent to 500mg standardized extract, twice daily for 4 days/week). Group II was given 2 tablets of Doxylamine (10mg) + pyridoxine (10mg) at bed time. If needed, one tablet was added in the morning and another in the afternoon. Severity of NVP was evaluated 24 hrs before and upto 4 days after treatment by Rhodes Index. (I) Ginger is more effective as compared to control group. P values in mild, moderate and severe gp of nausea were 0.01(S), <0.001(HS), <0.038(S) and vomiting <0.0001(HS), <0.0001(HS) and 0.008(S) respectively. Group II is more effective than control. P values in mild, moderate, and severe gp of nausea were 0.02(S), <0.001(HS), <0.039(S) and vomiting <0.0001(HS), <0.0001(HS), 0.015(S) respectively. Ginger is more effective and safe as compared to Control and comparable to Doxylamine plus Pyridoxine..

Keywords: Ginger, NVP, Placebo, Doxylamine, VitaminB6.

Introduction

Nausea and vomiting of pregnancy (morning sickness) are common complaints which usually lasts till end of 3rd month of pregnancy, but may continue up to 14-16 weeks. Although they are

worst in the morning but may continue the whole day (Williams,2005)^[1]. 70-85% and 40-50% women suffer by nausea and vomiting respectively. The use of currently available medications is restricted due to potential

teratogenic effect during the critical embryogenic period of pregnancy. So many alternative natural therapies are used. like herbal products, Homeopathic, natural drugs as ginger, peppermint. Only ginger has been evaluated in controlled trials (Borrelli F et al,2005)^[2]. Traditionally in Chinese and Aurvedic medicine, ginger is used to treat nausea and vomiting (Caroline Smith et al,2004)^[3]. Larger doses >2gms is contraindicated in pregnancy as it may impair development of male fetal brain.

The FDA classifies ginger as “Generally Recognised as Safe “ and German Commission E monographs report no side effects and no known drug/herb interactions (Bryer E ,2005)^[4] and (American Botanical council, 2004)^[5]

Medicinal actions of ginger are: General stimulant, Rubifacient, Antiemetic, Carminative, Antibiotic, anti-inflammatory, Spasmolytic and analgesic..

The main constituents in ginger are:

1. Volatile oils,(1-3%)
2. Starch proteins proteases, vitamins and resins.
3. The pungent or hot principles are attributed to gingerols [1-2.5%] and shogaols. Gingerols decompose into shogaols upon drying and storage. Shogaols has shown the ability to act as an analgesic.

DOXYLAMINE and vit B6 are few medications classified as risk factor “A” drugs i.e .trials fail to show fetal risk in first trimester and no evidence shown risk in later pregnancy.

From the literature, it is not clearly understood that which is the ideal management for nausea and vomiting of pregnancy. This prospective study was planned to compare the efficacy, safety and side effect of ginger and combination of doxylamine and pyridoxine in treating nausea and vomiting of pregnancy.

Aims and Objectives

1. To compare the safety and effectiveness of ginger versus combination of doxylamine

plus pyridoxine in treating nausea and vomiting of pregnancy..

2. To compare the side effects of ginger versus combination of doxylamine and pyridoxine in treating nausea and vomiting of pregnancy.

Material and Methods

This study was performed in the Department of Obstetrics and Gynaecology, Rajindra Hospital, Patiala Punjab India. 250 pregnant women were studied. They were divided into three groups.

Group-I: 100 Women received ginger.

Group-II: 100 women received combination of doxylamine plus pyridoxine.

Group-III: 50 women served as control where no antiemetics were given.

Inclusion Criteria for selecting the patients:

1. Gestational age upto 12 weeks.
2. Nausea and vomiting

Exclusion Criteria

1. Associated medical illness: Gastroenteritis (viral or bacterial), Thyroid disease, Hepatitis
2. Associated surgical illness: Appendicitis, Cholelithiasis, Urinary Tract Infection, Pancreatitis
3. Associated Psychiatric illness: Depression.
4. Patients with known allergy to ginger or doxylamine.

Methodology

A total of 250 healthy women with NVP were selected for the study and divided into three groups.

Group I. Women were put on ginger.

Group II. Women were put on combination of doxylamine and pyridoxine.

Group III women served as a control.

Each group was further classified into mild, moderate and severe according to the number of episodes of nausea and vomiting using the Rhodes Index of Nausea, Vomiting and retching (RINVR).

1. Mild: 0-1 episodes.
2. Moderate: 2-5 episodes.

3. Severe: >5 episodes.

Dosage Regimen

Group I. 100 women were given ½ (half) teaspoon of liquid extract of fresh ginger (equivalent to 500mg standardized extract) two times a day for 4 days per week.

Group II. 100 women were given 2 tablets of Doxylamine (10mg) + pyridoxine (10mg) at bed time. If symptoms persist, one tablet was added in the morning and another in the afternoon.

Group III. 50 women of control group were not given any antiemetics.

The severity of NVP was evaluated 24 hrs before entering the study and upto 4 days after treatment by Rhodes Index.

Statistical Analysis: The results in the study were statistically analysed by means of chi-square test, Students t test and statistical significance was defined as a p value of <0.05. A p value of <0.01 indicated highly significant result.

Observation

Table 1. Relief of nausea in mild cases

No. of Days	Group-I (Ginger) (n=31)		Group-II (Doxylamine plus pyridoxine) (n=30)		Group-III (Control) (n=10)	
	No. of Cases	%age	No. of Cases	%age	No. of Cases	%age
0-1	2	6.2%	3	10%	0	0%
0-2	8	25%	8	27%	0	0%
0-3	9	29%	10	33.33%	1	10%
0-4	11	35%	9	30%	5	50%
TOTAL	30	96.7%	30	100%	6	60%

The above table shows that, on day 4 of the treatment, 30 (96.7%) women in group I, 30 (100%) women in group II and 6 (60%) women in gpIII had relief of nausea respectively.

When group II and III were compared, the results were statistically significant (p 0.02) and also when group I and III were compared (p 0.01). However, when group I and II were compared, the results were statistically not significant.

Table II. Relief of nausea in moderate cases

No. of Days	Group-I (Ginger) (n=58)		Group-II (Doxylamine plus pyridoxine) (n=60)		Group-III (Control) (n=30)	
	No. of Cases	%age	No. of Cases	%age	No. of Cases	%age
0-1	9	15.5%	9	15%	0	0
0-2	10	17.24%	11	18.33%	0	0
0-3	14	24.13%	13	21.66%	5	16.66%
0-4	25	43.10%	27	45%	5	16.66%
Total	58	100%	60	100%	10	33.3%

The above table shows that on day 4 of treatment, in moderate cases, 58 (100%) patients had relief of nausea in group I which is comparable to 60 (100%) patients in group II. However only 10 (33.3%) patients had nausea relief in group III.

The results were not statistically significant when group I and II were compared. However, the results were highly significant when group II and

III were compared (p value <0.001) and when group I & III were compared (p value <0.001).

Table III. Relief of nausea in severe cases

No. of Days	Group-I (Ginger) (n=11)		Group-II (Doxylamine plus pyridoxine) (n=10)		Group-III (Control) (n=10)	
	No. of Cases	%age	No. of Cases	%age	No. of Cases	%age
0-1	0	0	0	0	0	0
0-2	0	0	0	0	0	0
0-3	4	36.3%	3	30%	2	20%
0-4	6	54.5%	7	70%	3	30%
Total	10	90.9%	10	100%	5	50%

The above table shows the relief of nausea in severe cases on day 4 of treatment. It is evident from the table that in group I, 10 (90.9%) women had relief from nausea as compared to 10 (100%) in group II and 5 (50%) in group III respectively.

The results were statistically significant when group II and III were compared (p 0.039) and when group I and III were compared (p 0.038). However, when group I and II were compared, the results were not statistically significant.

Table IV. Relief of vomiting in mild cases

No. of Days	Group-I (Ginger) (n=31)		Group-II (Doxylamine plus pyridoxine) (n=30)		Group-III (Control) (n=10)	
	No. of Cases	%age	No. of Cases	%age	No. of Cases	%age
0-1	5	16.1%	6	20%	0	0
0-2	8	25.8%	7	23.3%	0	0
0-3	7	22.5%	7	23.3%	1	10%
0-4	10	32.5%	10	33.3%	2	20%
Total	30	96.9	30		3	

The above table shows the relief from vomiting, in mild cases. on day 4 of treatment. 30 (96.9%) women in group I had relief as compared to 30 (99.9%) in group II and 3 (30%) in group III respectively. On statistical analysis, the results

were highly significant when group II and III were compared (p <0.0001) and when group I and III were compared (p <0.0001). However, when group I and II were compared, the results were statistically not significant.

Table V. Relief of vomiting in moderate case

No. of Days	Group-I (Ginger) (n=57)		Group-II (Doxylamine plus pyridoxine) (n=60)		Group-III (Control) (n=30)	
	No. of Cases	%age	No. of Cases	%age	No. of Cases	%age
0-1	9	15.7%	10	16.6%	0	0
0-2	9	15.7%	10	16.6%	0	0
0-3	14	24.5%	12	20%	5	16.6%
0-4	25	43.8%	28	46.6%	5	16.6%
Total	57	100%	60	100%	10	33.2%

The above table shows the relief of vomiting, in moderate cases, on day 4 of treatment. 57 (100%) women in group I & 60 (100%) in group II and 10 (33.2%) in group III had relief from vomiting. On statistical analysis, the results were highly significant when group II and III were compared (p <0.0001) and when group I and III were compared (p <0.0001). However, when group I

and II were compared, the results were statistically not significant

Table VI Relief of vomiting in severe cases

No. of Days	Group-I (Ginger) (n=12)		Group-II (Doxylamine plus pyridoxine) (n=10)		Group-III (Control) (n=10)	
	No. of Cases	%age	No. of Cases	%age	No. of Cases	%age
0-1	0	0	0	0	0	0
0-2	3	25%	2	20%	0	0
0-3	4	33.3%	3	30%	2	20%
0-4	5	41.6%	5	50%	2	20%
Total	12	100%	10	100%	4	

The above table shows the relief of vomiting, in severe cases, on day 4 of treatment. 12 (100%) women in group I had vomiting relief which is comparable to 10 (100%) in group II. However, 4 (40%) women in group III had relief from vomiting on day 4 of treatment. On statistical

analysis, when group I and II were compared, the results were statistically not significant. However, when group II and III were compared, the results were significant (p 0.015) and when group I and III were compared also the results were significant (p 0.008).

Table VII Showing side effects of drugs

Side effect	GP I(GINGER) No.=100		GP II(DOXYLAMINE+PYRIDOXINE) No.= 100	
	NO.	%	NO.	%
I.Gastrointestinal upsets				
1).Heart burn	25	25%	15	15%
2).Belching				
3).Difficulty in swallowing				
4).Reflux				
II. Headache	0	0	2	2%
III.Drowsiness	0	0	5	5%

The above table shows that the main side effect in Ginger GP was gastrointestinal upset ie heart burn, belching, reflux and difficulty in swallowing. 25 (25%) women in gp 1 experienced gastrointestinal upsets as compared to 15 (15%) in GP II. Two women (2%) in GP II experienced headache & 5 (5%) had drowsiness. No pt complained headache or drowsiness in gp I

Discussion

Nausea and vomiting of early pregnancy, if ignored, may risk the mother or fetus. Teratogenic effect of various medications, limits their use especially in embryogenic stage of pregnancy. Many complimentary medicines are perceived as being safe and natural. Ginger is considered most effective and safe’ FDA also classified ginger “Generally Recognised as safe “ and German Commission E Monograph report no side effects (Eva Bryer,2005)^{[4][5]}

Doxylamine 10mg with pyridoxine hcl 10gm were approved for treating nausea vomiting of

pregnancy by Health Protection branch of health & welfare Canada 1990. (Caddick R et al,1995)^[6] Doxylamine plus Pyridoxine was approved by USFDA for treatment of nausea vomiting of pregnancy (Jeffrey D et al.2003)^[7] In our study. 250 pts divided into 3 gps. (GPI 100 women received ginger, GPII 100 received Doxylamine plus pyridoxine and Gp III no medication).

Each group was further divided in to mild, moderat, severe depending on the degree of distress and no. of episodes of nausea & vomiting Relief was studied on day1,2,3,4 from baseline by RHODES Index.

➤ **Relief of Nausea**

1. Mild Group: 30(96.7%) pts in GP I, 30(100%) in GP II and 6 (60%) in gp III had relief respectively. The results were statistically significant when GP I and III were compared and when gp II and III were compared. But the results were not significant when group I& II were

compared. So results showed that ginger and doxylamine plus pyridoxine were more effective as compared to control & the results were statistically highly significant.

2. In Moderate Group: At the end of 4 days treatment. 58 (100%) womens had relief in gp I which is comparable to gp II in which 60 (100%) women had relief. But in gp III, only 10 (33.3%) had relief. The results were statistically significant when GP I and GP III were compared and when GP II and III were compared. But the results were not significant when gp I& II were compared The results showed that Ginger and Doxylamine plus Pyridoxine were equally effective relieving nausea of pregnancy. Both are more effective than control.

3. Severe Nausea: At End of 4 Days.

10 (90.9%) women in GPI had relief as compared to 10 (100%) in gp II. In GP III 5 (50%) pts had relief. The results showed that Ginger and Doxylamine plus Pyridoxine were equally effective relieving nausea of pregnancy. Both are more effective than control and results are highly significant.

However nothing has been mentioned by the other authors regarding relief of nausea in relation to grades of nausea (mild, moderate, severe).

Fischer-Rasmussen et al,(1990) [8] did a trial to know the efficacy of ginger in NVP. The comparison was made between 250 mg ginger in a capsule and a placebo filled with 250 gm of lactose. For the first 4 days, ginger was given 4 times /day followed by 2 days washed out period before giving placebo in the same regimen. Woman who used ginger were significantly improved.

Relief of Symptoms (Vomiting)

(1) In Mild Group: On day 4 of treatment 30 (96.9%) women in GP I relieved as compared to 30 (99.9%) in gp II and 3(30%) in gp III. On statistical analysis, results were highly significant when GP I and GP II were compared with GP III. The results were non significant when gpI and II were compared. The results showed that Ginger

and Doxylamine plus Pyridoxine were equally effective relieving nausea of pregnancy. Both are more effective than control.

(2) In Moderate Group: On day 4 of treatment. 57 (100%) pts in gp I, 60 (100%) in gp II and 10 (33.2%) in gp III were relieved results were highly significant when GP I and GP II were compared with III. The results were non significant when gp I and II were compared. So results showed that ginger and doxylamine plus pyridoxine were more effective as compared to control group.& the results were statistically highly significant.

(3) In Severe Group: On day 4 of treatment. There was vomiting relief in 12(100%) pts in GPI, and 10(100%) in GP II which is comparable. In GP III, 4(40%) women were relieved. On statistically analysis results were high significant when GP I and GP II were compared with III. The results were non significant when gpI and II were compared. So results showed that ginger and Doxylamine plus pyridoxine were more effective as compared to control.

1. Portnoi et al, (2003 [9]) reported a significant decrease in both NV in women who used ginger. Out of 32 patients,28 had relief in NV as compared to 10 out of 35 in placebo group (p <0.001

2. Smith et al,2004[10] showed that ginger was therapeutically equivalent to vit B6 for improving nausea, vomiting and dry retching.

3. Matthews et al (2014)[11] some studies support ginger over placebo in relieving NVP

4. Thomson et al (2014) [12] showed Ginger is an effective non pharmacological treatment for NVP

Side Effects of Drugs as Reported by Other Authors

Author	Group I (Ginger)	Group II (doxylamine +Pyridoxine)
Vatyavanich et al ,2001	No significant side effect	
K.E. Willets et al, 2003	Heart burn and Reflux in 27%	
Present study		
Heart burn and reflux	25%	15%
Headache	0%	2%
Drowsiness	0%	5%

In present study: 25% women of GP I had reflux and heart burn which is comparable to 27% women as reported by K.E. Willets et al, 2003.^[13] But, Vatyavanich et al, 2001^[14] reported no significant side effect with ginger.

In Present Study: 15% pts in GP II had reflux and heart burn, 2% had headache and 5% drowsiness which were not reported by other authors. According to Smith et al, 2004 most of the side effects with ginger were associated with swallowing. Vit B6 was slightly well tolerated.

Summary and Conclusion

Present study consisted of 250 women of NVP, up to 12 weeks of gestation fulfilling the inclusion criteria. & were divided into to 3 groups ie 1. Ginger gp, II. Doxylamine plus Pyridoxine gp and Control gp. Women of each group were further divided into mild moderate and severe depending on the episodes of nausea and vomiting. It is concluded that:

1. Ginger is more effective for the treatment of nausea vomiting of pregnancy as compared to women to whom no treatment was given.
2. Doxylamine plus pyridoxine is more effective in providing relief of nausea and vomiting as compared to control gp where no antiemetic was given
3. Ginger is equally effective and safe in alleviating nausea and vomiting of pregnancy and is comparable to Doxylamine plus Pyridoxine.

Grants: Nil

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