

A Single-masked, Randomized, Controlled Trial of Ginger Extract in the Treatment of Nausea and Vomiting of Pregnancy.

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Abstract: In order to evaluate the efficacy and tolerability of an oral ginger extract formulation in comparison to oral fixed dose combination of doxylamine 10 mg plus pyridoxine 10 mg, seventy eight (78) women between 6-16 weeks of pregnancy, complaining of nausea and vomiting (NVP), were randomized to receive either ginger formulation or pyridoxine-doxylamine preparation in a single blind fashion. Efficacy variables were the severity of nausea and vomiting scored by visual analog scale, on the day of each visit, as well as averaged over the past week; the average number of nausea spells or vomiting episodes per day over the past week; and subjective well-being assessed as a binary variable. Study was completed by 63 women (34 on ginger extract). Statistically, no appreciable difference in efficacy parameters was noted between groups. Tolerability of ginger extract was satisfactory with no severe or serious adverse events noted. Ginger extract can provide a safe and effective alternative for management of NVP.

Keywords: Ginger, pyridoxine, doxylamine, nausea and vomiting in pregnancy, randomized controlled trial, Indian medicinal plant

INTRODUCTION

Approximately 80% of pregnant women experience nausea and vomiting (NVP) to some degree, which usually occurs between 8 to 12 weeks of gestation, although 10% women will exhibit symptoms past the 20th week and less than 1% have the severe form for hyperemesis gravidarum¹. Many women are hesitant to take conventional medicines for NVP from fear of harming the fetus. However, they are often interested in natural remedies. The pharmacological effects of ginger [*Zingiber officinale*] has been investigated in various studies ranging from animal experiment to observations in healthy human volunteer and patients²⁻⁴ and the antiemetic potential in pregnancy has been explored in clinical trial⁵⁻⁷. Ginger is an important plant in traditional Indian⁸⁻¹⁰ and Chinese pharmacopoeias and World Health Organization monographs on selected medicinal plants also list nausea and vomiting among indications among ginger¹¹. Ginger is also listed in the United States Pharmacopoeia¹². The effectiveness and safety of its use in NVP is being studied more intensively through randomized controlled trials over the past few years¹³⁻¹⁶. Against this backdrop, the present study was conceived to evaluate the efficacy and tolerability of a single ingredient oral formulation of ginger in Indian women suffering from nausea and vomiting of pregnancy.

The formulation in question is manufactured by M/S Lupin Laboratories Ltd., Mumbai, from dried ginger rhizome but not yet marketed. The goal of the present study was to evaluate this monoherb formulation, LHR-2445AE, for its efficacy and tolerability when used, in recommended doses, in nausea and vomiting of pregnancy. The assessment was done in comparison to an oral fixed dose combination of doxylamine 10 mg plus pyridoxine 10 mg (DOXINATE, of M/s Sigma Laboratories Pvt. Ltd., Mumbai), that is currently widely used in India.

MATERIALS AND METHODS

The present study was designed as single blind, prospective, randomized, controlled trial and was conducted in accordance with good clinical practice guidelines. Enrollment was subject to signing of the informed consent from by the trial participants. Each of the two

participating centers, namely the Departments of Gynecology & Obstetrics at Institute of Postgraduate Medical Education & Research (IPGME&R) and SSKM Hospital, Kolkata and R.G. Kar Medical College Hospitals, Kolkata, received ethical clearance first their respective institutional ethics committee. Subject recruitment period was from November, 2004 to April, 2005.

Subjects were selected only if they sought treatment for the symptoms of morning sickness between 6 to 16 weeks of pregnancy without having received any treatment earlier for the same. USG confirmed singleton intrauterine pregnancy in all cases. Women were excluded from the study if they were beyond 16 weeks of gestation, had multiple gestation, gestational trophoblastic disease, hyperemesis gravidarum, ovarian cyst, gastroesophageal reflux disease or other forms of acid peptic disorders, chronic or serious diseases of major organs or if the containing food, spices, or beverages, or taking medication other than those permitted but the study protocol were also excluded.

Subjects were randomly allocated (using computer generated random number list) to one of the following two treatment groups- Group A: the study drug LHR-2445AE, one tablet 9each tablet containing 150 mg of standardized extract of dried ginger) three times daily or Group B; the comparator drug DOXINATE, one tablet 9each tablet containing doxylamine 10 mg, as succinate, and pyridoxine 10 mg, as hydrochloride) two or three times daily. The medication was supplied by the sponsor in coded packaging to protect its identity from the subject. This was, however, known to the investigators. For each individual subject, the study consisted of 3 weeks of active treatment, with follow-up visits at the end of first and second weeks. Routine laboratory tests (blood counts, liver function tests, serum creatinine and fasting glucose) were done at baseline and repeated at the end of study to assess safety. The subjects were followed up as per routine hospital protocol till delivery to note any untoward long-term effects in the fetus or mother.

The efficacy variables for this study were the severity of the nausea and vomiting scored by a 100 mm visual analog scale (VAS), on the day of each visit as well as averaged over the past week. The average numbers of spells of nausea or episodes of vomiting per day over the past week were also recorded. In addition, the subjective feeling of

well-being was assessed as a binary (yes/no) variable at each visit. A diary card was provided to each woman and explained carefully to enable them to keep track of the severity of their problem. At each visit, subjects were closely questioned and examined clinically to detect treatment emergent adverse events. Compliance was assessed by the traditional pill count method i.e., determined by the balance between the quantity of medication dispensed and the quantum returned as unused. It was graded as excellent if 19 or more days medication was taken, good for 16 or more days medication used and poor for anything less than good.

Statistical Analysis

The study protocol specified that efficacy data was to be evaluated on an intention-to-treat basis for subjects who presented for at least one follow-up visit, but any subject randomized was to be included in adverse event count. Parametric data were compared by the students't test. Non-parametric data was compared within groups by Friedman's analysis of variance followed by Wilcoxon's matched pairs signed rank test, and between groups by Mann Whitney U test. Categorical data were compared between groups by Chi-square test or fisher's exact test. All analysis were 2-tailed with p<0.05 as the cut-off level for statistical significance.

STATISTICA version 6 [Tulsa, Oklahoma: Stat soft Inc., 2001] and SPSS for Windows version 11.5 [Illinois, Chicago: Spss Inc., 2002] were the statistical software used for analysis. The initial database was created in Microsoft Access.

RESULTS AND DISCUSSION

Out of the total 78 subjects, 15 subjects [19.23%], six in Group A and five in Group AB were lost to follow-up, and an additional four (two in each group) were non-eligible due to protocol-violation. The difference in withdrawal numbers between groups was not statistically significant. The efficacy analysis, in essence was carried out with the 63 subjects who completed the study as per protocol, since withdrawn subjects did not present for even the first follow-up visit.

There were 82.35% primigravida women in Group A [28 out of 34] and 65.52% in Group B [19 out of 29]- this difference was statistically non-0 significant [p=0.154]. The age and anthropometric profile of the study subjects at recruitment were evenly matched at baseline, with the exception of the height parameter. A median age of 21 and 22 years in two groups, both close to their respective means, indicates a preponderance of young adult women subjects in both the groups (Table 1). Abnormalities were detected in a few women during systemic examination at baseline, including a history of rheumatic fever in one patient in Group A who was on long-term penicillin prophylaxis for rheumatic heart disease. However none were considered serious enough to preclude inclusion into the study.

Tables 2 and 3 present the changes in the efficacy variables in the two groups while the changes in nausea and vomiting VAS scores have

Table 1: Baseline age and anthropometric profile summary of study subjects

Parameter	Ginger extract Preparation [n=34]	Doxylamine-Pyridoxine preparation [n=29]
Age [Y]	21.7 ± 3.06 Median: 21.0	22.7 ± 4.46 Median: 22.0
Weight [Kg]	47.6 ± 8.38	48.1 ± 8.29
Height [cm]	151.3 ± 5.85	147.6 ± 4.99*

Abbreviations are standard; Values are Mean ± Standard deviation, unless otherwise stated.

*p< 0.01 in comparison to group A by independent samples t test.

been depicted in Figure 1. Evidently, in both groups there was a steady decline in the severity of nausea and vomiting that generally achieved statistically significant improvement from baseline by the time of the second follow-up visit. Vomiting scores in particular showed a precipitous decline, with the median values tending towards 0 at study end in both groups. However, nausea persisted, with considerably reduced severity, in both groups at study end.

Table 2: Serial changes in efficacy parameters in Ginger extract group (n=34)

	Baseline	End of week 1	End of week 2	Study end
Nausea severity by VAS scores:				
Median	34.50	22.00###	5.50###	0.00###
Interquartile range	25.00	31.50	21.00	10.00
Range	0.00-91.00	0.00-64.00	0.00-78.00	0.00-52.00
Vomiting severity by VAS score:				
Median	14.50	0.00#	0.00##	0.00###
Interquartile range	33.00	18.00	0.00	0.00
Range	0.00-73.00	0.00-72.50	0.00-26.00	0.00-30.00
Average number of nausea spells Per day in the last week:				
Median	3.00	1.78##	1.11###	0.32###
Interquartile Range	3.00	2.57	1.86	2.00
Range	1.00-10.00	0.00-7.28	0.00-11.00	0.00-12.00
Average number of vomiting Episodes per day in last week:				
Median	1.00	0.5	0.14###	0.14###
Interquartile Range	2.00	1.00	0.71	0.57
Range	0.00-6.00	0.00-5.57	0.00-3.71	0.00-5.50
Average severity of nausea in the last week by VAS score:				
Median	—	29.50	15.70##	5.00###
Interquartile range	—	32.00	25.20	13.00
Range	—	0.00-72.70	0.00-85.70	0.00-89.20
Average severity of vomiting in the last week by VAS score:				
Median	—	9.40	2.30###	1.00#
Interquartile Range	—	23.40	9.70	9.00
Range	—	0.00-78.00	0.00-65.1	0.00-88.20

VAS score = Visual Analog Scale Score; Repeated measures comparison by Friedman's test showed highly significant differences (p<0.001) between time points, with respect to all the parameters; ###/##/## denote 2-tailed p< 0.05 / 0.01/ 0.001 in comparison to baseline 9Comparison to first follow-up data in case of last two parameters) by Wilcoxon matched pairs signed rank test.

Table 3: Serial changes in efficacy parameters in Doxylamine-Pyridoxine group (n=0.294)

	Baseline	End of week 1	End of week 2	Study end
Nausea severity by VAS scores:				
Median	30.40	17.00#	10.00##	0.00###
Interquartile range	34.00	30.00	23.00	18.00
Range	0.00-100.00	0.00-100.00	0.00-72.00	0.00-65.00
Vomiting severity by VAS score:				
Median	22.00	0.00#	0.00##	0.00###
Interquartile range	35.00	15.00	11.00	0.00
Range	0.00-87.00	0.00-48.00	0.00-48.00	0.00-17.00
Average number of nausea spells Per day in the last week:				
Median	4.00	2.14###	1.28###	0.60###
Interquartile Range	4.00	1.99	2.28	1.70
Range	1.00-120.00	0.00-6.00	0.00-8.00	0.00-7.70
Average number of vomiting Episodes per day in last week:				
Median	2.00	0.43	0.42###	0.00###
Interquartile Range	5.00	1.53	1.14	0.60
Range	0.00-6.00	0.00-3.14	0.00-3.30	0.00-2.80
Average severity of nausea in the last week by VAS score:				
Median	—	37.50	22.00##	7.00###
Interquartile range	—	24.90	28.10	21.80
Range	—	0.00-78.00	0.00-88.00	0.00-70.00
Average severity of vomiting in the last week by VAS score:				
Median	—	13.2	10.30##	0.00#
Interquartile Range	—	27.40	18.00	14.20
Range	—	0.00-48.00	0.00-90.00	0.00-26.00

VAS score = Visual Analog Scale Score; Repeated measures comparison by Friedman's test showed highly significant differences (p<0.001) between time points, with respect to all the parameters; ###/##/## denote 2-tailed p< 0.05 / 0.01/ 0.001 in comparison to baseline 9Comparison to first follow-up data in case of last two parameters) by Wilcoxon matched pairs signed rank test.

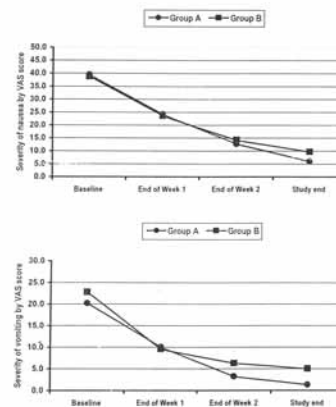


Figure 1. Line diagram depicting the declining and parallel trends in severity of nausea vomiting in the two study groups. Group A subjects (n = 34) received Ginger extract formulation while Group B subjects (n = 29) took Doxylamine-Pyridoxine fixed dose combination.

Between group comparisons of the nausea and vomiting parameters, did not reveal any difference at any time point. Thus the groups were comparable at baseline and remained so at study end and at both the intervening follow-up visits. Similarly, the subjective feeling of well—being showed an improving trend in both groups from baseline to study end, with no inter-group differences at any of the visits (Table 4).

Table 4.: Distribution of well being status in study subjects at different time points

Time Point	Group	Well- being YES	Well –being NO
Baseline	A	25 [73.53%]	9 [26.47%]
	B	17 [58.62%]	12 [41.38%]
End of Week 1	A	2 [64.71%]	12 [35.29%]
	B	20 [68.97%]	9 [31.03%]
End of week 2	A	11 [32.35%]	23 [67.75%]
	B	15 [51.72%]	14 [48.28%]
Study end	A	27 [79.41%]	7 [20.59%]
	B	29 [68.97%]	9 [31.03%]

* Group A subjects (n=34) received Ginger extract formulation while Group B subjects (n=29) took Doxylamine –pyridoxine fixed dose contribution

* Between group comparison was non-significant at all time points (Chi-square test).

There was a modest but statistically increase in body weight in both groups, which is to be expected in pregnancy. There was also clinically insignificant (1.5 beats per minute) but statistically significant decline in heart rate in Group A. All other parameters, in both groups, showed no significant deviations from baseline. Between group differences were also minor and neither significant statistically nor clinically. So far as the biochemical safety parameters are considered, there was no clinically significant difference between baseline and study end means, in either group. A few abnormalities were noted when individual subjects, rather than group means, were considered. This is to be expected in any clinical study. However, the abnormalities present at baseline were not severe enough to preclude inclusion in the study. Similarly, the abnormalities at study end were not severe enough to be reported as adverse events by the investigators. Anemia was noted in a substantial proportion of subjects in each group.

Regarding treatment emergent clinical adverse events, only 1 subject out of the 34 [0.68%] evaluated from Group A, complained of two different adverse events. This was body ache and loose stools, occurring at different times. Two subjects out of the 29 in group B [0.585] suffered from hyperacidity. The duration, in all three instances, was short (<2 days), the intensity moderate, and the outcome satisfactory. None of these events was considered to be related to study drug by the investigator concerned.

Serious adverse events (those that could be fetal, life-threatening, disabling or requiring hospitalization for management) were not encountered during the course of the present study. There were no withdrawals on account of adverse events and both preparations were well accepted by study subjects. Compliance was excellent for 28 subjects [82.35%] in Group A and 22 [75.86%] in Group B. Only one subject in each group showed poor compliance.

All subjects reported normal pregnancy outcome without any stillbirths, congenital malformations of the fetus or neonatal complications altogether, 16 subjects out of the total study population of 63 (25.4%) had their pregnancy terminated by Caesarian section at term due to obstetrical indication only. Thus the caesarian section rate found in the study population was not higher than that to be expected in the normal course of institutional deliveries.

The results of the present study are in concordance with other randomized controlled trials conducted recently. This include an equivalence trial, comparing ginger to pyridoxine, in 291 women less than 16 weeks pregnant undertaken at a teaching hospital in Australia¹⁵. These women took 1.05 g of ginger or 75 mg of pyridoxine

daily for 3 weeks, and ginger was found to be equivalent to pyridoxine. In another study in 138 women in a teaching hospital in Thailand¹⁶, ginger 500 mg and pyridoxine 30 mg per day, administered orally in divided doses, for 3 days, proved to be equivalent in relieving the symptoms of morning sickness.

However, the major limitation of the present study has been that the sample size, currently attained, does not give it enough power to detect a small difference between groups even if that exists. Taking nausea score, as assessed by Visual Analog Scale, as the primary efficacy parameter, and assuming a standard deviation of 20 mm, it would be require 64 evaluable subjects in each group to detect a 10 mm difference in mean nausea scores with 80% power and 5% probability of Type I error. Another limitation has been that the study was single masked rather than double masked. The logistical difficulties inherent in genuine double binding is considerable and could not be overcome in our case.

Therefore, the present study should be viewed as a preliminary report regarding the efficacy of the test preparation in pregnant Indian women.

CONCLUSION

The present study has shown that both the formulations used are effective to comparable extents in reducing the severity of nausea and vomiting, this effect being evident from the end of the first week of treatment. Tolerability of the preparations was excellent, with respect to the clinical safety profile as well as the biochemical parameters. No severe or serious adverse events were encountered and there were no hospitalizations or withdrawals on account of adverse events. Study subjects showed satisfactory compliance. Thus, ginger extract can provide a safe and effective alternative for management of nausea and vomiting of pregnancy in lieu of the doxylamine-pyridoxine formulation that is currently widely used in Indian women. A larger multicentric study, conducted in a double blind design, can provide confirmation of the encouraging trend noted in the current study.

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