Efficacy of Gingocap as compared to pyridoxine in the treatment of nausea and vomiting during pregnancy

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Abstract: Nausea and vomiting is the common problem disturbing almost 80% of the females in initial three months of conception and later sometime throughout pregnancy. To find out the efficacy and safety of herbal coded test drug Gingocap in comparison with the control drug Pyridoxine, a randomized clinical case control study was conducted at the OPD of Yusra Medical Centre, Karachi and Amir Habib Medical Center and Maternity Home, Karachi. After administration of test and control drug the frequency of nausea and vomiting was noted after every 2 weeks on 2nd, 4th, 6th and 8th weeks during 60 days of the course of study. The percentage of reduction of nausea and vomiting symptoms from the baseline in cases treated with test Gingocap compared to control drug Pyridoxine was recorded. Overall 35 and 30 patients were administered Gingocap and Pyridoxine between 6-16 weeks conception respectively. The data analyzed through T-test using SPSS version 18.0. It was concluded that Gingocap has the potential to relieve the symptoms of nausea and vomiting and exhibited no side effects and this drug was acceptable by maximum number of the patients.

Keywords: Nausea and vomiting, pregnancy, gingocap, hyperemesis gravidarum, prospective, multicentre, randomized, clinical trial.

INTRODUCTION

The most prevalent symptoms in women during pregnancy is nausea and vomiting, generally time limited and unpleasant medical condition of pregnancy (Enkin, 2000). If left untreated may lead to multiple problems related to physical and psychological health. Despite the availability of several anti-emetics, pregnant women usually hesitate to use conventional medicine due to side and possible teratogenicity effect. Therefore after the conception, the women suffer from nausea and vomiting in pregnancy and their co-morbidities (Ebrahimi *et al.*, 2010). These problems ultimately call for an alternative treatment for nausea and vomiting during pregnancy.

Nausea is described as an unpleasant feeling generally preceding vomiting (Thomas, 1997). Vomiting is a condition in which stomach contents ejected through mouth. It begins after last menstrual period between the fourth and seventh week, and peak at 8^{th} to 12^{th} weeks and then diminishes by the 20^{th} week of gestation for most women. The nausea and vomiting in pregnancy cannot be differentiated as mild, the moderate or the severe; it can significantly impair patient's quality of life. It can directly affect patient's eating habit, sleep pattern, performance of daily activities and quality of life, work efficiency and family relationship, especially when left unmanaged (Jewell *et al.*, 2003, Lacroix *et al.*, 2000). The most severe form of nausea and vomiting in pregnancy is regarded as the hyperemesis gravidarum, characterized as constant vomiting (causes as weight loss in more than 5% of the pre-pregnancy weight), dryness, ketonuria and the electrolyte imbalance. This less common form may ultimately lead to hospitalization, liver damage, fetal harm and in severe cases; it may be controlled by the outpatient interventions (Bsat *et al.*, 2001).

Several reports exhibited that the treatment of nausea and vomiting responded to drug than placebo, it also has no teratogenic effects on fetus. Therefore it is a need that more scientific proof from clinical trials of the alternate medicine for the efficacy and toxicity be established for the treatment of this ailment. In this context, while applying treatment to pregnant women, frequent assessment of responses and their medical condition are required. Women with nausea and vomiting in pregnancy should be assessed daily or weekly, whereas those with hyper emesis gravid arum are evaluated much frequently.

Usually an estimated 50%-90% of pregnant women experience nausea and vomiting in pregnancy during their pregnancy, in the first trimester between 6-12 weeks (Jewell, 2003, Miller, 2002).

Several different drugs includes vitamins, antihistamine, anticholinergic, dopamine antagonist, butyrophnones, serotonin antagonists and corticosteroids are prescribed for managing nausea and vomiting in early pregnancy. But drugs were withdrawn from US market. It is for this reason alternate therapy is quite in demand, therefore, ginger has been used since ancient times for its antiemetic effect. Pyridoxine is extensively used for its antiemetic property and its comparison to Gingocap for their relative efficacy and safety through clinical trials would be beneficial.

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Methodology

This is randomized clinical case control study conducted at the OPD of "Yusra Medical Centre", Karachi and "Amir Habib Medical Center and Maternity Home", Karachi for the comparison of efficacy of herbal coded test drug "Gingocap" with the control drug "Pyridoxine".

Inclusion Criteria: Pregnant women with first trimester of pregnancy, women of any age, ethnicity and socioeconomic background and patients living in Karachi and willing to comply with study requirements.

Exclusion Criteria: Patients with uncontrolled hypertension and diabetes mellitus, persistently abnormal vital signs, patients suffering from coma, meningitis, encephalitis, head injuries, severe electrolyte abnormality, acidosis, infection. Malnutrition, chronic illness, severe neurological disorders, chronic renal failure, polycystic ovarian syndrome.

Consent: All patients were asked to provide the informed consent for their participation.

The test group: Test group registered n=30 patients following inclusion criteria and were treated with Test Drug (Gingocap 500mg) twice daily for 60 days with follow up visits at different intervals.

The control group: Similarly control group n=30 was enrolled following inclusion criteria and were treated with pyridoxine 25mg once daily for 60 days and subsequently follow ups at different intervals.

Method of preparation of dosage form

The herbal dosage form was designed and manufactured as follows:

Batch manufacturing record	
Product: Ginger granules-extract	Document Ref.: EXT-GNG-054-BMR
Batch Size: 5.0Kg /5.6gm X 5,000 Sachets	Product ID: SB, PS (18886)
Issue Date: 16-08-2012	Supersedes Issue: NEW
Shelf Life: 01 Year	Batch No:

Manufacturing steps of ginger extract

Extraction: The 50 Liters D.I. water was taken in the extractor and powder rhizome of the herb added into it, started the stirring and then continued heated till boiling. The temperature kept at 110-120^{o}C, and then the temperature was slowed down and maintained up to 90-100^{o}C for 2.5 hours. Filtration: When extraction was completed, the steam was released and the aqueous extract was filtered through 100 No. mesh. Concentration of the filtrate. After filtration, the filtrate was transferred to evaporator and filtrate. was concentrated through evaporation. The temperature should be from 100 - 110^{0}C. Thick extract: The filtrate was evaporated to obtain thick extract. The temperature was kept between 100 to 110^{o}C.

Precautions
Wear gloves, cap and mask
Area environmental conditions are as per material requirement
Scales are calibrated and checked before dispensing
Dispensing is performed in clean equipments / utensils
All dispensed material should properly be identified by status label
Dispensed raw material and auxiliaries are stored on the pallets with proper identification labels
Extractor and evaporator unit should be checked before initiation of the process
All utensils, tanks and machines / equipments bear clean tag
Area environmental conditions are as per product requirement
Clearance for all equipments have been taken from QA before manufacturing starts
Manufacturing staff wear gloves, masks, caps, etc
Line clearance is taken from the Quality Assurance auditor

Addition of preservatives: Sodium Benzoate and Potassium Sorbate were added to the concentrated thick extract and mixed for about 10 minutes.
Sodium Benzoate = 5 gm; Potassium Sorbate = 5gm

Manufacturing steps of ginger powder/ Granules

Microbial profile: Administration of Drugs: 5.7.1 Administration of Test Drug: The test group n=30 patients having complaints of nausea and vomiting in pregnancy was prescribed to coded herbal formulation assigned as "Gingocap" twice daily comprise of *Zingiber officinalis.* Administration of Control Drug: The control group n=30 having complaints of pregnancy associated nausea and vomiting was subjected to allopathic drug, Pyridoxine 25 mg thrice daily. Follow up Visits: After administration of test and control drug the frequency of nausea and vomiting were noted after 2weeks and analyzed through T-test using SPSS version 18.0. Sample Selection: Sample size selection in this clinical study was done based on general physical examination, Clinical Assessment: The clinical outcome was defined as follows: the percentage of reduction of associated symptoms from the baseline in cases treated with test drug 'Gingocap' compared with the control drug 'Pyridoxine'.

Efficacy measurements: The efficacy measurements between the two medicines herbal coded medicine (Gingocap) and conventional medicine (Pyridoxine) were also compared. The efficacy was determined in terms of reduction in the associated symptoms from the base lines and the clinical complains related to pregnancy.

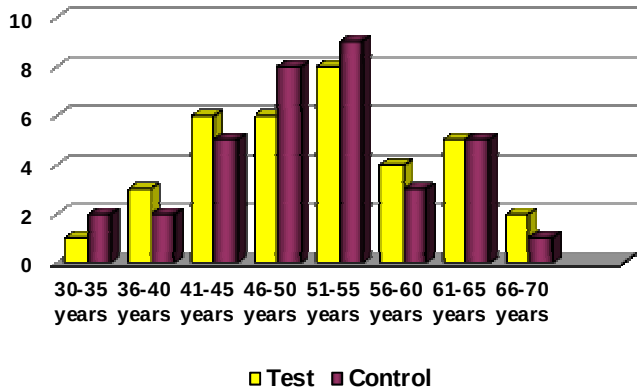
Data collection

The research data was collected for this study included history taking and physical examination, filling of clinical trial proforma, The trial conducted at Yusra Medical Centre, Karachi and Amir Habib Maternity Home, Karachi, between June 2012 and March 2013. Women with nausea or vomiting were eligible for the trial if they were between 6-16 weeks pregnant, with dates checked by LMP or ultrasound. Women were expelled if they had any signs of clinical dehydration, hyperemesis gravidarum, multiple gestation, ovarian cyst, gestational trophoblastic disease, acid peptic disorders, gastro esophageal reflux disease, any chronic or serious illness of major organs or taking medication other than those permitted by the study protocol or if they had any known allergy to ginger or vitamin B6. The previous use of antiemetic's, ginger, or vitamin B6, patients was exclude entry to the trial.

The ethical committee and research committee of the Faculty of Eastern Medicine has approved this study and written consent was obtained from all cases before the start of treatment. Patients were randomly distributed to receive either Gingocap or pyridoxine (vitamin B6). Women were instructed to take 500mg Gingocap twice daily or 25mg pyridoxine thrice daily for 8 weeks.

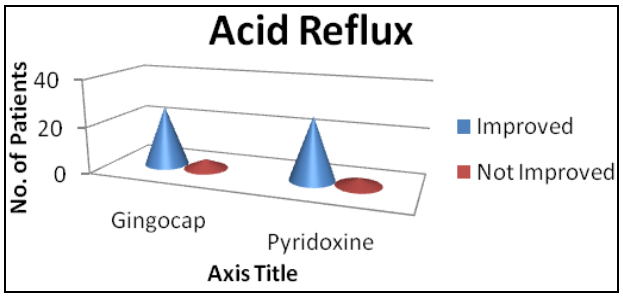
RESULTS

This multi-centered case control clinical trial was under taken to find out the efficacy of selected herbal medicines Gingocap for nausea and vomiting in pregnancy and compared with the conventional Allopathic medicine (Pyridoxine). The study conducted on 60 patients (graph 1) as an outdoor patient at Yusra Medical Centre and Amir Habib Medical Center and Maternity Home and their treatment strategy through both drugs.

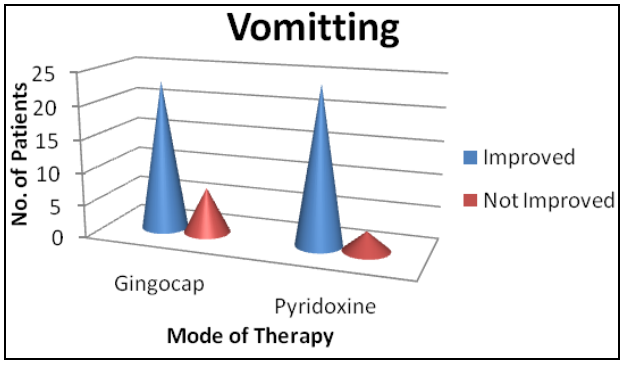


Graph 1: Distribution of class intervals in patient's age

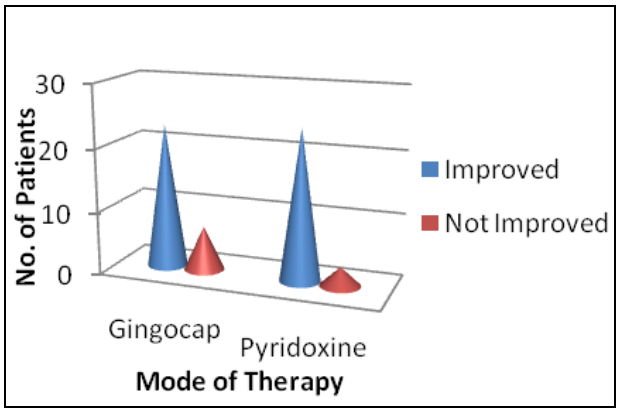
All selected cases were carefully examined and clinical history was recorded in the clinical trial proforma. The therapeutic evaluation of the drug was made on the basis of improvement in the nausea and vomiting in pregnancy at periodic intervals of 2 week on 2nd, 4th, 6th and 8th weeks for 60 days of the course of study. The data of 60 cases was collected from 1st Jun 2012 to 30th May 2013, which completed the clinical trial protocol.



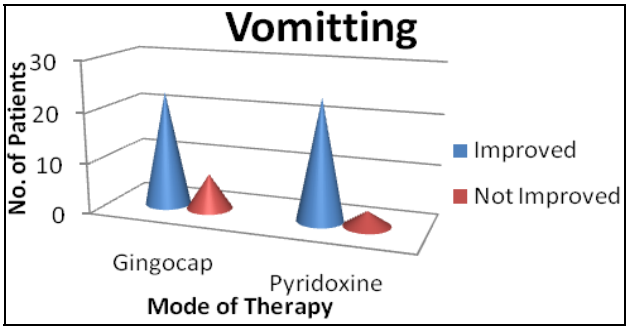
Graph 2: Acid Reflux



Graph 3: Vomiting



Graph 4: Heartburn



Graph 5: Palpitation

Table 2: Certificate of analysis

STEP #	PROCESS / PROCEDURE
STEP 01	DRY mixing: Took the following materials in Z - mixer and mix for 15 minutes. Icing sugar = 26.89Kg Citric acid (Grinded) =0.450Kg Aspartame =0.250Kg
STEP 02	Blending: Add Lemon Oil in Step – 1 with continuous mixing to get uniform powder blend. Lemon Oil =0.350Lit.
STEP 03	Preparation of wetting solution: Take 0.5 liter D.I water in a glass beaker, Add product Extract to it and mix for 10 minutes.
STEP 04	Granulation: Granulate blended powder (STEP -II) with wetting solution (STEP -III) for 20 minutes to achieve proper wet mass.
STEP 05	Sieving: Pass the wet mass through granulator with mesh # 10.
STEP 06	Drying: Dry the granules of STEP - 5 in tray drier at 65^{O}C Check LOD of the granules, which should be NMT 2%.
STEP 07	Sieving: Sieve the dry granules through mesh # 16 and collect the resulting granules in S.S bowl.
STEP 08	Final blending: Transfer the granules into Z - Mixer and add following material and mix for 15 minutes. Ascorbic acid =0.125Kg Collect the granular powder in polyethylene bag.

Table 3: Distribution of Age Group in Total Patients

Material:	*Zingiber officinale* Roscoe	
Local name:	Sonth/ Adrak	
English name:	Ginger	
Part used:	Rhizome	
Batch number:	2340	
Inspection	LIMITS	Results
Color:	Internally pale yellow to brown	--
Odor:	Characteristic	--
Taste:	Pungent and aromatic	--
Total ash:	NMT 6%	--
Ash insoluble in acid:	NMT 2%	--
Foreign matter:	NMT 2%	--
Moisture content:	NMT 5%	--
Qunatitative analysis: (HPLC)	Gingerols >5%	--

Table 4: Severity of nausea and vomiting in pregnancy before and after intervention with acid-reducing pharmacotherapy; *=p<0.05 compared to initial interview, (n=60)

Measures	Initial Interview	Follow-up Interview
Mean PUQE score ± SD	9.5±2.7	6.5±2.5*
Mean Well-being score ± SD	4.0±2.0	6.8±1.6*
Mean effectiveness of acid therapy in reducing HB/RF	n/a	8.2/10
Mean effectiveness of acid therapy in reducing nausea and vomiting in pregnancy	n/a	7.7/10

Table 5: Complaint-3, Acid reflux

Level of Improvement	Improved	Not Improved	p value
Gingocap	26 (86.66%)	4 (13.44%)	0.000
Pyridoxine	27 (90%)	3 (10%)	

Table 6: Complaint-4, Vomiting

Level of Improvement	Improved	Not Improved	p value
Gingocap	23 (76.66%)	7 (23.44%)	0.000
Pyridoxine	24 (80%)	6 (20%)	

Table 7: Complaint-5, Heartburn

Level of Improvement	Improved	Not Improved	p value
Gingocap	23 (76.66%)	7 (23.44%)	0.000
Pyridoxine	24 (80%)	6 (20%)	

Table 8: Complaint-6, Palpitation

Level of Improvement	Improved	Not Improved	p value
Gingocap	23 (76.66%)	7 (23.44%)	0.000
Pyridoxine	24 (80%)	6 (20%)	

The herbal coded formulation test drug (Gingocap) and 50% for Allopathic medicine as control drug (Pyridoxine). All data was analyzed by applying Paired Samples T-test and the level of significance was applied to validate and confirm the efficacy of both treatment drugs of test and control group. When compared the mean of age of over all patients, assigned for Gingocap and for allopathic, it was observed that there is not significant different between them as shown in table and graph.

Age distribution of the patients

The mean age of 35 patients in test group was 48.62+9.48 and the mean age of 35 patients in control group was 47.34+10.11 as shown in table. The distribution of patients was classified in different class interval ranging as shown in table 3.

Treatment assignment and follow-up

After adjustment 60 patients were consented to participate in the trial. Their pre-treatment nausea and vomiting in pregnancy and well-being score were noted and recorded and 35 patients were administered test drug Gingocap and 30 patients were administered for control drug Pyridoxine. Their follow-ups were recorded for the changes in nausea and vomiting in pregnancy and any observed side effects. All cases were clinically studied and completed the assigned therapy at the end of May 2013.

Consent to participate in the study was taken from 65 women. Three women were excluded because they scored >13 on the PUQE on 1st visit and were referred to their physician. Two women did not complete all the required interviews, and withdrew from the study. The remaining 60, who completed all four follow-ups, were included in the study (see table 5).

Clinical improvement

PUQI

The women having PUQI score at 1st visit was less than 13 were enrolled in this study 13. a significant decrease in PUQE scores at baseline and at end of treatment (from 9.6 ±3.0 to 6.5±2.5) ($p<0.0001$) (table 6.1). and significant improvement in the Well-being scores from the initial (4.0±2.0) to the follow-up (6.8±1.6) ($p<0.0001$) (table 4).

After analyzing paired sample t-test acid reflux in pre-treatment and post-treatment *Test* group. Since out of 30 subjects from test group 18 women were suffered from moderate complaint, 08 had severe and 4 had mild complaint. Among those, 26 showed complete improvement and 4 have shown no improvements. While in control group, after analyzing paired sample t-test, the acid reflux in pre-treatment and post-treatment groups. Since out of 30 subjects 10 had severe complaint, 16 had moderate and 4 had mild complaint. Among those 27 showed complete improvement and 3 no improvements as shown in table 5.

Vomiting

In *test* group, 22 had moderate and 08 had mild complaint. Among those 20 showed complete improvement and 3 mild improvements. While in *control group* 1 had severe complaint, 10 had moderate and 19

had mild complaint. Among those 24 showed complete improvement and 6 no improvement as shown in table 6.

Heartburn

In *test* group, 22 had moderate and 08 had mild complaint. Among those 20 showed complete improvement and 3 mild improvements. While in *control group* 1 had severe complaint, 10 had moderate and 19 had mild complaint. Among those 24 showed complete improvement and 6 no improvement as shown in table 7.

The results showed that the heartburn was a major complaint of the study and the prescribed control drug did not show the total efficacy as shown by the test drug-1 and test drug-2 for the complaint.

Palpitation

In *test* group, 22 patients had moderate and 08 had mild complaint. Among those 20 showed complete improvement and 3 mild improvements. While in *control group* 1 had severe complaint, 10 had moderate and 19 had mild complaint. Among those 24 showed complete improvement and 6 no improvement as shown in table 8.

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Overall analysis

An overall result of individual group is given in table 9 by using Paired sample t-test and level of significance of all the symptoms is calculated. Generally all the prescribed medicines has shown efficacy equal to each other. When we compare all these and their effects and patients compliances then Gingocap group have shown better results because of no side effects.

DISCUSSION

To our knowledge, this is the first study to be conducted prospectively, beginning prior to pregnancy until and including the post partum period, attempting to and an association with nausea and vomiting in pregnancy and depression, using questionnaires specially designed and validated to measure both nausea and vomiting in pregnancy and depression in pregnancy. Several published studies have linked nausea and vomiting in pregnancy with depression. Kitamura and colleagues administered a set of questionnaires in order to examine the severity of nausea and vomiting in pregnancy and Zung's Self Rating Depression Score to 1329 women who were attending a prenatal clinic. They observed that women in the depressed group had a significantly higher mean score of nausea and vomiting in pregnancy than the comparison group (Sripramote *et al.,* 2003). Chou and coworkers5 examined the relationship between psychosocial factors and incidence of nausea and vomiting in pregnancy in 113 women. They used the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) to measure depressive symptoms and a checklist to examine the frequency of occurrence of nausea and vomiting in pregnancy (occasional, frequent or absent) to establish nausea and vomiting in pregnancy. They concluded that pregnant women without nausea and vomiting in pregnancy had significantly lower CES-D scores than did women with frequent nausea and vomiting in pregnancy, suggesting that depressive symptoms were positively correlated with nausea and vomiting in pregnancy (Ensiyeh *et al.,* 2008). To measure psychiatric morbidity, Swallow and colleagues (Chittumma *et al.,* 2007) evaluated 273 women using the General Health questionnaire (GHQ), and to measure mood and illness perception, using visual analogue scales. These scores were compared with the scores of incidence and severity of nausea and vomiting in pregnancy, which had been measured using the nausea and vomiting in pregnancy instrument. They determined that high GHQ scores were associated with severe nausea and vomiting in pregnancy (Portnoi *et al.,* 2003). It was concluded that women with a psychiatric diagnosis suffered from more nausea and vomiting in pregnancy than did women with no psychiatric diagnosis (Portnoi *et al.,* 2003). The anxiety and depression in 230 pregnant women using the Hospital Anxiety and Depression Scale was examined. These results were compared to the total Rhodes scale score, and they found that there was an association with anxiety and depression during early pregnancy and severity of nausea and vomiting in pregnancy. Thus, there appears to be a correlation between nausea and vomiting in pregnancy and depression. The main limitation of the above studies is they did not examine this relationship prospectively; therefore, were not able to establish if depression preceded or resulted from symptoms of nausea and vomiting in pregnancy.

Many researches have conducted research to evaluate the efficacy of *Zingiber officinale*, almost 33 studies were focused in the past among them 15 to 20 trials can be corroborated the same findings as in our study and these were included in systemic review (Fischer *et al.,* 1991, Vutyavanich *et al.,* 2001). Almost all systemic trials exhibited the same findings regarding the efficacy and safety of *Zingiber officinale* as met in present clinical trial (Ernst *et al.,*, 2000, Jewell *et al.,* 2003). The argument can be put forth systemic reviews have cited that this herb with has the added benefit of safety in managing nausea and vomiting symptoms during pregnancy.

In this study, an association between high PUQE scores and high EPDS scores was not evident, although high PUQE scores were associated with low Wellbeing scores. While several of the questions on the EPDS scales measure somatic symptoms, which were similar to some

of the Wellbeing questions, an association was not observed between these two scores. In addition, the woman who scored highest on the EPDS scale (156) scored 4 on the PUQE scale, and the woman who scored the highest on the PUQE scale 12 scored 2 on the EPDS scale. Ere was one woman who scored 13 on 2 occasions, at 8 and 11 weeks, and at both time points, her PUQE scores were 7. Subsequently, she was treated for depression in the postpartum period. These findings suggest that she may have been suffering from an unidentified depression, which was not related to her symptoms of nausea and vomiting in pregnancy. The main limitation of our present study was that few of the women had severe nausea, with most cases reported as mild. A far larger sample size would be required to able to follow enough women to include individuals suffering from more severe nausea and vomiting in pregnancy, and therefore to allow a satisfactory comparison between high EPDS scores and high PUQE scores. Nevertheless, we have demonstrated a rigorous method for conducting such a study and other researchers could use this approach to conduct a similar study.

All patients enrolled in the study were evaluable for safety. Side effects were defined as sign and symptoms that first occurred or become more severe during the course of treatment. The majority of adverse events were assessed as mild in severity and self-limiting in nature.

Three patients treated with the test drug experienced the dryness of mouth, bloating of abdomen and mild sweating, which disappeared within two to three days and continued the treatment. Therefore, none of the patients withdrew from the study due to these adverse events in test and control group. No significant adverse effects were recorded in any group.

CONCLUSION

It is concluded that Gingocap has potential to relieve the symptoms of nausea and vomiting in pregnancy as effective within control and did not exhibit any of the side effects and this remedy as acceptable by maximum of the patients using this remedy.

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