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Efficacy of Doxylamine and Pyridoxine during Pregnancy Induced Nausea and Vomiting

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Abstract

Introduction: *Nausea and vomiting in pregnancy (NVP) is the most common medical condition of pregnancy causes a significant clinical, psychological and economic burden. Therefore, it is very important to treat this condition appropriately and effectively. The combination of Doxylamine and Pyridoxine is recommended as first-line therapy for nausea and vomiting in pregnancy.* **Objectives:** *To observe the therapeutic efficacy of combined Doxylamine and Pyridoxine for treatment of nausea and vomiting in pregnancy.* **Materials and Methods:** *An observational study was conducted on patients with nausea and vomiting in pregnancy attended the Model Family planning clinic in the Department of Obstetrics and Gynaecology, Sylhet MAG Osmani Medical College Hospital, Sylhet during the period from January 2019 to December 2019. A total 90 patients with clinically meaningful nausea vomiting (Pregnancy-Unique Quantification of Emesis [PUQE] score > 6) were selected and given 2-4 tablets each containing combined Doxylamine succinate 10 mg and Pyridoxine hydrochloride 10 mg based on a pre-specified titration protocol response to symptoms by respective physician and PUQE score was recorded in all participants before initiation of treatment and at 8th day and 15th day of treatment. In course of follow up period 7 patients were dropped out and finally 83 patients were analyzed in this study.* **Result:** *The mean PUQE score was decreased from 10.27 ± 1.76 to 7.94 ± 1.75 at 8th day and to 5.35 ± 1.47 at 15th day of treatment was significant ($p<0.001$). The percentage reduction of PUQE score was 23.14% at 8th day and 46.91% at 15th day of treatment. The difference was significant ($p<0.001$).* **Conclusion:** *Combined Doxylamine-Pyridoxine is effective and well tolerated in the treatment of nausea and vomiting in pregnancy (NVP).*

Keywords: *Nausea, Vomiting, Pregnancy, Combined Doxylamine-Pyridoxine.*

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Introduction:

Nausea is the unpleasant, painless sensation that may potentiate to vomit. Vomiting is an organized, autonomic response that ultimately results in the forceful expulsion of gastric contents through the mouth[1]. Nausea and vomiting of pregnancy (NVP) is the most common symptoms associated with pregnancy. The symptoms are usually worse in the morning, hence the name 'morning sickness', but it can occur throughout the day and night. Symptoms of NVP include nausea, retching and vomiting, usually appear between 4 and 9 weeks of pregnancy and subside between 12 and 16 weeks of pregnancy; however, about 15% of women, symptoms continue up to 20 weeks gestation and less than 10% of women suffer throughout their entire pregnancy[2].

Nausea and vomiting of pregnancy affect up to 90% of pregnant women[3,4]. NVP affects the health of both pregnant woman and her fetus. It can diminish the woman's quality of life and also contributes significantly to health care cost and time lost from work. The severity of NVP ranges from mild to severe by using the Pregnancy Unique Quantification of Emesis (PUQE) Score, severity of symptom are ranged between 3 (no symptom) to 15 (the worst symptoms). The most severe form of NVP is hyperemesis gravidarum (HG), affects between 0.3 and 2% of pregnant women[5].

The etiology of NVP is multi-factorial and still remains unknown. The hormonal changes during the first trimester of pregnancy include increase production of human chorionic gonadotropin hormone (hCG), oestrogen and progesterone. There is a temporal relationship between peak of hCG concentration and peak symptoms of NVP[6]. Numerous other factors such as psychiatric diseases, liver abnormalities, elevated cytokine levels, deficiencies in vitamin B_1, B_6 and also genetic predisposition have been suggested to contribute to the etiology of NVP[7-9].

Many non-pharmacological (Dietary and lifestyle modification) and pharmacological treatment regimens are available for treatment of NVP. Pharmacologic treatments include Antihistamines (Meclizine, Doxylamine), Dopamine antagonists (Metoclopramide, Domperidone), vitamin B6 (Pyridoxine), serotonin ($5HT_3$) antagonists (Ondansetron) or combinations of these substances[10].

The American College of Obstetricians and Gynecologists recommends combined Doxylamine and Pyridoxine as first-line agents when dietary and lifestyle changes is unsuccessful[11]. Antihistamines are commonly used during early pregnancy in the treatment of nausea and vomiting. Diphenhydramine, Dimenhydrinate, Meclizine and Doxylamine are first generation H1-receptor antagonists[12]. Doxylamine directly inhibit the action of histamine at the H1 receptor and indirectly affvestibular system and decreasing stimulation of the vomiting center. It has also inhibitory action on muscarinic receptor causing antiemetic activity[13].

Pyridoxine is a water-soluble vitamin, essential co-enzyme for the metabolism of amino acids, lipids and carbohydrates[14]. It is also a co-factor in γ-amino butyric acid (GABA) synthesis and GABA acting as the inhibitory neurotransmitter at Chemoreceptor trigger zone (CTZ) and suppresses vomiting[15]. The combination of Doxylamine and Pyridoxine, have a synergistic effect in the alleviation of NVP. In April 2013, the US Food and Drug Administration (FDA) approved combination of Doxylamine and Pyridoxine, for the treatment of NVP and considered as a Pregnancy Category A[16]. Several trials of combined Doxylamine and Pyridoxine shows improvement of NVP compared to placebo[17, 18].

So, this study is planned to assess the effectiveness of combined Doxylamine and Pyridoxine for the treatment of nausea and vomiting in pregnancy (NVP).

Materials and Methods:

This was an observational study conducted in the Department of Pharmacology and Therapeutics, Sylhet MAG Osmani Medical College, Sylhet in collaboration with Model Family planning clinic of Department of obstetrics and Gynaecology, Sylhet MAG Osmani Medical College Hospital, Sylhet during the period from 1st January 2019 to 31st December 2019. Patient's nausea with or without vomiting related to pregnancy, less than 16 weeks of gestation and clinically meaningful nausea and vomiting (PUQE score > 6) were included in this study. Women were excluded from the study if their nausea or vomiting predated the pregnancy, hyperemesis gravidarum (HG), medications taken in the past week that aggravate or alleviate nausea or vomiting, such as iron tablets, anti-emetics etc, others medical, surgical and gynecological causes of vomiting in pregnancy and history of allergy to the study medications. Convenient sampling method was applied to select sample.

Informed written consent was taken from the patient after detailed explanation of the process and purpose of the study. Clinical histories, physical examination, obstetrical evaluation and relevant investigation (USG of uterus for pregnancy profile or urine for pregnancy test) of the patient were done. After confirmed the diagnosis of NVP by respective gynaecologist, patients were asked to complete the Pregnancy-Unique Quantification of Emesis (PUQE) score at initial enrollment to grade the severity of nausea and vomiting experienced last 24 hours . The PUQE score incorporates the number of daily vomiting episodes, number of daily retching and length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe). Scores of 4–6 denote mild, Scores of 7–12 denote moderate and scores of 13–15 denote severe NVP. Those with PUQE score > 6 were enrolled in this study[19].

In this way 90 patients with nausea and vomiting in pregnancy were selected. Before initiating treatment, age, estimated gestational age, BMI, current medications, gravidity and parity were recorded for each patient. The patients were prescribed combined Doxylamine succinate 10 mg and

Pyridoxine hydrochloride 10 mg two tablets orally at bedtime on Day 1. If this dose adequately control symptoms, continue taking two tablets daily at bed times. If symptoms persist into the afternoon of Day-2, take the usual dose of two tablets at bed time that night then take three tablets starting on Day-3 (one tablet in the morning and two tablets at bedtime). If three tablets adequately control symptoms, continue taking three tablets daily. Otherwise take four tablets starting on Day-4 (one tablet in the morning, one tablet in mid-afternoon and two tablets at bedtime) by attending gynaecologist. The maximum recommended dose is four tablets daily. The total period of study was 15 day consisting of 14 dosing days[20].

Patients were reevaluated on 8th and 15th day after initiating the drug regimen using PUQE score. All the collected data were compiled and analyzed using the Statistical Package for Social Science (SPSS) version 25.0. Quantitative data were expressed as mean and standard deviation and qualitative data were expressed in frequency and percentage. Analysis was done by repeated measure ANOVA and Z-test for proportion accordingly.

Result:

Total 90 pregnant women with NVP were enrolled and in course of follow up period 7 patients failed to complete study follow up visit were excluded from analysis. So, 83 patients were analyzed in this study.

Table-I: Distribution of the patients by baseline characteristics.

Parameters	Study group (n=83)
Age in years (Mean ± SD)	24.45 ± 4.39
Gestational age in weeks (Mean ± SD)	9.00 ± 2.62
Gravida	
Primigravida n (%)	25 (30.1)
Multigravida n (%)	58 (69.9)
BMI in Kg/M^2 (Mean ± SD)	20.14 ± 1.88

Table- II: showed the effects of Combined Doxylamine and Pyridoxine on the PUQE score in patients with NVP estimated at baseline, 8th and 15th day of treatment.

The mean PUQE score was 10.27 ± 1.76 before the initiation of treatment which decreased gradually to 7.94 ± 1.75 at 8th day and to 5.35 ± 1.47 at 15th day of treatment. The overall difference from the baseline to the end point of treatment was significant (F=843.620; df=2; p<0.001). Post hoc analysis revealed that PUQE score decreased significantly at 8th day (p<0.001) and at 15th day (p<0.001) of treatment from baseline; and between 8th and 15th day (p<0.001) of treatment.

Table-II: Effects of Combined Doxylamine-Pyridoxine on the PUQE score

PUQE Score (Mean ± SD)					
Study (n=83)	group	Baseline '0' day	At 8th day	At 15th day	*p value
		10.27 ± 1.76	7.94 ± 1.75	5.35 ± 1.47	p<0.001

* Repeated measure ANOVA.

Table-III: showed the percentage reduction in PUQE score estimated at 8th day and 15th day of treatment. The percentage reduction of PUQE score was 23.14 at 8th day and 46.91 at 15th day of treatment. Difference between 8th day and 15th day was statistically significant (Z=-3.314; p<0.001).

Table–III: Percentage reduction of PUQE score on combined Doxylamine-Pyridoxine treatment

Percentage reduction of PUQE score				
Study (n=83)	group	At 8th day	At 15th day	*p value
		23.14	46.91	p<0.001

*Z-test for proportion

Discussion:

In this study the age of the patients ranged from 18 to 38 years with the mean age of 24.45 ± 4.39 years. This result was consistent with the study of Koren et al., (2015) which reported the maternal age of 25.9 ± 6 years in combined Doxylamine-Pyridoxine treated group of NVP and 25.0 ± 5.7 years in placebo group; difference was not significant (p=0.23)[20].

In the present study the mean gestational age was 9.00 ± 2.62 weeks. This finding was concordant with the study of Koren et al., (2015) which reported the mean gestational age of patients with NVP was 9.3 ± 2.0 weeks in combined Doxylamine-Pyridoxine treated group and was 9.3 ± 1.8 weeks in placebo group; which was not significant (p=0.75)[20]. Oliveira et al., (2014) found the median gestational age of women with NVP was 8 (IQR, 7.1-8.9) weeks in Ondansetron group and 8.1 (IQR, 7.2-9.9) weeks in Doxylamine-Pyridoxine treated group; the difference was not statistically significant (p=0.54)[21].

In the current study 30.1% patients were primigravid and 69.9% patients were multigravida. This result was in line with the study of Koren et al., (2015) where they found 77.1% of patients with NVP treated with combined Doxylamine-Pyridoxine were multipara[20]. Oliveira et al., (2014) found median gravid was 2 (IQR, 1-3) in Ondansetron treated group and was same in combined Doxylamine-Pyridoxine group; the difference was not statistically significant (p>0.05)[21]. In the present study the mean BMI (Kg/M^2) was 20.14 ± 1.88. In this regards Koren et al., (2015) found the mean BMI of patients with NVP of combined Doxylamine-Pyridoxine treated group was 28.77 ± 7.60 Kg/M^2; whereas the mean BMI of patients with NVP of placebo treated group was 29.67 ± 11.20 Kg/M^2; difference was not significant (p=0.95)[20] .

This study showed the effect of combined Doxylamine and Pyridoxine on PUQE score in patients with NVP estimated at baseline, 8th and 15th day of treatment. The mean PUQE score was 10.27 ± 1.76 before the initiation of treatment which decreased gradually to 7.94 ± 1.75 at 8th day and to 5.35 ± 1.47 at 15th day of treatment. The overall difference from the baseline to the end point of treatment was significant (p<0.001) and the Post hoc results indicated significant

decrease at 8th day ($p<0.001$) and at 15th day ($p<0.001$) of treatment from baseline; and between 8th and 15th day ($p<0.001$) of treatment. In this aspects Koren et al., (2016) found that combined Doxylamine and Pyridoxine treatment lead decrease of PUQE score in NVP symptoms at end of treatment from baseline (PUQE score 9.0 ± 2.1 to 4.2 ± 1.9)[18]. In another study Koren et al., (2010) found that combined Doxylamine and Pyridoxine treatment lead to significantly greater improvement in NVP symptoms as compared with placebo (-4.8 ± 2.7 PUQE score vs -3.9 ± 2.6; $p=0.006$)[17].

This study revealed that the percentage reduction of PUQE score was 23.14 at 8th day and 46.91 at 15th day of treatment. The difference between 8th day and 15th day of treatment was significant ($p<0.001$). Koren et al., (2016) reported the percentage reduction of PUQE score was 44.4% at 5th day and 53.0% at 15th day of treatment in combined Doxylamine-Pyridoxine treated group[18].

This study was conducted in tertiary hospital and did not represent the actual situation of the country. Sample size was small and duration of treatment period was short.

Conclusion:

This study, concluded that combined Doxylamine-Pyridoxine up to 40 mg daily is effective in the treatment of nausea and vomiting in pregnancy with good safety profile.

A further study involving multicenter, large sample size should be conducted to evaluate the efficacy and safety of combined Doxylamine-Pyridoxine in the treatment of nausea and vomiting in pregnancy.

Conflict of Interest: None.

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