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ORIGINAL ARTICLE

Comparison of Efficacy of Granisetron and Promethazine in Control of Hyperemesis Gravidarum

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Abstract

Purpose Hyperemesis gravidarum is the third leading cause of hospitalization during pregnancy. 5-HT3-receptor antagonists are the most effective against chemotherapy-induced nausea and vomiting and radiation. This randomized study aimed to compare and evaluate the efficacies of granisetron and promethazine for controlling nausea and vomiting of pregnancy.

Methods The included patients were administered (oral and intravenous) granisetron and promethazine randomly. The patients were evaluated for nausea and vomiting by a senior gynecology resident blinded to designated drugs.

Results This study revealed that granisetron significantly decreased nausea and vomiting in pregnant women

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($p < 0.05$). Greater patient satisfaction and lesser adverse drug reactions in women receiving granisetron observed in this study suggest that it can be introduced as a more effective and safer drug in comparison with promethazine. *Conclusions* Considering the prevalence of nausea and vomiting of pregnancy and hyperemesis gravidarum, we can state that it is a health-related problem with economic, social and psychological dimensions. All efforts especially simple outpatient strategies to reduce its severity will help the pregnant woman continue her pregnancy with more satisfaction.

Keywords Granisetron · Hyperemesis Gravidarum · Promethazine

Introduction

Nausea and vomiting of pregnancy affect approximately 75–80 % of pregnant women. Symptoms generally cease by the 12th week of pregnancy; however, up to 15 % of the pregnant women experience persistent nausea and vomiting until delivery [1]. Hyperemesis gravidarum is the third leading cause of hospitalization during pregnancy [1, 2]. Although the condition is most commonly self-limiting, nearly 0.3–2.3 % of the pregnant population may experience hyperemesis gravidarum, typically in the first trimester, which is a condition diagnosed by exclusion; other causes of vomiting such as urinary tract infection, gastrointestinal infection, and pancreatitis must be considered first [1–3]. Hyperemesis gravidarum is defined as persistent vomiting, retching, severe dehydration, electrolyte disturbances, weight loss greater than 5 % of prepregnancy weight, and significant ketonuria [1, 4, 5]. The etiology and pathogenesis of hyperemesis gravidarum are complex and multifactorial, which results in the difficulty in its management. Different theories suggest anatomical, hormonal, infective, and psychological factors [1, 2].

The management of hyperemesis gravidarum includes dietary changes, intravenous fluid administration, electrolyte abnormality correction, vitamin supplementation (pyridoxine), antiemetic therapy, and psychological support. Hospitalization is recommended for any patient who is ketotic and unable to maintain adequate hydration [1, 2].

A number of dopamine antagonists (phenothiazines like prochlorperazine and promethazine), 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists (like ondansetron and granisetron), and corticosteroids have been used for treatment of nausea and vomiting of pregnancy [1]. Treatment of hyperemesis gravidarum is started with the replacement of intravenous fluid and phenothiazine or metoclopramide. If symptoms persist, ondansetron can be added. In severe or refractory cases, corticosteroids are prescribed [1].

5-HT$_3$ receptor antagonists are the most effective against chemotherapy-induced nausea and vomiting and radiation (total body and fractionated abdominal radiation). This class of antiemetics is less effective in postoperative nausea and vomiting and has no efficacy in motion sickness [6]. Although ondansetron from this class of antiemetics has been used for controlling nausea and vomiting of pregnancy, there are limited safety data regarding 5-HT$_3$ receptor antagonists in pregnancy. Further studies are needed to confirm their safety [7–9].

Granisetron (a selective 5-HT$_3$ receptor antagonist with little or no affinity for other serotonin receptors) has never been used for hyperemesis gravidarum. In contrast, promethazine (an H_1 receptor-blocking agent), which is recommended for the prevention and control of postoperative nausea and vomiting and motion sickness, has been used widely for controlling nausea and vomiting of pregnancy [1–3, 6, 10].

This double-blind, randomized, controlled clinical trial was planned to assess the efficacy of oral granisetron versus oral promethazine for the management of hyperemesis gravidarum to determine whether granisetron may be a superior antiemetic. The secondary outcome was to assess the incidence of adverse drug reactions of the two medications and to determine the patient satisfaction with antiemetic therapy.

Materials and Methods

This randomized, controlled, double-blinded clinical trial was conducted in Dr. Shariati Hospital, a tertiary care university hospital in Tehran, Iran. This clinical trial is registered with www.irct.ir, number IRCT201108144927N2. Approvals of our institutional ethics committee and informed written consent from each patient were obtained. The trial was conducted from February 1, 2011 to February 1, 2012.

Thirty two patients, aged between 18 and 35 years with presumed hyperemesis gravidarum, were approached to participate in this trial as soon as they were determined to require an antiemetic. Inclusion criteria were clinical hyperemesis gravidarum with detectable ketonuria by urine dipstick (more than +1 ketonuria) at a gestation of 20 weeks or less. Patients were excluded from the study if they showed evidence of hepatic and thyroid dysfunction. Patients with molar pregnancy, patients with preexisting medical conditions that can cause nausea and vomiting (like urinary tract infections, gastrointestinal causes of vomiting, and diabetic ketoacidosis), and patients who had a hypersensitivity reaction to any of the study medications were excluded.

On arrival in the obstetrics emergency room, the patients were randomized into two treatment groups of 16 patients each. The two treatment groups were randomized into blocks of four each containing equal number of the patients.

In our hospital, initially as standard treatment, patients with hyperemesis gravidarum receive intravenous rehydration with the addition of potassium chloride as required if hypokalemic. Also during the first 24 h, patients receive intravenous ranitidine and pyridoxine. The history of vomiting was quantified with the Pregnancy-Unique Quantification of Emesis (PUQE) scoring system, shown in Table 1. All patients were reassessed after the first 24 h. Those patients with a PUQE score of 13 or higher were included in this study. The PUQE score for each patient was calculated by focusing on the number of episodes of nausea, the number of episodes of retching, and the number of episodes of vomiting in the preceding 12 h. The PUQE score ranges from 1 to 15 [5].

The investigator, the patient, and the nurse were blinded to the randomization and treatment type. The first doses of both drugs were administered intravenously to prevent gastrointestinal adverse reactions. The intravenous medications were prepared by the hospital investigational drug service. The drugs were labeled A as Phenergan® (promethazine) 25 mg/1 ml (Sanofi-Aventis pharmaceuticals) or B as Kytril® (granisetron) 1 mg/ml (Roche pharmaceuticals). The syringes were identical in color, clarity, and volume. The nurse placed a peripheral intravenous catheter and administered the drug over 2 min. The investigator assessed the adverse drug effects in patients 30 min after the intravenous administration. From the second day onward, both drugs were administered orally until 2 weeks after discharge. Tablet Phenergan® 25 mg (Promethazine, Sanofi-Aventis pharmaceuticals) was administered 25 mg every 6 h, and Gratil® 1 mg (Granisetron, Aburaihan pharmaceutical Co.) was administered 1 mg every 12 h plus two placebo tablets to maintain the blindness of the study. After discharge, patients were instructed to take the drugs on an as-per-needed basis.

The patients were evaluated for nausea and vomiting by a senior gynecology resident blinded to designated drugs. Nausea and vomiting were assessed by direct questioning of the patients. Nausea was defined as an unpleasant feeling associated with awareness of the urge to vomit, whereas vomiting was defined as the forceful expulsion of gastric contents from the mouth [11]. Incidence and severity of nausea and vomiting were documented on arrival, after 48 h, 1, and 2 weeks after discharge. Nausea was scored using a 5-point linear verbal rating scale (VRS) from 0 to 5, with "0" representing no nausea and "5" representing nausea as bad as it can possibly be.

At 1 and 2 weeks following discharge, the patients were contacted by telephone to assess the adverse drug reactions of the medications and also patients' satisfaction with the antiemetic drug using a 0 (very dissatisfied) to 10 (very satisfied) scale. The adverse effects were constipation, diarrhea, fever, headache, abdominal pain, dyspepsia, chest pain, allergic reactions, somnolence, weakness, seizure, blurred vision, anorexia, dry mouth, syncope, difficulty in urination, asthenia, arrhythmia, hypertension, and weight gain.

Descriptive statistics (means, standard deviations, and percentages) were used to characterize the population by using the Statistical Package for Social Sciences (SPSS for MS windows version 19, 2010). Student's t test was used for comparison of demographics (age and gestational age) and lab results between the two groups. Wilcoxon-Signed Rank Test was used to compare vomiting episodes frequencies on admission day and 48 h later within each group and between groups, and also to compare nausea scores on admission day and 48 h later within each group. Mann–Whitney *U* test was used to compare nausea scores on admission day and 48 h later between groups. Independent Samples Test was used to find the probable correlation between sex of fetus or multiple gestation and vomiting episodes or weight changes between groups. Chi-square tests were used to assess the correlation between the sex of fetus or multiple gestations, and nausea score. All

Table 1 Motherisk PUQE-24 scoring system

In the last 12 h, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 h or less (2)	2–3 h (3)	4– h (4)	> 6 h (5)
In the last 12 h, have you vomited or thrown up?	≥7 times (5)	5–6 times (4)	3–4 times (3)	1–2 times (2)	I did not throw up (1)
In the last 12 h, how many times have you had retching or dry heaves without bringing anything up?	≥7 times (5)	5–6 times (4)	3–4 times (3)	1–2 times (2)	None (1)

PUQE score: Mild ≤ 6; Moderate = 7–12; Severe = 13–15.

How many hours have you slept out of 24 h? Why?

On a scale of 0–10, how would you rate your well-being? 0 (worst possible) 10 (The best you felt before pregnancy)

Can you tell me what causes you to feel that way?

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tests were two-sided. A p value less than 0.05 was considered as statistically significant.

Results

A preliminary analysis sought to determine the comparability of the two groups before treatment in terms of patients' age, gestational age, sex of fetus, the number of episodes of nausea, the number of episodes of vomiting, and weight loss due to nausea and vomiting of pregnancy. The results are shown in Table 2. There were no differences in patient demographics between the groups.

The granisetron group was superior to promethazine group at 48 h after treatment. The patients in the granisetron group experienced significantly less vomiting episodes than the patients in the promethazine group. Also the nausea scores were significantly lower in the granisetron group than those in the promethazine group. The results showed that the patients in granisetron group were more satisfied with the treatment than patients in the promethazine group (Table 3). Although there was a numerically higher weight gain 2 weeks after discharge in the granisetron group, this difference did not reach statistical significance ($p = 0.863$).

There were no serious adverse reactions noted in any of the study participants. Only six patients in promethazine group showed adverse drug reactions including somnolence, weakness, anorexia, and dry mouth.

Despite the shorter length of hospital stay, higher weight gain and lower rehospitalization at the end of the first week of treatment were observed in the granisetron group, these differences did not reach statistical significance (Tables 3, 4).

Discussion

This study revealed that granisetron significantly decreased nausea and vomiting in pregnant women. Greater patient satisfaction and lesser adverse drug reactions in women receiving granisetron suggest that it can be introduced as a more effective and safer drug in comparison with promethazine. These statistically significant differences in addition to nonsignificant differences such as more weight gain, shorter hospital stay, and lower rehospitalization make this 5-HT3 receptor antagonist an alternative treatment for hyperemesis gravidarum.

Hyperemesis gravidarum causes psychosocial morbidity. Some of the social and psychological consequences are negative impact on mental health and decision to terminate pregnancy [4]. Financial burden of nausea and vomiting on health care system cannot be overlooked. In addition to the cost of hospitalization and drug therapy, nausea and vomiting of pregnancy significantly affect a woman's personal and professional life and reduces job efficiency and productivity [1]. It strengthens the need to provide appropriate treatment of nausea and vomiting of pregnancy.

Promethazine an H1 receptor-blocking agent is used for the prevention and control of postoperative nausea and vomiting and motion sickness [11]. Although it is classified as drug group C in pregnant patients, it is used widely for controlling nausea and vomiting of pregnancy.

5-HT3 receptor antagonists have exerted an appropriate efficacy in nonpregnant patients with nausea and vomiting of various etiologies. Although animal studies have shown the safety of ondansetron in pregnancy, we lack enough human data on its safety for hyperemesis treatment. In addition, there are few data on the safety of other 5-HT3 receptor antagonists in pregnant patients, and a majority of studies evaluating the efficacy of antiemetic drugs have been conducted in postoperative and chemotherapy-associated populations [8–10].

On the other hand, although ondansetron has been used for controlling nausea and vomiting of pregnancy, there are limited safety data regarding 5-HT3 receptor antagonists for treatment of nausea and vomiting of pregnancy [11]. However, it should be remembered that this drug is used for approximately a short period in pregnancy.

Granisetron is a selective 5-HT3 receptor antagonist with little or no affinity for other serotonin receptors is classified as drug group B in pregnant patients and approved by the FDA (Food and Drug Administration) for the treatment of post-operative nausea and vomiting in adults [7]. 5-HT3

Table 2 Characteristics of trial participants according to random assignment to granisetron or promethazine

Variables	Granisetron ($n = 16$)	Promethazine ($n = 16$)	p value
Age (year)	26.7 ± 4.4	28.7 ± 7.0	0.341
Gestational age (week)	9.8 ± 2.3	9.8 ± 3.1	0.989
Sex of fetus (male/female/twin) (n)	5/6/5	5/8/3	0.675
Vomiting episodes per day (n)	6.8 ± 3.0	4.9 ± 3.0	0.105
Nausea score (0–5)	4.9	5.0	0.164
Weight loss due to nausea and vomiting (Kg)	2.1 ± 1.8	2.9 ± 2.2	0.310

Data presented as mean ± SD

Table 3 Vomiting episodes and nausea scores after treatment (first outcome)

Variables	Granisetron ($n = 16$)			Promethazine ($n = 16$)			p value
	Base	After 48 h	p value	Base	After 48 h	p value	After 48 h
Nausea score (0–5)	4.9	0.1	0.001	5.0	2.5	0.002	0.001
Vomiting episodes per day (n)	6.8	1.1	0.001	4.9	1.5	0.002	0.007

Table 4 Adverse drug reactions and patient satisfaction after treatment (second outcome)

Variables	Granisetron ($n = 16$)	Promethazine ($n = 16$)	p value
Patient satisfaction level (Score 0–5)- *mean*	5.0	4.5	0.018
Adverse drug reaction (number)—*n*	0	6	0.007
Hospital stay (day)—mean ± SD	3.2 ± 1.1	2.2 ± 1.6	0.108
Weight gain (kg)—mean ± SD	1.28 ± 0.82	1.21 ± 0.99	0.863
Rehospitalization (number)—*n*	0	1	0.259
Change between treatment groups(number)—*n*	1	6	0.033

receptor antagonists exert appropriate clinical efficacy and low incidence of adverse drug reactions. In comparison with ondansetron, granisetron is a more potent antagonist with a longer duration of action [12].

No data have been published so far to support the superiority of either of these two drugs (granisetron and promethazine) over the other. There are head-to-head comparisons in prevention and treatment of nausea and vomiting between 5-HT3 receptor antagonists and other antiemetics (e.g., metoclopramide, droperidol, and dexamethasone) [10, 13, 14]. There are no randomized clinical trials to evaluate and compare the effectiveness and safety of granisetron for hyperemesis gravidarum. Although it has shown no teratogenicity in animal studies, no evidence is available for its efficacy in hyperemesis gravidarum [2].

Although there exist certain data about effects of other 5-HT3 receptor antagonist (ondansetron) on hyperemesis gravidarum [15], our study was novel in using granisetron for pregnancy-related nausea and vomiting. Regarding management of hyperemesis gravidarum, promethazine has been compared with ondansetron, but no controlled clinical trial has been reported for granisetron in this context.

Considering the prevalence of nausea and vomiting of pregnancy and hyperemesis gravidarum, we can state that it is a health-related problem with economic, social, and psychological dimensions. All efforts especially with easy and outpatient strategies to reduce its severity will help the pregnant woman to continue her pregnancy with more satisfaction. According to our results, granisetron has the aforementioned benefits.

There are limitations to this study. The conclusion is only valid relative to the doses used in this clinical trial. No placebo group was included, because institutional review boards considered it unethical to deprive the patients from antiemetics. Major limitation in this clinical trial is its small sample size. However, our randomized design, similar basal characteristics between two comparison groups, and a 2-week timescale add higher value for our evidences; further studies with randomized design and power calculation in a larger population are warranted.

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Compliance with Ethical Requirements and Conflict of Interest The authors also state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004). We state our study does not violate the policies and/or procedures established by journals such as those described in "Specific Inappropriate Acts in Publication Process". The authors declare that they have no competing interests.

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