

A Comparable Study on Efficacy of Granisetron and Promethazine in Controlling Hyperemesis Gravidarum

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Abstract

Purpose: Hyperemesis gravidarum is one of the leading causes of hospitalization during pregnancy. This randomized study was aimed to compare and evaluate the efficacy of granisetron and promethazine in controlling nausea and vomiting in pregnancy.

Materials and Methods: This study was done in the Department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, over a period of 6 months from February 2019 to July 2019. The included patients were administered granisetron and promethazine randomly and evaluated for nausea and vomiting by senior gynecologist blinded to designated drugs.

Results: This study showed that granisetron was more effective than promethazine in controlling nausea and vomiting in pregnant patients. Greater patient satisfaction and less adverse drug reaction were observed in women receiving granisetron.

Conclusion: Hyperemesis gravidarum is a health-related problem with social, economic, and psychological dimensions. All efforts, especially simple outpatient strategies, can reduce the severity of this condition and will help pregnant women to continue her pregnancy with satisfaction.

Key words: Granisetron, Hyperemesis gravidarum, Promethazine

INTRODUCTION

Pregnancy frequently causes nausea and vomiting; the cause appears to be rapidly increasing levels of estrogen or the beta-subunit of human chorionic gonadotropin (β -hCG). Vomiting usually develops at about 5-week gestation, peaks at about 9 weeks, and disappears by about 16 or 18 weeks. It usually occurs in the morning, although it can occur at any time of day. Women with morning sickness continue to gain weight and do not become dehydrated.

Hyperemesis gravidarum is probably an extreme form of normal nausea and vomiting during pregnancy. It can be distinguished because it can cause the following.

- Weight loss (>5% of weight)
- Dehydration
- Ketosis
- Electrolyte imbalance.

Hyperemesis gravidarum may cause mild transient hyperthyroidism. Hyperemesis gravidarum that persists the past 16–18 weeks is uncommon but may seriously damage the liver causing severe centrilobular necrosis or widespread fatty degeneration and may cause Wernicke's encephalopathy or esophageal varices rupture.

Clinician's suspects hyperemesis gravidarum based on symptoms such as onset, duration, and frequency of vomiting; exacerbating and relieving factors; and type and amount of emesis. Serial weight measurements can support the diagnosis. If hyperemesis gravidarum is suspected, urine ketones, thyroid-stimulating hormone, serum electrolytes, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, magnesium, phosphorus, and, sometimes, body weight are measured. Obstetrics ultrasonography should be

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Month of Submission : 06-2019
Month of Peer Review : 07-2019
Month of Acceptance : 08-2019
Month of Publishing : 08-2019

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done to rule out hydatidiform mole and multifetal pregnancy.

The management includes dietary changes, intravenous fluid infusion, electrolyte imbalance correction, vitamin supplementation, antiemetic therapy, and psychological support. Dehydrated and ketotic patient should be hospitalized for the management of hyperemesis gravidarum. A number of dopamine antagonist (phenothiazines such as prochlorperazine and promethazine), 5HT₃ receptor antagonists (ondansetron and granisetron), and steroids have been used for the treatment of nausea and vomiting.^[1,2] Treatment of hyperemesis gravidarum is initiated with intravenous fluid and antiemetics. Granisetron (selective 5HT₃ receptor antagonist) has not been regularly used for hyperemesis gravidarum.^[3] In contrast, promethazine (an H₁ receptor blocking agent) is being used for prevention and control of post-operative nausea and vomiting and hyperemesis gravidarum.^[4,5] This double-blinded, randomized controlled clinical trial was planned to assess the efficacy of oral granisetron and oral promethazine for the management of hyperemesis gravidarum and to determine whether granisetron may be a superior antiemetic over promethazine.

MATERIALS AND METHODS

This randomized controlled, double-blinded clinical trial was conducted at the Department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, from February 2019 to July 2019. Twenty patients between 18 and 35 years with hyperemesis gravidarum attending gynecology outpatient department (GOPD) and labor room were enrolled in this trial.

Inclusion Criteria

The following criteria were included in the study:

1. Clinical symptoms such as nausea and vomiting
2. Ketonuria by urine dipstick (more than +1 ketonuria)
3. Gestational age 20 weeks or less.

Exclusion Criteria

The following criteria were excluded from the study:

1. Molar pregnancy and multifetal pregnancy
2. Hepatic and thyroid dysfunction

3. Pre-existing medical conditions such as urinary tract infection, gastrointestinal infection, and diabetic ketoacidosis
4. Hypersensitivity reaction to drugs being studied.

On arrival in labor room and GOPD, the patients were randomized into two treatment groups of 10 patients each. On admission, the patients with hyperemesis gravidarum receive intravenous fluid, ranitidine, and pyridoxine. Based on the history of vomiting, patients were quantified with Pregnancy-Unique Quantification of Emesis scoring system [Table 1]. Patients with score of 13 or higher were included in the study.

The patients and the nurse were blinded to the randomization and treatment type. The drugs were labeled as (a) promethazine, 25 mg/ml or (b) granisetron, 1 mg/ml. The drugs were given through intravenous line over 2 min. The adverse effect of drugs was assessed in patients after 30 min of intravenous administration.

From the 2nd day onward, both drugs were administered orally until 2 weeks after discharge. Tab promethazine 25 mg was administered 4 times a day or every 6 h. Tab granisetron 1 mg was administered every 12 hourly with two placebo tablets to maintain blindness of study. The patients were assessed for nausea and vomiting by gynecologist blinded to designated drugs.

Nausea is an unpleasant feeling associated with awareness of the urge to vomit, whereas vomiting was defined as forceful expulsion of gastric content from mouth.^[6] Severity of nausea and vomiting was assessed at the time of admission, after 48 h, 1 week, and 2 weeks after discharge. Nausea was scored using a 5-point linear verbal rating scale from 0 to 5, with "0" representing no nausea and "5" representing nausea as bad as it can possibly be.

At 1 week and 2 weeks following discharge, the patients were contacted to assess the adverse drug reaction and satisfaction with the antiemetic drug using a 0 (very dissatisfied) to 10 (very satisfied) scale. The adverse effects were fever, headache, constipation, dyspepsia, allergic reaction, seizure, anorexia, dry mouth, difficulty in urination, hypertension, and arrhythmia.

Table 1: PUQE scoring system

In the past 12 h, for how long you feel 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 past 12 h, have you vomited or thrown up?	≥7 times (5)	5–6 times (4)	3–4 times (3)	1–2 times (2)	Nil (1)
In the past 12 h, how many times have you had retching or dry heave without bringing anything up?	≥7 times (5)	5–6 times (4)	3–4 times (3)	1–2 times (2)	Nil (1)

PUQE score: Mild ≤6; moderate: 7–12; severe: 13–15. PUQE: Pregnancy-Unique Quantification of Emesis

Table 2: Vomiting episodes and nausea scores after treatment (first outcome)

Variables	Granisetron (n=10)			Promethazine (n=10)		
	Base	After 48 h	P-value	Base	After 48 h	P-value
Nausea scores (0–5)	4.5	0.2	0.001	4.7	2.3	0.002
Vomiting episodes/day (n)	6.3	0.8	0.001	5.4	1.2	0.002

Descriptive statistics were used to characterize the population using the Statistical Package for the Social Sciences. Wilcoxon signed-rank test was used to compare vomiting episode frequencies on admission day and 48 h later within each group. Mann scores on admission day and 48 h later between groups. $P < 0.05$ was considered statistically significant.

RESULTS

In this study, it was found that granisetron group was superior to promethazine group at 48 h after treatment. The number of vomiting was significantly lower in granisetron group than promethazine group. The nausea scores were significantly lower in the granisetron group than promethazine group. The patients on granisetron were more satisfied than those in promethazine group [Table 2].

There was no serious adverse reaction noted in any of the patients. Less rehospitalization at the end of the 1st week was noted in granisetron group. Three patients in promethazine group showed drug reactions including somnolence, anorexia, and dry mouth [Table 3].

DISCUSSION

This study showed that granisetron was more effective than promethazine in decreasing symptoms of nausea and vomiting in pregnant patients. Greater patient satisfaction, less adverse drug reaction, and rehospitalization in granisetron group suggest that it can be introduced as more safer and effective drug as compared to promethazine. Hyperemesis gravidarum is the most severe form of nausea and vomiting in pregnancy and is characterized by intractable nausea and vomiting that leads to dehydration, electrolyte, and metabolic disturbances, and nutritional deficiency that may require hospitalization.^[7,8] Hyperemesis gravidarum has also been defined as severe vomiting with onset at <16 weeks of estimated gestational age that causes 5% weight loss and considerable ketonuria.^[9,10] The cause of hyperemesis gravidarum is not well understood but appears to have both physiological and psychological components. Estrogen, progesterone, adrenal, and pituitary hormones have been proposed as cause, but currently, there is no conclusive evidence implicating any of them. The main

Table 3: Adverse drug reactions and patient satisfaction after treatment (second outcome)

Variables	Granisetron (n=10)	Promethazine (n=10)
Patient satisfaction level (score 0–5) mean	4.9	4.4
Adverse drug reaction (n=number)	0	3
Hospital stay (day) mean±standard deviation	2.4±1.2	2.8±1.4
Rehospitalization (n=number)	0	1

treatment of hyperemesis gravidarum is supportive care. Various lifestyle and diet changes can help patients to tolerate oral intake. Patients should try to avoid unpleasant odors; eat bland, dry, carbohydrate diet; eat small, frequent meals; and separate solid and liquid foods by at least 2 h. Immediate correction of fluids and electrolyte deficits and base disorders must be accomplished.^[11] The patients should initially have nothing by mouth until deficits are corrected. One study found that treatment with intravenous fluid led to cessation of vomiting and increase tolerance to oral intake within 24 h in hyperemesis gravidarum patients.^[12]

Promethazine is an H1 receptor blocking agent used for prevention and control of post-operative nausea and vomiting and motion sickness.^[13] Although Promethazine is classified as drug Group C in pregnant patients but, is widely used for controlling nausea and vomiting in pregnancy. Granisetron is a selective 5-HT₃ receptor antagonist and is classified as drug Group B in pregnant patients and approved by the Food and Drug Administration for the treatment of post-operative nausea and vomiting in adults.^[14] In comparison with ondansetron, granisetron is more potent antagonist with longer duration of action.^[15] Not much data had been published so far to support the superiority of granisetron over promethazine.

Ashraf *et al.* had done double-blinded clinical trial on 32 antenatal patients in Iran. Her study showed that the episodes of nausea and vomiting in granisetron group were much less than in promethazine group. Furthermore, patients were more satisfied and had less adverse drug reaction in granisetron group as compared to promethazine group.^[16] This was similar to this study which also supports the superiority of granisetron over promethazine.

Guikontes *et al.* found no benefit of ondansetron compared to promethazine.^[17] Regarding the management of hyperemesis gravidarum, promethazine has been compared with ondansetron, but not much controlled clinical trial has been reported for granisetron.

CONCLUSION

Hyperemesis gravidarum is a health-related problem with economic, social, and psychological dimensions. Efforts should be made to reduce its severity and help pregnant women to continue her pregnancy with more satisfaction. According to this study, granisetron has more benefits over promethazine. Granisetron is more effective in controlling nausea and vomiting as compared to promethazine. Less drug adverse reaction and rehospitalization suggest aforementioned benefits of granisetron over promethazine.

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How to cite this article: Prasad A, Singh M. A Comparable Study on Efficacy of Granisetron and Promethazine in Controlling Hyperemesis Gravidarum. *Int J Sci Stud* 2019;7(5):66-69.

Source of Support: Nil, **Conflict of Interest:** None declared.