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Comparison of the effectiveness of ondansetron versus metoclopramide in hyperemesis gravidarum: a randomized clinical trial

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Abstract: **Objective:** Nausea and vomiting are the most common complications and the first cause of hospitalization of pregnant women in the first trimester of pregnancy. Given the maternal and fetal complications as well as the negative psychosocial and economic effects of nausea and vomiting, the present study aimed to compare the antiemetic effects of ondansetron and metoclopramide.

Methods: The present double-blind randomized clinical trial study was conducted on 153 pregnant women with a complaint of nausea and vomiting during pregnancy referred to the obstetrics and gynecology ward. Patients were randomly divided into two metoclopramide and ondansetron groups. The outcomes of interest were nausea and vomiting, the number of used doses of the drug, and the length of hospital stay. The Pregnancy-Unique Quantification of Emesis (PUQE) questionnaire was used to assess the severity of nausea and vomiting.

Results: The mean age was significantly higher in the metoclopramide group (28.44±6.45 vs. 25.43±5.42 years, P=0.004). On day 3, the PUQE score was significantly higher in the ondansetron group (6.60±1.10 vs. 6.56±0.88, P<0.001). The decrease in the severity of nausea and vomiting was significantly higher in the ondansetron group (5.29±1.35 vs. 4.90±1.17, P=0.05) in the second day compared to the first day. In the repeated measure analysis, significant differences were found between the two treatment groups (F=7.01, P=0.009). There was no significant difference between the two groups in terms of the length of hospital stay (P>0.05).

Conclusion: In this study, ondansetron revealed more efficacy than metoclopramide on the nausea and vomiting of pregnancy (NVP) management. Ondansetron may, therefore, be considered as a safe and effective alternative for metoclopramide in the treatment of NVP.

Keywords: Metoclopramide; Nausea; Ondansetron; Pregnancy; Vomiting

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1. Introduction

Nausea and vomiting of pregnancy (NVP) are the most common complications in pregnancy and about 91% of pregnant women reportedly experience these symptoms (1). The onset of symptoms often occurs in 6-8 weeks after the first day of menstruation, with the highest occurrence in the 12^{th} week of pregnancy. In most pregnant women, however, these symptoms improve by the 20^{th} week of pregnancy and 20–30% of them will experience symptoms beyond 20 weeks up to the time of delivery (2). Nearly 1% of pregnant women develop a more serious condition, i.e., hyperemesis gravidarum (HG) (3). NVP has negative maternal consequences and affects their quality of life (4). Moreover, it may cause some adverse fetal outcomes, including low birth weight and preterm birth (5-7). As one of the drugs used in the treatment of nausea and vomiting, metoclopramide is commonly used as a first-line agent after hydration in the treatment of hospitalized cases with NVP (8, 9). Ondansetron has also been used in this regard. In animal studies, it has no teratogenic effects, and in the human population, its use in early pregnancy has no role in the formation of major malformations (10, 11). In recent years, the use of ondansetron to treat NVP has been on the rise; but there have been limited studies to determine its effectiveness. This study aimed to compare the effects of ondansetron versus metoclopramide on the NVP management.

2. Methods

2.1. Study design and setting

This double-blind randomized clinical trial study was conducted in Mousavi Hospital in Zanjan, Iran between June 2019 and September 2019. The proposal of the study was approved by the ethics committee of Zanjan University of Medical Sciences (ethics code: ZUMS.REC.1395.40). The study was registered in the Iranian Registry of Clinical Trials (IRCT20190528043735N1). All the participants presented written informed consent before participation in the study.

2.2. Study population

The least required sample size of 154 was determined based on Chhetry et al. (12) study, considering α=0.05 and a power of 80%. Pregnant women with symptoms of nausea and vomiting, oral intolerance, and gestational age less than 16 weeks were included. Those with allergy or previous adverse reactions to metoclopramide or ondansetron, multiple pregnancies, patients with diabetes, asthma, and urinary tract infections, or taking any drugs (except folic acid) during pregnancy were excluded. Qualified patients entered the study using convenience sampling.

2.3. Blinding and randomization

The used drugs were packed in nameless syringes and the patient and the physician were not aware of the medication prescribed to the patient, and only the nurse in charge of the patient was aware of the prescribed medication. Using balanced block randomization (block size=4), the patients were randomly divided into two groups of treatment with metoclopramide (10 mg/2 ml, slow injection) and ondansetron (4 mg/2 ml, slow injection).

2.4. Intervention

Both groups were on nil per os (NPO) for at least the first 24 hours (h) of hospitalization and were treated with normal saline (1000 cc every 8 h), intravenous (IV) potassium (in case of hypokalemia), and IV antiemetic. In one group, ondansetron (4 mg every 8 h) and in the other group, metoclopramide (10 mg every 8 h) were administered intravenously, and it was continued for at least 24 hours and at most until patients tolerated oral administration, after which they were treated with oral metoclopramide or ondansetron (depending on their allocated group).

Patients who tolerated water and food for 24 h, their urine ketone was negative, and did not vomit in the last 24 h were considered as an improvement and could be discharged with oral medication. Patients who did not show any improvement in nausea and vomiting for up to 96 h were considered as treatment failures and excluded from the study.

2.5. Data gathering

Basic information, including body mass index (BMI), serum levels of sodium and potassium, urinary ketone, gravidity, and gestational age, was collected from patients by trained midwifery experts under the supervision of a gynecologist.

The Pregnancy-Unique Quantification of Emesis (PUQE) questionnaire (13) was used to assess the severity of nausea and vomiting. This questionnaire contains three questions regarding the time-span of nausea, vomiting, and retching, respectively. The reliability of this questionnaire was approved previously in Iran (14) and was completed by the patients in all stages. The PUQE checklist was also filled out daily by patients.

2.6. Outcome

Then, nausea and vomiting were evaluated at several stages, namely the first, second, and third days of hospitalization, through direct observation by nurses as well as by asking from the patients. The mean score for reduction of nausea and vomiting, the number of drug doses received, and the length of hospital stay were considered as the outcomes of interest and compared between the two groups.

2.7. Statistical analysis

The SPSS version 21 software was used to analyze data. Qualitative and quantitative variables were characterized by frequency and mean ± standard deviation, respectively. Baseline characteristics, i.e., the number of doses received and the length of hospital stay between the two groups were compared using the Student's t-test. Mean PUQE-scores in days 1, 2, and 3 of hospitalization were compared between the two groups using the analysis of covariance (ANCOVA) test and adjusted on potential confounders at baseline. Repeated measures analysis of variance (ANOVA) was also used to compare changes in mean scores of PUQE over three time points. Statistical significance was considered at P-value < 0.05.

3. Results

Out of 172 screened pregnant women with NVP, 11 patients did not meet inclusion criteria and seven patients withdrew from the study. Therefore, 154 patients were evaluated in two groups. These patients were randomly assigned to two groups each with 77 patients treated by metoclopramide or ondansetron. In the ondansetron group, one patient was lost to follow-up, and finally 77 and 76 patients from metoclopramide and ondansetron groups, respectively, were included in the final analysis (Figure 1). Baseline clinical characteristics of the patients in the two groups are shown in table 1. The mean age was significantly higher in the metoclopramide group (P=0.004), while the mean of gestational age was significantly higher in ondansetron group (P=0.022). Moreover, patients in this group had significantly lower serum level of sodium (P=0.0123). There were no significant differences between the two groups in baseline characteristics, including BMI, serum levels of potassium, urinary ketone, and gravidity (P>0.05). The means (±SD) of doses of prescribed drug, the length of hospital stay, and hours of receiving IV fluid were not significantly different between the two groups (P>0.05).

There were no statistically significant differences between the mean scores of PUQE in days 1 and 2 of initial treatment between the ondansetron and metoclopramide groups (P>0.05). On day 3, however, the PUQE score was significantly higher in ondansetron group (6.60±1.10 vs. 6.56±0.88, P<0.001). The decrease in the severity of nausea and vomiting was significantly higher in the ondansetron group on the second day compared to the first day (5.29±1.35 vs. 4.90±1.17,

Table 1 Baseline characteristics of patients in the two study groups

Variable	Ondansetron group	Metoclopramide group	P-value
	Mean±SD		
Age (year)	25.43±5.42	28.44±6.45	0.004
BMI (Kg/m^2)	23.7±2.54	23.16±3.32	0.263
Gestational age (week)	11.32±3.63	10.19±2.35	0.021
Serum level of sodium (mEq/L)	138±2.67	139±2.24	0.0123
Serum level of potassium (mEq/L)	3.73±0.30	3.76±0.38	0.618
Urinary ketone (mmol/L)	2.39±0.81	2.12±0.86	0.052
Gravidity	165±1.14	198±1.16	0.086

Table 2 The means (± SD) of doses of drugs, the length of hospital stay, and hours of receiving IV fluids in the two study groups

Variable	Ondansetron group	Metoclopramide group	P-value
	Mean±SD		
The number of doses of drug received	4.80±1.77	4.21±1.93	0.055
The length of hospital stay	3.01±1.33	3.12±1.05	0.571
Hours of intravenous fluids received	34.43±13.71	36.06±16.0	0.502

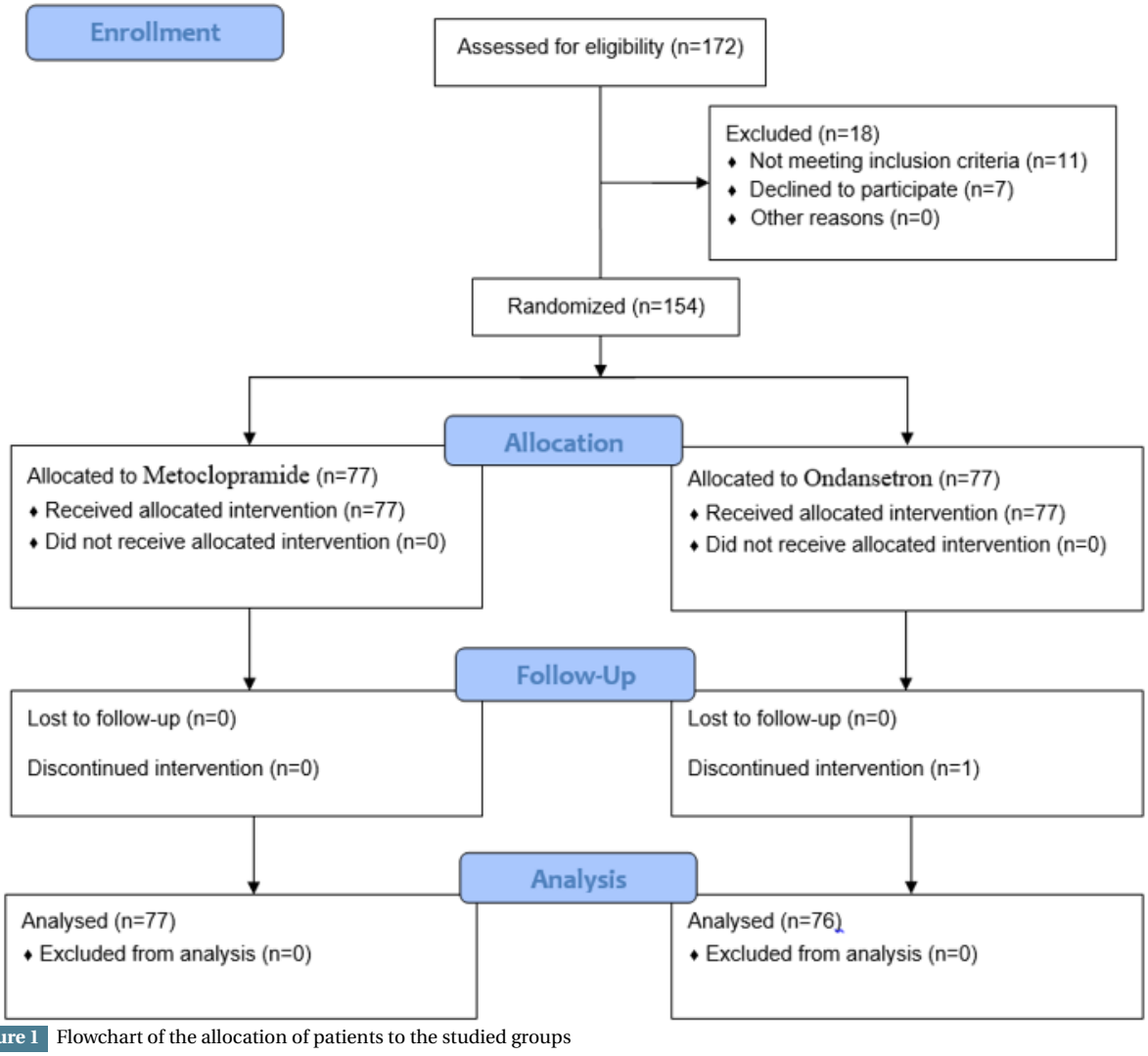

Figure 1 Flowchart of the allocation of patients to the studied groups

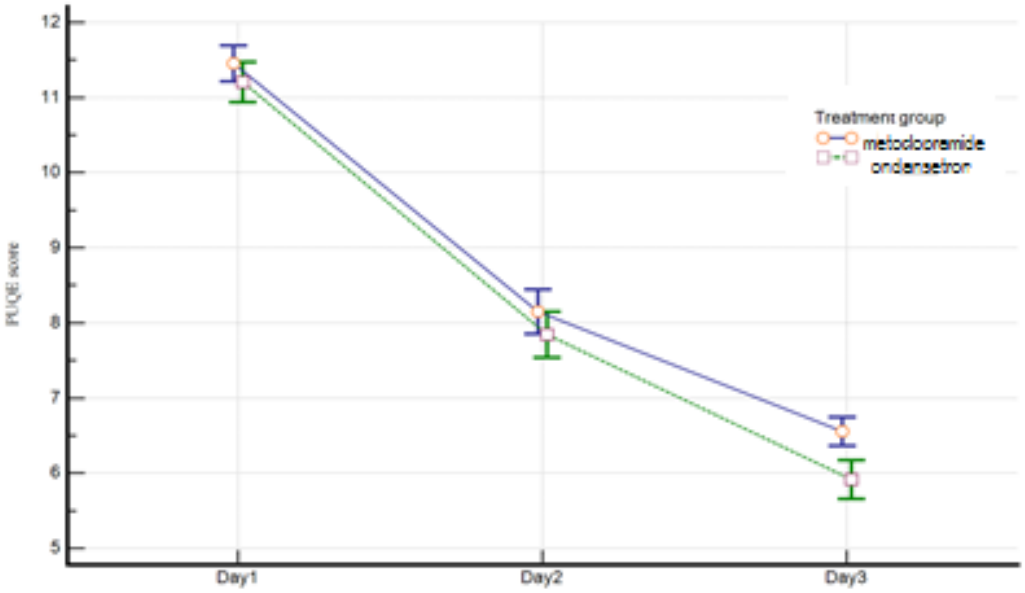

Figure 2 Changes in means of PUQE-score in days 1, 2, and 3 of hospitalization in the two investigated groups PUQE: Pregnancy-unique quantification of emesis

Table 3 The mean PUQE-scores and their changes in days 1, 2, and 3 of hospitalization between the two study groups

Variable	Ondansetron group	Metoclopramide group	P-value*
	Mean±SD		
PUQE score on day 1	11.21±1.14	11.46±1.08	0.155
PUQE score on day 2	7.85±1.30	8.15±1.33	0.103
PUQE score on day 3	5.92±1.10	6.56±0.88	<0.001
PUQE score difference (day 1 – day 2)	3.36±1.14	0.558	
PUQE score difference (day 1 – day 3)	5.29±1.35	4.9±1.17	0.050
PUQE score difference (day 2 – day 3)	1.93±1.23	1.59±1.12	0.301

*ANCOVA test adjusted for age, gestational age, urinary ketone, and gravidity
PUQE: Pregnancy-unique quantification of emesis

P=0.05) (Table 3). The NVP categories in days 1, 2, and 3 of hospitalization in the two study groups are presented in table 4. Accordingly, there was a significant difference between the two treatment groups regarding NVP categories on day 3 (P=0.005).

In Figure 2, changes in means of PUQE-score were assessed on days 1, 2, and 3 of hospitalization in the ondansetron and metoclopramide groups. The mean of PUQE-score decreased significantly over time in both groups (P<0.001). In the repeated measures ANOVA, significant differences were found between the two treatment groups (F=7.01, P=0.009). The interaction of time by group was not statistically significant (F=2.48, P=0.09), suggesting that the differences between groups were not significant in PUQE-score reduction at each time point.

4. Discussion

The present study showed that although there were no significant differences between the two drugs in terms of doses of prescribed drug, the length of hospital stay, and hours of receiving IV fluid, ondansetron had a greater effect on the decrease in the severity of nausea and vomiting.

Contrary to our study, Chhetry et al. (12) found no significant difference between the two drugs in the reduction of vomiting and nausea. However, the result of their study in terms of the length of hospital stay in the two groups is in line with our finding, indicating no significant difference between the two groups. The small sample size and subsequently low power tests in the study of Chhetry et al. could justify some differences in the results between the two studies. In contrast with our study, Abas et al. (15) could not find significant differences between the two drugs in terms of the effectiveness in the severity of nausea and vomiting. Differences in the tools used to measure vomiting and depression scores might have caused this inconsistency; but, consistent with our findings, ondansetron was more effective in the control of vomiting and depression than metoclopramide in a study by Ghahiri et al. (16). Although the type and time of the intervention, as well as the follow-up of patients in their study, were different from our study, they used oral doses of the drug. In line with our study in the first week, they reported no difference between the average frequencies of vomiting in both groups,

Table 4 The NVP categories in days 1, 2, and 3 of hospitalization in the two study groups

Day	Treatment group	Mild NVP (PUQE≤6)	Moderate NVP (PUQE:7-12)	Severe NVP (PUQE≥13)	P-value*
		Number (%)			
1	Ondansetron	-	60 (78.95)	16 (21.05)	0.76
	Metoclopramide	-	66 (85.71)	11 (14.29)	
2	Ondansetron	8 (10.53)	64 (84.21)	4 (5.26)	0.36
	Metoclopramide	7 (9.09)	61 (79.22)	9 (11.69)	
3	Ondansetron	58 (76.32)	18 (23.68)	-	0.005
	Metoclopramide	42 (54.55)	35 (45.45)	-	

*Chi-square test

NVP: Nausea and vomiting of pregnancy; PUQE: Pregnancy-unique quantification of emesis

but the ondansetron recipient group had a better improvement from the second week onwards.

5. Limitations

A shortcoming in the present study was the lack of registration and comparison of side effects between the two groups. In addition, selection bias was inevitable due to the use of convenience sampling.

6. Conclusion

In this study, ondansetron revealed more efficacy than metoclopramide on the NVP management. Ondansetron may, therefore, be considered as a safe and effective alternative for metoclopramide in the treatment of NVP in clinical practice until more evidence becomes available.

7. Declarations

7.1. Acknowledgment

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7.2. Authors' contribution

HG and FM developed the original idea, the protocol, and study design. FM and HG collected and managed the data. HG participated in data analyses. FM and HG participated in drafting and SF participated in editing manuscript. All authors provided comments, participated in writing manuscript, and approved the final manuscript.

7.3. Conflict of interest

None declared.

7.4. Funding

None declared.

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