Ondansetrone or metoclopromide? Which is more effective in severe nausea and vomiting of pregnancy? A randomized trial double-blind study

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Summary

Background: Nausea and vomiting of pregnancy (NVP) are seen in 50-80% of pregnancies. However, in severe NVP, called hypermesis gravidarum (HG), medical therapy to reduce nausea and vomiting is inevitable and ondansetron (OND) as an effective drug has recently been proposed. This study evaluated the effectiveness of OND versus metoclopramide (MET) in the treatment of HG. *Methods:* In this clinical trial study, 83 pregnant women with HG were enrolled in 2011-2012 and randomly divided in two groups. The first group received oral administration of MET and the second group was treated with OND for two weeks. Severity of nausea and vomiting were evaluated according to visual analogue scale (VAS) criteria. Data analysis was done by χ^2, Fisher exact test and Student's t-test. *Results:* Comparison of the trend of change of vomiting in the two groups during the 14-day treatment showed the OND group had significantly lower vomiting scores versus the MET group ($p = 0.042$), while there was no significant difference in the trend of nausea. *Conclusion:* OND has a more favorable effect in controlling severe vomiting.

Key words: Methoclopramide; Ondansetron; Nausea; Vomiting; Pregnancy.

Introduction

Nausea and vomiting of pregnancy (NVP) is a common condition which involves about 80% of women during pregnancy [1]. The most severe form is known as hyperemesis gravidarum (HG) which widely is used characterized by "intractable vomiting associated with weight loss of more than 5% of prepregnancy weight, dehydration, ketosis, and electrolyte imbalances which may lead to hospitalization". HG is estimated to occur in 0.5%-2% of pregnancies. The patients are more likely to be non-white and younger than 30 years [2].

Although NVP can be divided into three categories; mild, moderate, and severe, severity of vomiting may not adequately reflect the problems caused by pregnancy [3]. Physical and psychological effects of NVP often lead to feelings of anxiety and concerns about the impact on the fetus. As well as unfavorable effects on family relationships, it has undesirable consequences on a women's job efficiency, as 47% out of employed women who suffer from NVP feel that their work efficiency is reduced [3]; also 35% of work hours are wasted (mean of 62 work-hours/month) [3] and 25% also have difficulty with household chores (mean of 32 work-hours/month) for each woman [1-4].

NVP is also considered as one of the reasons for termination of pregnancy [5]. It should not be surprising as it has been observed that some pregnant women experience severe nausea which is comparable with nausea in cancer patients after chemotherapy [6]. Each year a significant number of women are hospitalized due to NVP (14 admissions in 1,000 births) [7], so early diagnosis and proper treatment as healthcare management have a significant impact on quality of life during pregnancy.

The pathogenesis of NVP is not well known and seems to be multifactorial. Other causes of nausea and vomiting should be ruled out such as gastrointestinal, urogenital, and cerebral nerve system diseases as well as metabolic and toxic elements. Idiopathic NVP should be differentiated from the diseases which are associated with hydatidiform mole and multiple pregnancies [2].

The treatment of nausea and vomiting during pregnancy is approximately unendurable and miscellaneous types of treatments have been used so far.

We previously studied the effect of ginger (in biscuit form) as a nonpharmacological (herbal remedy) approach to nausea and vomiting in early pregnancy and found it was effective for relieving nausea and to some extent vomiting [8].

Within the antiemetic drugs, prochlolorperazine, promethazine, metoclopromide, and pyridoxine (B6) have often been often used as the first-line therapy [9]. Antiemetic effects of metoclopramide (MET) are a result of its anti-dopaminergic and likely the prokinetic function [10, 11]. A query revealed MET is effective in NVP and HG, with a good balance of efficacy and tolerability [12]. The newer treatment regimens of ondansetron (OND) or steroid-compounds have been considered as the first-line treatment while other treatments lead to failure. OND is a 5-hydroxytryptamine3 (5HT3) antagonist receptor that influences the central and peripheral nerves and reduces the activity of the vagus nerve which can stimulate the vomiting center in the medulla oblongata.

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Its other effect includes blocking serotonin receptors in the chemoreceptor trigger zone (CTZ). It seems this drug is more efficient with minimum side-effects than previous antiemetic drugs (without drowsiness or extrapiramidal complications) [13]. One study examined treatment outcomes in women with severe nausea and vomiting of pregnancy receiving outpatient nursing support and either subcutaneous metoclopramide or subcutaneous ondansetron via a microinfusion pump and concluded treatment with either metoclopramide or ondansetron resulted in significant improvement of NVP symptoms with half the women showing a reduction in severe symptoms to moderate or mild symptoms within three days of treatment initiation. Alteration in treatment was significantly greater in patients initially prescribed metoclopramide [14].

Nausea and vomiting, especially in it severe forms, may reduce the quality of life of a pregnant woman, and information about OND in the pregnancy is limited [15], which is why its management is of interest [2]. Moreover, OND is not used for treatment of HG in our center, thus we decided to evaluate the effect of this medicine in the management of HG.

Materials and Methods

This randomized clinical trial double-blind study was done on 83 pregnant women with HG who were referred to the Ruhani Hospital of Babol University of Medical Science in the north of Iran from June 2011 to March 2012. The study was approved by the ethical committee of Babol University of Medical Science.

Inclusion criteria included hyperemesis pregnant women aged 18-35 years with primary or secondary pregnancy, gestational age less than 16 weeks, vomiting three times a day with weight loss more than 3 kg, and presence of ketonuria [2].

Patients with thyroid and gastrointestinal disease, hydatidiform mole, and multiple pregnancies were excluded from the study [16]. Gestational age less than 16 weeks was confirmed according to the patient's last menstrual period and ultrasonography. All eligible patients signed an informed consent to enter the study.

After assessment of eligibility and recruitment and before the intervention, patients are randomly allocated to receive one or another of the alternative treatments under study. A computer-generated randomization schedule was used and investigators and participants were all blinded to treatment arm assignments.

Unblinding took place after all participants had returned the final day of receiving medicine and a final letter was sent to them explaining which treatment arm they were in along with the preliminary study results. Both groups were matched for weight and age.

It is notable that none of the patients has used antiemetic medicines two weeks before the study. Also, at the onset of the study, the two groups were in a similar status for nausea and vomiting according to VAS criteria. All processes of the study were described to the patients. Subjects graded the severity of nausea by themselves according to VAS criteria and recorded the number of vomiting episodes in the last 24 hours before treatment.

The patients were randomly divided in two groups (1: metoclopramide tablets, 10 mg, TDS, Hakim Pharmaceutical Co, Tehran, Iran. 2: ondansetron hydrochloride tablets, 4 mg, TDS, Chemie Pharmaceutical Co. Tehran, Iran) by a study coordinator who also encoded the drugs with matching random numbers.

All patients were evaluated as responding to treatment within two weeks according to VAS. Subjects graded the severity of their nausea and recorded the number of vomiting episodes in the last 24 hours before treatment and again during treatment days by themselves. Nausea is a subjective symptom, which is why VAS was used to quantify the changes in its severity [17, 18].

For VAS criteria, patients recorded the grade of severity of nausea on their first visit over the previous 24 hours by marking an "X" corresponding to their perceived states on a 10 cm vertical line, ranging from 0 (no nausea) to 10 (severe nausea).

On the following 14 days, recording the severity of nausea was done daily at bed time. The subjects also recorded the number of vomiting episodes in the 24 hours before the study, and then during the 14-day treatment. All patients received the medicine three times daily over a week. After one week the dose was gradually reduced and discontinued as follows: twice/days for three days, once/day for four days within the final week. The

Table 1. — *Severity of vomiting in the two groups within treatment days*.

Treatment days	Severity of vomiting (mean ± SD) Ondansetron	Metoclopromide	*p* value
1	6.7 ± 3.1	5.1 ± 4.1	0.06
2	6.0 ± 3.2	3.7 ± 3.8	0.006
3	5.3 ± 3	3.2 ± 3.4	0.006
4	5 ± 3.1	3.3 ± 3	0.013*
5	5.1 ± 3	3 ± 3.1	0.011
6	3.8 ± 2.9	2.5 ± 2.6	0.047
7	3.7 ± 2.8	2.7 ± 3.2	0.010
8	3.1 ± 4.2	2.8 ± 3.4	0.028
9	3.0 ± 3.7	2.9 ± 3.2	0.06
10	3.1 ± 3.5	3.3 ± 3.3	0.36
11	2.7 ± 3.2	2.8 ± 2.7	0.09
12	6.9 ± 3.4	2.9 ± 2.5	0.10
13	3.2 ± 3.3	2.8 ± 2.2	0.07
14	2.9 ± 3.1	2.9 ± 2.4	0.10

*: Significant; $p < 0.05$.

Table 2. — *Severity of nausea in the two groups within treatment days*.

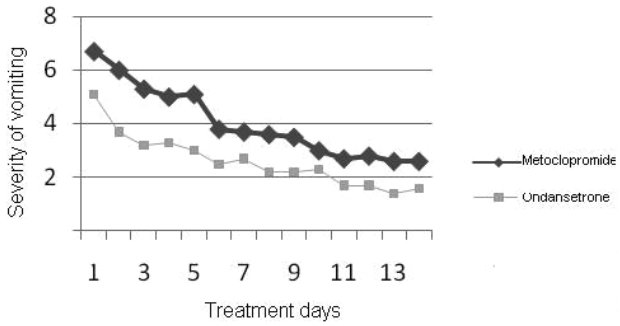
Treatment days	Severity of vomiting (mean ± SD) Ondansetron	Metoclopromide	*p* value
1	6.8 ± 3.2	7.4 ± 2.8	0.39
2	5.4 ± 3.2	6.7 ± 3.0	0.068
3	5.4 ± 2.9	6.0 ± 2.9	**0.024***
4	4.1 ± 2.9	5.7 ± 2.8	**0.023***
5	4.1 ± 2.8	4.8 ± 2.5	0.32
6	3.7 ± 2.7	4.3 ± 3.0	0.54
7	3.7 ± 2.7	4.3 ± 2.8	0.25
8	3.4 ± 2.8	4.2 ± 3.1	0.22
9	3.2 ± 2.9	3.7 ± 3.0	0.52
10	3.3 ± 3.3	3.5 ± 3.1	0.76
11	2.7 ± 2.8	3.2 ± 2.7	0.53
12	2.5 ± 2.9	3.4 ± 6.9	0.10
13	2.2 ± 2.8	3.3 ± 3.2	0.12
14	2.4 ± 2.9	3.1 ± 2.9	0.32

*: Significant; $p < 0.05$.

Table 3. — *Severity of nausea and vomiting in the first and second days one week after treatment in the groups under study*.

Treatment days		Severity of vomiting (mean ± SD) Ondansetron	Metoclopromide	*p* value
Severity of nausea	Day 1	5.3 ± 3.2	5.7 ± 2.6	0.53
(mean ± SD)	Day 2	3.4 ± 5.2	5.1 ± 3.4	0.87
Severity of vomiting	Day 1	4.6 ± 3.4	5.2 ± 3.1	0.42
(mean ± SD)	Day 2	4.8 ± 3.5	4.7 ± 3.5	0.85

Fig. 1



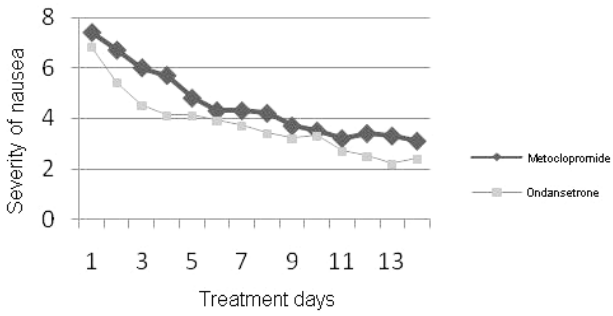


Fig. 2

Figure 1. — Severity of vomiting within 14 days of treatment between the two groups.
Figure 2. — Severity of nausea within 14 days of treatment between the two groups.

single dose was totally stopped at the end of the second week). All patients' symptoms were evaluated within the first two days one week after stopping the medicine by the VAS criteria. After stopping the oral treatment, response to treatment was assessed, and if no improvement was observed in symptoms, the treatment protocol was revised according to the patient's condition. Data of the two groups were collected and entered using statistical software SPSS18 and analyzed by central statistical indicators: t-test, Anova, and chi-square tests; $p < 0.05$ was considered significant.

Results

Eighty-three patients were included in the study (41% (34) in the MET group and 59% (49) in the OND group). The mean age of the MET group was 25.2 ± 4.9 years and the mean age of the OND group was 25.3 ± 5.5 years. At the onset of the study, the mean weight was 63.9 ± 11.2 kg. Both groups were matched for age and weight, and the mean weight loss was 2.4 ± 2.8 kg. The minimum gestational age was five weeks and the maximum was 16 weeks (mean 8.7 ± 2.6 weeks). No significant difference was shown between the two treatment groups for mean gestational age and no relationship was seen between maternal age and number of nausea and vomiting episodes between the groups in the study.

No significant difference was found between the gestational age and number of nausea and vomiting episodes prior to treatment. The severity of nausea in the OND group was significantly less on the third and fourth days of treatment versus the MET group (p = 0.024, p = 0.023). Also, the number of vomiting episodes in the OND group were fewer than the MET group from the second to the eighth days (Table 1, 2).

Tables 3 and 4 show the mean severity of nausea and number of vomiting episodes in the first and second days one week after discontinuing the treatment. There was no significant difference between the two treatment groups.

Comparison of the trend of change of the number of vomiting episodes in the two groups during the 14 days of treatment have shown that the OND group had a significantly lower vomiting score versus the MET group (p = 0.042), while there was no significant difference in the trend of nausea (Figures 1, 2).

None of the patients showed any side-effects of the offered medicines. All mothers and infants were healthy at the time of birth.

Discussion

Although the findings of the study did not indicate any total superiority in all treatment days (14 days) in favor of one of the enrolled medicines, but a relative advantage was shown in favor of OND for nausea and vomiting in the first days of treatment versus MET. It is noteworthy that the trend of reduction of intensive vomiting was higher in the OND group.

Dabbous and *et al*. conducted a study on 200 patients and compared the antiemetic effects of OND with MET and droperidol. The results showed that both OND and droperidol were more effective than MET and patients were more satisfied with OND due to the rapid influence and less drowsiness [19]. Afhami and *et al*. compared the impact of MET and OND at post strabismus surgery in children. Patients were divided into two groups (48 children in each group) and demographic, hemodynamic, and duration of anesthesia were matched. The results suggest that the two groups were comparable with each other in incidence and severity of nausea and vomiting [13].

Gupta *et al*. [19] compared the antiemetic effects of OND and MET with granisetron in 60 patients undergoing laparoscopic cholecystectomy. Results revealed that in the first 12 hours postsurgery, there were fewer nausea and vomiting episodes in the granisetron group versus the two other treatment groups.

However after 12 hours, there were no significant differences observed between these medicines [20]. Also, Krobbuaban *et al*. compared the effects of OND and MET to reduce nausea and vomiting post-gynecological surgery among 382 patients. In this study, the number of women who complained of post-surgical nausea and vomiting were fewer in patients who received 4 mg of OND versus those who received 10 mg of MET (47% vs 60%) [21].

There have not been many studies on the antiemetic effects of these drugs on gestational nausea and vomiting in pregnant women, and most studies have been conducted on the patients after surgery or after chemotherapy.

Many queries have been done on the effects of newer antinausea drugs like OND and granisetron compared with older medicines such as MET. In a few studies the antiemetic effects of metoclopramide were comparable with OND, but most researches indicate OND has a stronger effect. In a random control trial study, Sullivan

et al. compared OND with promethazine in the treatment of HG. They divided 30 patients in two groups and concluded OND was as effective as promethazine, however with less drowsiness. The authors of this article suggested increasing the dose of OND or using continuous infusion improves the response to treatment [15].

Shings *et al*. reported on a pregnant woman whose three previous pregnancies had been terminated due to severe HG and increased liver enzymes. They also intended to terminate her present pregnancy due to severe HG again. At the beginning they prescribed OND for the patient and two days after treatment, the patient was able to start a normal diet. The patient occasionally used MET after discharge.

Termination of pregnancy was done due to premature rupture of membranes and repeat cesarean at 35 weeks of pregnancy. The mother and baby were healthy. Also, the morphology and growth of the baby were within normal range after one year [22].

Ghahiri and *et al*. conducted a clinical trial study similar to our research with 35 pregnant women (in the first trimester) in each group; they were prescribed OND and MET and evaluated within three weeks. They findings showed that there was no a significant difference between groups in the mean of nausea episodes during the three weeks of treatment, but comparing both groups revealed OND made the mean number of vomiting episodes significantly lower after one week [23], while in our study the influence of both drugs appeared within the first week. Apparently, our difference is based on our chosen criteria; we used VAS and they used the number of nausea or vomiting episodes. Moreover, we enrolled severe NVP patients whereas they selected mild or moderate NVP, patients.

It should be noted that we had a limitation in our study; pregnant women used antiemetic drugs or nonmedication herbal medicines at the onset of their nausea and vomiting episodes and we hardly found patients who had received no antiemetic medicine within two weeks before the beginning of our study.

A well-designed study is required focusing on nausea and vomiting during pregnancy to compare herbal and synthetic medicines.

Conclusion

Our results showed that OND was able to diminish vomiting treatment more rapidly than MET and may be used effectively in the treatment of vomiting during pregnancy instead of MET.

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References

[1] Matthews A,. Dowswell T., Haas D.M., Doyle M., O'Mathúna D.P.: "Interventions for nausea and vomiting in early pregnancy". *Cochrane Database Syst. Rev*., 2010 Sep 8, CD007575.
[2] Quinlan J.D., Hill D.A.: "Nausea and vomiting of pregnancy". *Am. Fam. Physician*., 2003, *68*, 121.
[3] Bsat F.A., Hoffman D.E., Seubert D.E.: "Comparison of three outpatient regimens in the management of nausea and vomiting in pregnancy". *J. Perinatol*., 2003, *23*, 531.
[4] Basirt Z., Moghadamnia A., Kashifard M., Sarifi-Razavi A.: "The effect of ginger biscuit on nausea and vomiting in early pregnancy". *Acta Medica Iranica*, 2009, *47*, 51.
[5] Sahakian V., Rouse D., Sipes S., Rose N., Niebyl J. *et al*.: "Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebocontrolled study". *Obstet. Gynecol*., 1991, *78*, 33.
[6] Briggs G.G.: "A guideline for treating hyperemesis gravidarum". *Contemporary OB/GYN*, 1997, *42*, 70.
[7] Attard C.L., Kohli M.A., Coleman S., Bradley C., Hux H., Atanackovic G., Torrance G.M.: "The burden of illness of severe nausea and vomiting of pregnancy in the United States". *Am. J. Obstet. Gynecol*., 2002, *185*, S220.
[8] Holmgren C., Agaard-Tillery K.M., Silver R.M.: "Hyperemesis in pregnancy: an evalution of treatment strategies with maternal and neonatal outcomes". *Am. J. Obstet. Gynecol*., 2008, *198*, 56.c 1.
[9] Free encyclopedia, http://en.wikipedia.org/wiki/metoclopramide.
[10] Dorre N.: "The Postanesthesia Care Unit". In: Miller R.D. (ed.): "Miller's Anesthesia", 7th ed., Philadelphia, Elsevier, Churchill Livingstone, 2010, 2744.
[11] Tan P.C., Omar S.Z.: "Contemporary approaches to hyperemesis during pregnancy". *Curr. Opin. Obstet. Gynecol*., 2011, *23*, 87.
[12] Afhami M., Hassanzadeh-Salmasi P., Rahimi-Panahi J., Soleimanpour H.: "Comparison of hemodynamic changes in administration of ondansetron and metoclopramide to preventing post operative nausea and vomiting after strabism surgery". *J. Cardiovasc. Thorac. Res*., 2010, *2*, 29.
[13] Klauser C.K., Fox N.S., Istwan N., Rhea D., Rebarber A., Desch C. *et al*.: "Treatment of severe nausea and vomiting of pregnancy with subcutaneous medications". *Am. J. Perinatol*., 2011, *28*, 715.
[14] Einarson A., Maltepe C., Navioz Y., Kennedy D., Tan M.P., Koren G.: "The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study". *BJOG*, 2004, *111*, 940.
[15] Sulivane A., Johnson C.A., Roach H., Martin R.W., Stewart D.K., Morrison J.C.: "A pilot study of interavenous ondansetron for Hyperemesis gravidarum". *Am. J. Obstet. Gynecol*., 1996, *174*, 1565
[16] Guyatt G.H., Townsend M., Berman L.B., Keller J.L.: "A comparison of Likert and visual analogue scale for measuring change in function". *J. Chronic. Dis*., 1987, *40*, 1129.
[17] Aitkin R.C.B.: "A growing edge of measurement of feeling". *Proc. R. SOC Med*., 1969, *62*, 960.
[18] Dabbous A., Khoury S.J., Chehab I.R., Bartelmaos T., Khoury G.: "Ondansetron versus dehydrobenzoperidol and metoclopramide for management of postoperative nausea in laparoscopic surgery patients 2001". *JSLS*, 5, 139.
[19] Gupta V., Wakhloo R., Lahori V.U., Mahajan M.K., Gupta S.D.: "Prophylactic antiemetic therapy with ondansetron, granisetron and metoclopramide in patients undergoing laparoscopic cholecystectomy under general anaesthesia". *J.K. Science*, 2008, *10*, 74.
[20] Krobbuaban B., Pitakpol S., Diregpoke S.: "Ondansetron vs. metoclopramide for the prevention of nausea and vomiting after gynecologic surgery". *J. Med. Assoc. Thai*., 2008, *91*, 669.
[21] Siu S.S., Yip S.K., Cheung C.V., Lau T.K.: "Treatment of intractable hyperemesis gravidarum by ondanseton". *Eur. J. Obstet. Gynecol. Reprod. Biol*., 2002, *105*, 73-74.
[22] Ghahiri A.A., Abdi F., Mastoo R., Ghasemi M.: "The effect of ondansetron and metoclopramide in nausea and vomiting of pregnancy". *JIMS*, 2011, *29*, 259 (in Persian).

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