Effectiveness of Ondansetron versus Metoclopramide in Hyperemesis Gravidarum

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Aims: The aim was to evaluate the effectiveness of intravenous ondansetron as compared to intravenous metoclopramide in hyperemesis gravidarum.

Methods: Sixty-eight patients with hyperemesis gravidarum were randomized to receive either intravenous ondansetron or intravenous metoclopramide according to randomization group, till they started tolerating orally along with supportive therapy and various treatment parameters were compared.

Results: No statistically significant differences were found in the number of doses of intravenous medication used (three doses of ondansetron vs four doses of metoclopramide; p value 0.77), weight changes (ondansetron - 0 kg vs. metoclopramide – 1 kg; p value 0.11) during treatment, duration of intravenous fluids (ondansetron – 24 hours vs. metoclopramide- 24 hours; p value 0.48) in the two groups. The duration of hospital stay of the patients in the two groups was comparable (ondansetron - 3 days vs. metoclopramide - 3 days; p value 0.83).

Conclusions: Metoclopramide and ondansetron appear to be equally effective to treat hyperemesis gravidarum. Although this was a prospective randomized controlled study, it had a small sample size and the results should be confirmed in a larger and powered study.

Keywords: hyperemesis gravidarum; metoclopramide; ondansetron.

INTRODUCTION

Hyperemesis gravidarum (HG) is characterized by severe nausea and vomiting, inability to tolerate food or fluids and the presence of ketonuria.[1] The severity can be quantified with the Pregnancy Unique Quantification of Emesis (PUQE) Score (Table 1)[2] which has been validated and shown to correlate with clinical outcomes.[3]

Treatment for HG is supportive and the aims are to manage the symptoms of nausea and vomiting, correct dehydration and electrolyte abnormality and prevent complications. There have been very few randomized control trials to evaluate and compare the effectiveness or safety of different antiemetics for HG.[4] Hence, this study was designed with the specific objective to compare the effectiveness of intravenous ondansetron versus metoclopramide with respect to improvement of the PUQE score, duration of hospital stay, duration of intravenous fluid therapy, number of doses of intravenous medication, weight gain during treatment.

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METHODS

It was a randomized controlled trial conducted on patients admitted to gynecology ward for the first time in their current pregnancies with presumed hyperemesis gravidarum during the study period of one year (April 2011 – March 2012) and meeting the inclusion criteria. A convenience sample size was used with a plan to enroll 30 patients in each arm. First 60 patients were enrolled using computer generated random number table. All additional patients were allotted in each arm alternately. The study was started after ethical clearance from the Institutional Ethical Review Board and written informed consent from the patients enrolled in the study. The study design has been illustrated in Figure 1.

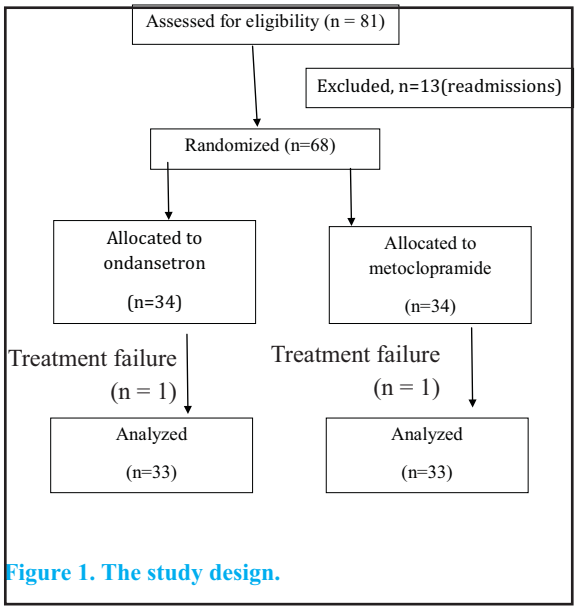

Figure 1. The study design.

All the pregnant patients with hyperemesis occurring during the first or early second trimester (≤16 weeks) who met the following criteria were included in the study: inability to hold food, ketonuria, electrolyte abnormalities, weight loss ≥2.25 kg (if weight documented), two visits to OPD requiring treatment for emesis. The following patients were excluded: patients who could be managed on outpatient basis, patients with eating disorder, previous psychiatric diagnosis, patients with previous hospitalization for HG in current pregnancy and refusal to consent. For all patients recruited into the study, a detailed history reviewing the severity of symptoms, possible risk factors including significant past history and family history was taken. Period of gestation (POG) was calculated at the time of admission, on basis of last menstrual period (LMP) or the early trimester ultrasound available if cycles were irregular. Clinical examination and investigations were performed as per proforma; the resident on duty calculated PUQE score at admission (Table 1). Daily PUQE score was calculated by the resident in-charge of the inpatients in gynecology ward.

Table 1. Modified PUQE score.[2]

1. On average in a day, for how long do you feel nauseated or sick to your stomach?

Not at all	<1 hr	2-3 hr	4-6 hr	>6 hr
(1)	(2)	(3)	(4)	(5)

2. On average in a day, how many times do you vomit or throw up?

I did not vomit	1-2 times	3-4 times	5-6 times	≥7 time
(1)	(2)	(3)	(4)	(5)

3. On average in a day, how many times do you have retching or dry heaves without bringing up anything?

None	1-2 times	3-4 times	5-6 times	≥7 times
(1)	(2)	(3)	(4)	(5)

Total score (sum of replies to 1, 2 and 3): mild NVP ≤6; moderate NVP 7-12 and severe NVP≥13

Daily weight was recorded and weight change during therapy was calculated at discharge. Patients were given either intravenous ondansetron 4 mg or intravenous metoclopramide 10 mg stat dose and then eight hourly according to randomization group, till they started tolerating orally. At least two doses were given to all patients. Once the patients improved they were started on oral medication and fluid therapy was weaned off. In addition, patients were managed as per routine protocol which included nil per orally for first 24 hours, intravenous hydration therapy till they tolerated well orally, thiamine and folic acid supplementation, H2 receptor antagonists – ranitidine iv 50 mg thrice daily dosing till they could tolerate oral medications. Patients were labeled as treatment failure if there was no improvement in their nausea or emesis till 96 hours. These patients were excluded from further data collection. Patients were discharged on oral medications only after they met the following criteria: were able to hold food and water for 24 hours, no ketonuria, no further weight loss, no vomiting for last 24 hours. The outcome measures considered were improvement in the PUQE scores, duration of hospital stay (in days), duration of intravenous fluid therapy (in hours), number of doses of iv medications, weight gain during treatment (in kg).

All analysis was carried out using the statistical

software SPSS version 11.5 for Windows. Normally distributed continuous data were analyzed with the Student's t test. Two-by-two categorical data sets were analyzed with the Fisher exact test and larger categorical data sets with Pearson's χ^2 test; ordinal data and non-normally distributed continuous data were analyzed with the Mann-Whitney U test. P value < 0.05 was considered to be statistically significant. The values have been expressed as Mean ± Standard Deviation or Median (Interquartile Range) whichever applicable.

RESULTS

The total number of admissions for HG was 81 out of which 68 women were hospitalized for the first time while 13 patients had readmissions. These 68 patients were randomized 34 in each group. The baseline characteristics of both the groups were comparable (Table 2).

Table 2. Baseline of patients in ondansetron and metoclopramide group (n=68).

Characteristics	Ondansetron N1= 34	Metoclopramide N2= 34	p value
Mean age ± S (yrs)	24.06± 4.40	24± 4.15	0.935
Mean parity± SD	1.88± 1.20	1.74± 0.99	0.580
Mean period of gestation±SD (wks)	8.56± 2.12	9.29± 2.49	0.195
Previous hyperemesis (N1=15, N2=18)	9 (60.00)	7 (38.89)	0.230
Previous mole (N1=15, N2=18)	0 (0.00)	1 (5.50)	0.350
Family history of hyperemesis	8 (23.53)	13 (38.23)	0.294
Twin pregnancy	2 (5.88)	3 (8.82)	0.990

The mean age of the patients was 24 ± 4.43 years. The patient condition at admission in the two groups with regards to signs of dehydration and their baseline investigations were also comparable (Table 3).

Table 3. Patient condition at admission in the two groups (n=68).

Characteristics/ Investigations		Groups: Ondansetron Number (%)	Groups: Metoclopramide Number (%)	p value
Signs of dehydration at admission		5 (14.7)	7 (20.58)	0.723
LFT Abnormal		9 (26.47)	8 (23.53)	0.779
Urine C/S Growth		5 (14.70)	3 (8.82)	0.438
Na/K Abnormal		2 (5.88)	1 (2.94)	0.555
Ketonuria present at admission		27 (79.41)	29 (85.29)	0.525
Ketonuria resolved in >3 days		4 (14.81)	3 (10.34)	0.555
Ultrasound finding	Missed abortion	0 (0.00)	2 (5.88)	0.309
	Single	32 (94.12)	29 (85.29)	
	Twin	2 (5.88)	3 (8.82)	

Most of the patients had moderate to severe disease at presentation, the mean PUQE scores being 12.29 ± 1.59. Paired t-test showed significant improvement in the PUQE scores after treatment, and hence the decrease in the severity of disease. The mean PUQE scores of the two groups have been compared as shown in Figure 2.

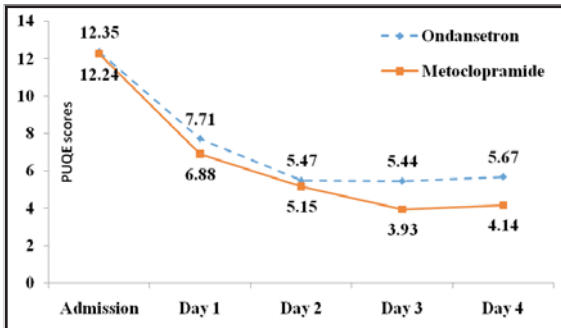

Figure 2. Comparison of the daily mean PUQE scores of the two groups (n=68).

Applying the paired t- test, the mean difference between the admission and day 1 PUQE scores was 5.38 ± 2.11 for the ondansetron group and 5.65 ± 2.30 for the metoclopramide group and the difference was not significant when the two groups were compared to each other. Excluding the patients who failed to respond adequately by 96 hours of treatment (N1=1, N2=1), the different treatment parameters of the two groups have been compared as in Table 4.

Table 4. Treatment parameters compared between two groups (n=68).

Treatment parameters	Median (IQR)		p value (Mann Whitney test)
	Ondansetron (n = 33)	Metoclo-pramide (n = 33)	
Number of doses of iv medication	3 (3-6.5)	4 (3-6)	0.767
Weight changes (in kg)	0 (0-1)	1 (0-1)	0.110
Duration iv fluids (hours)	24 (24-42)	24 (24-48)	0.477
Hospital stay in days	3 (2-4)	3 (2-4)	0.827

The median number of doses of ondansetron needed was 3 while that of metoclopramide needed was 4, (p value 0.767); the median duration of iv fluids needed was 24 hours for both groups (p value 0.477), which was comparable. Although the median weight gain was 1 kg for the metoclopramide group the interquartile range (IQR) was same (0-1 kg), the difference was not significant with p value 0.110. The median number of days of hospital stay for both groups was 3 (p value 0.827).

DISCUSSION

Upto 80% of women experience nausea or vomiting in early pregnancy (NVP), but HG affects only 0.3–1.5% of the pregnant women.[5-7] Asian populations tend to have higher incidence rates. A Malaysian study identified 192 recorded cases (3.9%) out of 4937 maternities.[8] In a study done at Nepal medical college teaching hospital, the incidence of HG was 2.5% of all pregnancy.[9] In this study, the admission for hyperemesis (n=81, including 13 readmissions) was found to be 10.64% of total early pregnancy admissions for any pregnancy complication (n=735).

All the patients had moderate to severe disease at presentation, the mean PUQE scores being 12.29 ± 1.59, which is expected since HG is considered to be the end of the spectrum of NVP. The mean duration of hospital stay was 3.22 ± 1.48 days. In another study the range of hospital stay was 1-10 days with mean hospital stay 2.26 days.[9] There were no statistically significant differences in the presence of risk factors among the patients in each group, the admission PUQE score denoting the severity of disease and the baseline investigation between the two groups. This shows that both groups were highly homogenous in their composition, adding tremendous statistical value to the study.

Prior to this study, there has been no published study to compare the effectiveness of ondansetron and metoclopramide in HG. The hypothesis of this study was that therapy with ondansetron was better than metoclopramide in the management of HG in terms of duration of hospital stay, duration of iv fluids, weight gain during treatment, number of doses of iv medication used and improvement in the PUQE scores. However, when the two groups were compared no statistically significant difference was found in the outcome variables. In a preliminary investigation done by Sullivan,[10] ondansetron offered no advantage when compared with promethazine in the relief of nausea, weight gain, days of hospitalization (4.5 ± 2.3 vs. 4.5 ± 1.5) and total doses of medication per hospitalization (2.1 ± 1.2 vs. 1.9 ± 1.3).The results of the patients' visual analog scores showed no difference between the two drugs. Daily weight gain progressed equally in the two groups. In the present study the median number of days of hospital stay in ondansetron group was 3 (IQR, 2 - 4), number of doses of iv medication 3 (3-6.5). PUQE score was used in this/our study.

In a randomized controlled trial,[11] promethazine and metoclopramide have similar therapeutic effects in patients who are hospitalized for hyperemesis gravidarum. The median vomiting episodes were one (range 0–26) compared with two (range 0–26) (p=0.81) and well-being visual numerical rating scale scores were 8 (range 1–10) compared with 7 (range 2–10) (*p=0.*24) for metoclopramide and promethazine respectively. Repeat-measures analysis of variance of the nausea visual numerical rating scale scores showed no significant difference between study drugs (F score = 0.842, *p* 0.470). In my study the median number of days of hospital stay in metoclopramide group was 3 (IQR 2 - 4), numberof doses of iv medication 4 (IQR 3- 6). The PUQE score was 6.88 ± 2.18 at end of 24 hours of therapy used in this study, which means that the symptoms were mild.

Epidemiological studies have, in general identified some common threads between women with HG and other common nausea and vomiting syndromes like postoperative nausea and vomiting and chemotherapy related nausea and vomiting.[12] In a study done by Jee[13] on prophylactic antiemetic effects of combined treatment with ondansetron and dexamethasone with metoclopramide and dexamethasone in gynecologic patients receiving fentanyl iv-patient controlled analgesia, it was found that treatment with a combination of 20 mg metoclopramide and 5 mg dexamethasone was as effective to prevent postoperative nausea and vomiting syndrome as compared to treatment with 4 mg ondansetron and 5 mg dexamethasone. This data, if extrapolated to HG, can suggest that both drugs will be equally effective in HG, which is similar to the finding of our study on HG.

There were a few limitations encountered in this study. Since a convenience sample was used with a small sample size, the results of the study need to be confirmed by larger powered study. Blinding was not done, so there is possibility of bias.

CONCLUSIONS

Metoclopramide and ondansetron appeared to be equally effective to treat hyperemesis gravidarum. Although this was a prospective randomized controlled study, it had a small sample size and the results should be confirmed in a larger powered study.

DISCLOSURE

The authors report no conflicts of interest in this work.

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