

Original Article

A Comparative Study on the Efficacy of Prednisolone and Promethazine in the Treatment of Hyperemesis Gravidarum.

F. Mardanian MD*, F. Kargar MD**

ABSTRACT

Background: Severe nausea and vomiting during pregnancy is one of the most frequent and difficult to treat obstetric problems. Different drugs and techniques have been suggested for its treatment with variable success rates. This study was designed to compare the efficacy of prednisolone with promethazine for treatment of hyperemesis gravidarum.

Methods: Fifty six pregnant women with hyperemesis gravidarum were randomly divided into two groups to receive either prednisolone or promethazine orally. Severity of nausea and vomiting, severity of malaise, body weight and serum electrolytes were measured and compared before and after treatment.

Results: The severity of nausea and vomiting decreased significantly in both groups, but the decrease was significantly higher in the prednisolone group.

Conclusion: The result of this study shows that oral prednisolone is a better choice for the treatment of hyperemesis gravidarum.

Keywords: Hyperemesis Gravidarum, Pregnancy, Obstetric Complication, Nausea and Vomiting

One of the most important complications in midwifery is nausea and vomiting during pregnancy which are seen in 60 - 80% of pregnancies¹. The severe form, hyperemesis gravidarum appears in 1% of pregnancies². Yet, there is no known causes for it³. The complications for mothers include weight loss, electrolyte disorders and frequent hospitalization. Complications for fetus may be fetal growth disorders (due to blood keton passage through the mother's placenta), low birth weight and intrauterine growth retardation³. The treatment consists of dietary modification to frequent meals, correction of electrolyte imbalances and prescribing antiemetics. The goal of our study was to compare the effects of prednisolone and promethazine in the treatment of hyperemesis gravidarum

Materials and Methods

After institutional approval and informed patients' consent the study was performed as a double blind clinical trial at Beheshti hospital, Isfahan, Iran, from June 2001 till March 2002. Fifty six pregnant mothers with gestational ages of 7-20 weeks were chosen by simple convenient sampling, each having an alive and normal fetus. They had no history of corticosteroid and promethazine consumption, no diagnosed digestive disorders in the past or present, no systemic diseases no acute febrile infections. Each mother needed to have at least 2 of the conditions below to be included in our study.

- Single or repeated vomiting in a day.
- Severe nausea hindering from eating and drinking or ptyalism.
- Urine keton 1 (+) or higher.
- Weight loss following vomiting.

*Associate Professor, Department of Obstetrics and Gynecology, Isfahan University of Medical Sciences, Isfahan, Iran.

**Resident, Department of Obstetrics and Gynecology, Isfahan University of Medical Sciences, Isfahan, Iran.

Correspondence to: Dr Farahnaz Mardanian, Shahid Beheshti hospital, Research Office, Isfahan, Iran.

Tel: 09113144779, 0311 - 2367001-5 (291)

This work is from the Research Department, Isfahan University of Medical Sciences, Isfahan, Iran (Project No: 80166)

Before and after treatment, the daily frequency of vomiting, severity of nausea (using a ten-point visual analogue scale), severity of malaise (again a ten-point visual analogue scale), the status of eating and drinking, serum electrolyte and fasting blood glucose were evaluated.

Fluid therapy was performed with intravenous infusion of dextrose water 5% and Ringer solutions 1 L/6h. When urine keton turned negative, fluid therapy was stopped.

From the beginning of the study, the diet was given at the tolerance level at frequent times and in small portions.

The patients were randomly divided into 2 groups (prednisolone, n= 28; promethazine, n=28). Drugs were coded as A and B and were prescribed by an assistant. Data were collected by another assistant who did not know the codes. In corticosteroid group the prednisolone 10 mg / 12h) was given orally. In case of no response after 48 hours as indicated by vomiting more than twice a day, hydrocortisone 100 mg / 12h was administered intravenously. Those in the promethazine group received 25 mg of oral promethazine every 12 hours, and in those with no response after 48 hours, promethazine 25 mg every 12 hours was administered intravenously. The course of therapy was 4 days; the cases were put out of the study in case of stomach-ache, irritation or unwillingness to continue the study. In cases with vomiting less than twice a day and negative urine keton, the course of treatment was continued orally.

Data were presented as mean \pm SD. Quantitative data were compared between the two groups using Student t-test. Nominal data were compared between the two groups with chi-square test. Wilcoxon rank test was used to compare the drinking and eating scores between the two groups. Before and after treatment comparisons were performed using paired t-test. A P value $<$ 0.05 was considered as statistically significant. Data were analyzed on computer using SPSS 10.0.

Results

The mean age in the prednisolone and promethazine groups showed no significant differences (26.4 ± 4.7 vs. 26.9 ± 4.5 years in promethazine group). In both groups the mean gestational age (9.96 ± 2.2 and 10 ± 2.2 weeks) and

the mean number of pregnancies (2 ± 1.1 and 2 ± 1.2) had no significant differences ($P = 0.45$). The condition of both groups before therapy was shown in table 1. After therapy, the severity and the times of vomiting decreased and this improvement was seen more significantly in the prednisolone group ($P < 0.05$, table 2). The hospitalization period in the prednisolone group was significantly lower than that in the other group (2.6 ± 0.9 vs. 3.4 ± 1.3 days, $P < 0.05$).

The response to oral therapy was 30% and 56.7% in promethazine group and prednisolone group respectively. 70% and 43.3% of therapy transformed to intravenous injection in prednisolone and promethazine group respectively. 46.9% in the former and 84.6% in the latter group responded to it. All together 60% of promethazine group and 93.3% of prednisolone group responded to therapy and showed statistically significant differences.

Discussion

Hyperemesis gravidarum is one of the most torment complications of pregnancy. It causes frequent hospitalization during pregnancy. Corticosteroid has proved helpful in suppressing vomiting resulting from chemotherapy. It is believed that it affects through the chemoreceptor trigger zone⁴. It is not obvious if it acts the same in case of pregnancy vomiting.

In a relatively similar study by Safari et al⁵ the study group was given prednisolone tablet 16 mg every 8 hours for 3 days then gradually tapered in 2 weeks. The control group received promethazine tablets 25 mg every 8 hours for 2 weeks. Results showed that prednisolone improved symptoms faster and shortened the period of fluid therapy, thus the duration of hospitalization decreased⁵. In a study in 1998 prednisolone tablet 48 mg was administered to the study group for 3 days and then was reduced gradually during 12 days. The results were compared with placebo. In this study, prednisolone improved the symptoms in 94% of cases who had vomiting for 3 days so that they could tolerate their diet⁶.

In a study by Piercy, patients were given prednisolone 20 mg every 12 hours intravenously for 7 days while the control group received the same volume of placebo. The improvement in vomiting

was seen in 80% of the cases in the study group and 30% of the control group⁷.

To avoid moral problems, in this study placebo was not used and due to the short period of therapy, there was no need for gradually reducing corticosteroid⁸.

In this study, weight gain was not seen in contrast to other studies with corticosteroids. The reason may be the short period of study. It seems that in case of a longer study, weight would increase. No antacid was used with prednisolone in our study.

The combination of NSAIDs (Non Steroidal Anti Inflammatory Drugs) and corticosteroids may increase the risk of peptic ulcer⁹. Not consuming antacid with corticosteroids slightly increase the risk of peptic ulcer versus those who do not consume corticosteroids (2% vs. 1%)⁸. Those with a history of digestive disorders and those who were likely to

develop a digestive problem were therefore excluded. Disorder of glucose metabolism is considered a serious side effect of corticosteroid therapy. In this study there were not any significant differences in fasting blood glucose after and before therapy (table 1, 2).

Knowing the fact that prednisolone and hydrocortisone become inactive in placenta and do not pass to the fetus make our study even safer. Cleft palate has only been reported in animals as a complication of steroid administration during pregnancy but there is no such report in human⁸. As 93.3% (vs. 60% in the promethazine group) of cases were controlled with prednisolone, it seems prudent to suggest prednisolone as a first step in cases of protracted and non-responsive hyperemesis gravidarum.

Table 1. Characteristics of patients in the two groups. Data are mean \pm SD

	Groups		
	Prednisolone	Promethazine	P Value
Urine ketone on admission	1.5 \pm 0.6	1.6 \pm 0.65	0.88
Vomiting / day	7.3 \pm 2.5	6.8 \pm 2.2	0.17
Weight loss after HG (kg)	1.86 \pm 1.9	1.76 \pm 1.8	0.41

HG = Hyperemesis Gravidarum

Table 2. Comparison of patients' status before and after treatment in the two groups. Data are mean \pm SD

	Groups				Between groups P value
	Prednisolone		Promethazine		
	Before	After	Before	After	
Severity of Nausea*	8.2 \pm 1.3	1.6 \pm 1.8†	8.3 \pm 1.2	3 \pm 2.6†	0.005
Malaise score*	6.8 \pm 1.6	0.73 \pm 1.4†	7.6 \pm 1.5	2.6 \pm 3†	0.02
Weight (kg)	61.5 \pm 9	61.7 \pm 9	64.5 \pm 14	65 \pm 14	0.21
[Na ⁺] (mEq/L)	136.6 \pm 5	136.7 \pm 5	135.4 \pm 6	136.6 \pm 5	0.37
[K ⁺] (mEq/L)	3.8 \pm 0.4	3.9 \pm 0.4	3.6 \pm 0.6	3.8 \pm 0.4	0.14
FBS (mg/dL)	83 \pm 7	84 \pm 3	82 \pm 8	83 \pm 7	0.29

* Based on a ten-point visual analog scale

† P < 0.05 compared to before treatment value

References

1. Weston KD, Malee MP. Medical and surgical complications of pregnancy. In: Scott JR, Disaia PJ, Hammond CB, Spellacy WN. Danforth's Obstetrics and Gynecology. 8th ed. Philadelphia: Lippincott W and Wilkins; 1999, P331.
2. Walters BNJ. Hepatic and gastrointestinal disease. In: James DK, Steer Pj, Weiner CP, Gonik B. High risk pregnancy: management options. 2nd ed. London: WB Saunders; 1999. p.791-792.
3. Scott LD. Gastrointestinal disease in pregnancy. In: Resink R, creasy K. Maternal Fetal medicine. 4th ed. Philadelphia: WB Saunders; 1999. p. 1042-1043.

4. Pasircha PJ. Prokinetic agents antiemetic and agents used in irritable bowel syndrom. In: Harman JG, Limbird LE. Goodman and Gilman's the pharmacological basis of therapeutics. New York: MC Grow Hill; 2001, P1031.
5. Safari HR, Fassett MJ, Souter IC, Alsulyman QM, Goodwin TM. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: A randomized double blind controlled study. *AM J Obstet Gynecology* 1998; 179:921-4.
6. Safari HR, Alsulyman QM, Gherman RB, Goodwin TM. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum. *AM J Obstet Gynecol* 1998; 178: 1054-8.
7. Piercy KN, Fayers P, Swiet MD. Randomized double placebo controlled trial of corticosteroids for treatment of hyperemesis gravidarum. *BJ obstet Gynecol* 2001; 108: 9-15.
8. Parfitt K. *Martindale: The complete drug reference*. 32ed. London: Pharmaceutical press; 1999: P 397-400, 1010-1014, 1048-1048.
9. Spiro HM. The steroid ulcer a myth? *N Engl J Med* 1983; 309: 45-7