Just a Placebo?
Doxylamine-Pyridoxine May Not Help Pregnancy-Related Nausea and Vomiting

Doxylamine-pyridoxine, a commonly prescribed first-line treatment for pregnancy related nausea and vomiting, may not be any more effective than placebo.

Kaci Durbin

January 31, 2018- First trimester pregnant women with nausea and vomiting are commonly prescribed doxylamine-pyridoxine; however, based on a post-hoc re-analysis of a 2010 study, the medication is no more effective than placebo.

Navindra Persaud and colleagues reported their analysis and findings in the January 17, 2018 issue of *PLoS ONE*.

Doxylamine-pyridoxine is a commonly prescribed treatment for pregnancy-associated nausea and vomiting. Its use as a first-line drug was supported by a 2010 double-blind randomized controlled trial comparing doxylamine-pyridoxine to placebo. In this trial, 140 pregnant women with a gestational age between 7 and 14 weeks were divided into two equal groups: the first received doxylamine-pyridoxine, 10mg each, while the second group received placebo. Each participant took 1 tablet 2 to 4 times per day depending on symptoms.

The primary outcome of the 2010 trial was improvement in nausea and vomiting symptoms. Symptoms were objectively measured using the Pregnancy Unique Quantification of Emesis score. Secondary outcomes included three subscores of the Pregnancy Unique Quantification of Emesis score, a global assessment of wellbeing, the number of tablets taken, the time lost from household tasks or employment, the total number or physician visits, the rates of hyperemesis gravidarum, and patient compliance with medication.

While the authors of the original study concluded that the medication performed significantly better than placebo with regard to the primary outcome, Persuaud and colleagues disagree based on their re-analysis. They argue that the difference between the groups was not *clinically* significant and that the statistical analysis was flawed.

To start with, based on prior research, a clinically important difference in the Pregnancy Unique Quantification of Emesis score is 3 points. This was also the “expected difference” in the original study protocol for doxylamine-pyridoxine. However, in the 2010 study, the difference between doxylamine-pyridoxine and placebo was less than 1 point on the Pregnancy Unique Quantification of Emesis score, indicating that the difference, if accurate, was not clinically significant. In fact, the maximum observed difference between the two groups was only 0.73.

Furthermore, the authors argue that the statistical analysis was flawed. Sample size was based on an alpha value of 0.01 while 0.05 was used to determine statistical significance. More importantly, however, missing data were misinterpreted. The original researchers used a

statistical assumption called “last observation carried forward” imputation. This assumption replaces a missing follow-up value with the last observed value, meaning that if the participant had a score of 5 during the third week of the study and then left, the researchers assumed that her score would have been 5 for the remainder of the study.

Yet, as Persuad and colleagues point out, more patients left the placebo arm compared to the treatment arm. Since all patients, both treated and placebo, improved throughout the study secondary to the natural course of nausea and vomiting of pregnancy, this approach skewed the results. As more data was missing in the control group, the scores in this group were falsely elevated, giving the appearance that the control group experienced more nausea than the treatment group.

The authors concluded, after their independent analysis of the data, that the original reported interpretation was flawed. Doxylamine-pyridoxine is no more effective than placebo. As stated in the article, this finding “calls into question the conclusion of the original report that the medication is efficacious.” Persuad and colleagues recommend, “Clinical practice and guidelines should be updated.”

This study was sponsored by a Physicians’ Services Incorporated Graham Farquharson Knowledge Translation Fellowship. The sponsors did not contribute to study design, data collection and analysis, decision to publish, or preparation of the manuscript.

PLoS ONE. Published January 17, 2018