OBSTETRICS

Esomeprazole to treat women with preterm preeclampsia: a randomized placebo controlled trial

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BACKGROUND: Preterm preeclampsia has a high rate of fetal death or disability. There is no treatment to slow the disease, except delivery. Preclinical studies have identified proton pump inhibitors as a possible treatment.

OBJECTIVE: The purpose of this study was to examine whether esomeprazole could prolong pregnancy in women who have received a diagnosis of preterm preeclampsia.

STUDY DESIGN: We performed a double-blind, randomized controlled trial at Tygerberg Hospital in South Africa. Women with preterm preeclampsia (gestational age 26 weeks+0 days to 31 weeks+6 days) were assigned randomly to 40-mg daily esomeprazole or placebo. The primary outcome was a prolongation of gestation of 5 days. Secondary outcomes were maternal and neonatal outcomes. We compared circulating markers of endothelial dysfunction that was associated with preeclampsia and performed pharmacokinetic studies.

RESULTS: Between January 2016 and April 2017, we recruited 120 participants. One participant was excluded because of incorrect randomization, which left 59 participants in the esomeprazole and 60 participants in the placebo group. Median gestational age at enrolment was 29+4 weeks gestation. There were no between-group differences in median time from randomization to delivery: 11.4 days (interquartile range, 3.6−19.7 days) in the esomeprazole group and 8.3 days (interquartile range, 3.8−19.6 days) in the placebo group (3 days longer in the esomeprazole arm; 95% confidence interval, −2.9−8.8; P=.31). There were no placental abruptions in the esomeprazole group and 6 (10%) in the placebo group (P=.01, P=.14 adjusted). There were no differences in other maternal or neonatal outcomes or markers of endothelial dysfunction. Esomeprazole and its metabolites were detected in maternal blood among those treated with esomeprazole, but only trace amounts in the umbilical cord blood.

CONCLUSION: Daily esomeprazole (40 mg) did not prolong gestation in pregnancies with preterm preeclampsia or decrease circulating soluble fms-like tyrosine kinase 1 concentrations. Higher levels in the maternal circulation may be needed for clinical effect.

Key words: esomeprazole, trial, preterm preeclampsia, sFlt1, pharmacokinetics

Preeclampsia is one of the most serious complications of pregnancy. It affects 3−8 % of pregnancies and is a leading cause of maternal, fetal, and neonatal morbidity.[1,2] There is no treatment that can slow disease progression, and the only treatment option is to deliver the pregnancy. For preeclampsia that occurs at preterm gestations, clinicians are often required to deliver the fetus early, which results in iatrogenic prematurity with a risk of major disability that includes cerebral palsy, intracerebral bleeding, retinopathy of prematurity, chronic lung disease, and death. The risks of these complications are higher if pregnancies are delivered at earlier gestations.[3] If a treatment were available that temporizes disease progression, it could be used to safely delay delivery to gain gestation, thereby decreasing the degree of prematurity and improving perinatal outcomes.

The preeclamptic placenta releases elevated levels of soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin into the maternal circulation.[4] These antiangiogenic factors cause maternal endothelial dysfunction, hypertension, and multiorgan injury.[5] Esomeprazole is a proton pump inhibitor (PPI) that is prescribed widely in pregnancy to relieve symptomatic gastric reflux. Members of our team have performed preclinical laboratory studies that have shown that PPIs such as esomeprazole are a candidate therapeutic for preeclampsia.[6] Esomeprazole, in particular, has been shown to have diverse biologic actions. Firstly esomeprazole decreases sFlt1 and soluble endoglin production and release from primary trophoblast cells and placental tissue explants and primary endothelial cells/tissues in both normal and preeclamptic pregnancies. Secondly esomeprazole was able to dilate whole human vessels from both normal pregnancies treated with a constrictor and vessels that were obtained from women with preeclampsia. Thirdly, preclinical studies also showed that esomeprazole decreased endothelial dysfunction by mitigating tumor necrosis α−induced endothelial injury, as demonstrated by reducing expression of endothelial vascular cell adhesion molecule-1 and reduced leucocyte adhesion to the endothelium. Lastly important animal studies clearly show that esomeprazole reduces blood pressure in a transgenic mouse model of preeclampsia in which human sFlt1 is overexpressed in the placenta and released in excess into the maternal blood, as seen in women with preeclampsia.[6] Others have subsequently found decreased circulating sFlt1 and soluble endoglin levels in an existing cohort of bloods of women with suspected or confirmed preeclampsia that were coincidentally taking PPIs.[7]

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AJOG at a Glance

Why was this study conducted?

Preeclampsia has high rates of fetal death or disability. There is no treatment to slow the disease, except delivery. Preclinical studies have identified proton pump inhibitors as a possible treatment.

Key findings

Daily oral esomeprazole (40 mg) did not prolong gestation in pregnancies with preterm preeclampsia or decrease circulating soluble fms-like tyrosine kinase 1 concentrations.

What does this add to what is known?

This is the first trial for preterm preeclampsia that has integrated clinical outcomes, mechanistic studies, and pharmacokinetics. Oral esomeprazole (40 mg) may be too low a dose to treat preterm preeclampsia; higher doses may still be effective. This may be the fastest completed randomized clinical trial of a treatment for preterm preeclampsia. It is possible to complete clinical trials for preterm preeclampsia in a reasonable timeframe by running the trials in settings in which the incidence of disease is high.

These promising preclinical data suggest that esomeprazole is a potential candidate treatment; we therefore set out to examine whether oral esomeprazole may be an effective treatment for preterm preeclampsia.

Methods

Trial design

In this single-site phase II double-blind, randomized, placebo-controlled clinical trial, we compared oral esomeprazole with placebo. A 40 mg daily dose was selected based on pharmacokinetic data that showed effective suppression of gastrointestinal symptoms in nonpregnant patients and on reassuring data that showed no adverse effects if taken during pregnancy.[8-11] The trial site was Tygerberg Hospital, Cape Town, South Africa, which is a large academic referral center that is situated in a region with high rates of preeclampsia. We have published the protocol,[12] and the trial was registered with the Pan African Clinical Trials Registry (PACTR201 504000771349).

Pregnant women with singleton pregnancies were invited to participate if they had been diagnosed with preterm preeclampsia between 26+0 and 31+6 weeks gestation. The gestation at enrolment was determined by either menstrual dates (if the women was certain of her last menstrual period) or by an early or mid-trimester pregnancy ultrasound examination. Both the managing perinatologist and neonatologist had to agree that expectant management could benefit the fetus.

Women were not eligible if they had an indication for immediate delivery because they could not be treated expectantly to gain further fetal maturity. Exclusion criteria therefore included established maternal or fetal compromise that necessitated delivery, the current use or contraindications to the use of PPIs, and the use of medications that could interact with PPIs (which included warfarin, ketoconazole, voriconazole, atazanavir, nelfinavir, saquinavir, digoxin, St John's Wort, rifampin, cilostazol, diazepam, tacrolimus, erlotinib, methotrexate, and clopidogrel). Specific clinical exclusion criteria included eclampsia, severe hypertension not be controlled within 48 hours of admission, a cerebrovascular event, posterior reversible encephalopathy syndrome, severe renal impairment with a creatinine >125 μmol/L, pulmonary edema, disseminated intravascular coagulation, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, liver hematoma or rupture, severe ascites on ultrasound examination. We excluded pregnancies with a suspicion of a major fetal anomaly or malformation. Expectant management involved hospital admission with close maternal and fetal surveillance. Maternal surveillance involved 4 hourly blood pressure measurement, twice daily clinical assessments, daily urinalysis, and twice weekly biochemical testing. Fetal surveillance involved 6 hourly cardiotocography and ultrasound assessments every 2 weeks or more frequently, if indicated. To enhance fetal lung maturity, all participants received 2 doses of betamethasone that were given 24 hours apart, followed by a single repeat dose 1 week later if not delivered, as per local protocol.[13] Expectant management ended at 34 weeks gestation; women who reached this gestation were delivered. Delivery at <34 weeks gestation was a clinical decision made by the patient's treating team.

The study participants provided written informed consent. The study had Health Research Ethics Committee (HREC) approval, was approved by the South African Medicines Control Council. Study data were collected and managed with the use of REDCap electronic data capture tools.[14]

Randomization and masking

Randomization was performed in a 1:1 ratio with the use of an online, web-based sequence generator. Because gestation at randomization could possibly impact the length of pregnancy prolongation, randomization was stratified (strata 1 was ≤28+6 weeks; strata 2 was 29+0 until 31+6 weeks gestation). Randomization was done within blocks of random size within 4−6. The tablets and treatment packs were manufactured, packed, and labelled by the Institute of Drug Technology Limited (en.idtaus.com.au) in Victoria, Australia, and were identical with respect to variables such as size, thickness, physical properties, and appearance. The investigators had no access to the randomization list, and allocation concealment was maintained throughout the trial.

Placental and blood collection to measure angiogenic markers of preeclampsia and endothelial dysfunction and to perform pharmacokinetics

Plasma samples to measure circulating preeclampsia and angiogenic biomarkers were collected at randomization and twice weekly until delivery. Placental tissue