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Research Article

Role of Esomeprazole in Early Preeclampsia: A Randomized Controlled Trial

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Abstract

Objective: To investigate the efficacy of esomeprazole in managing early preeclampsia.

Methods: This randomized controlled trial was conducted at the Obstetric/Gynecology department of Suez Canal University Hospital. We included 160 women between 26-31 years of age, with a singleton pregnancy. Eighty women received esomeprazole along with expectant treatment, whereas 80 women received expectant treatment alone. They were followed up from the date of diagnosis up to four weeks after delivery. The gestational age at termination as well as any complications during the follow-up period were documented and compared between both groups.

Results: The mean age of the participants was 30.64 ± 1.62. The gestation of women in the intervention group was longer than those within the control group, with a gestational age at termination of 34.53 ± 1.21 versus 32.78 ± 1.60, respectively (P<0.001). Moreover, women in the intervention group had significantly lower incidences of fits (P= 0.005), antepartum hemorrhage (P=0.005), DIC (P=0.032), and IUFD (P<0.001).

Conclusions: Esomeprazole is associated with a significant prolongation of gestation in women with early preeclampsia.

Keywords: Preeclampsia; Esomeprazole; Complications

Introduction

Preeclampsia is a life-threatening condition seen in pregnant women usually beyond the 20th week of gestation [1], in which, the placenta releases increased amounts of certain antiangiogenic factors into the maternal circulation, such as the soluble Fms-like tyrosine kinase 1 (sFlt-1) and soluble Endoglin (sEng) [2]. These factors are believed to play an important role in the endothelial dysfunction and subsequent maternal organ injury associated with preeclampsia [3]. Thus, preeclampsia is characterized mainly with hypertension, proteinuria, glomerular endotheliosis (a classical lesion of preeclampsia), placental abnormalities and small fetal size [4]. Furthermore, a variant of severe preeclampsia may occur, called the Hemolysis, Elevated Liver Enzymes, Low-Platelet count (HELLP) syndrome [5].

Preeclampsia affects 3% to 8% of pregnancies and is considered the third leading cause of maternal mortality during pregnancy, coming after hemorrhage and embolism. In fact, it is responsible for 60,000 annual deaths across the globe and even higher rates of fetal losses [3]. The only definitive treatment for preeclampsia is to deliver the placenta, which would remove the source of placental-derived factors responsible for the maternal organ injury [6]. However, this results in delivering premature babies, who would have to face the neonatal complications of prematurity. Therefore, therapeutic options that block the pathophysiological changes associated with preeclampsia will enable clinicians to postpone the delivery and thus, improve both maternal and fetal outcomes [7]. Interestingly, such an action has been reported for Esomeprazole; a Proton Pump Inhibitor (PPI) safely prescribed in pregnancy for gastric reflux, which can also effectively decrease sFlt-1 and sEng secretion from the placenta and endothelial cells. Therefore, esomeprazole is believed to have a promising therapeutic effect in preeclampsia and other diseases associated with endothelial dysfunction [6]. In the light of improving pregnancy outcomes and reducing the incidence of preterm birth, we conducted this study in order to investigate the efficacy of 40 mg esomeprazole daily in managing early preeclampsia.

Patients and Methods

This randomized controlled trial was conducted at the Obstetrics and Gynecology department of Suez Canal University Hospital (SCUH), Ismailia, Egypt from December 2017 to December 2018. The Ethical Committee of Faculty of Medicine, Suez Canal University has approved this trial before its commencement and informed consents were obtained from every enrolled woman. Women were selected from the pregnant population presenting to SCUH with an evidence of preeclampsia. Preeclampsia was defined as gestational hypertension (high blood pressure after 20 weeks of gestation) plus a new-onset proteinuria (proteins ≥300mg per 24 hours urine collection or protein/createnine ratio ≥0.3mg/dl or a dipstick reading of +1 proteinuria) [7]. We included women between 26-31 years of age, with a singleton pregnancy and an estimated fetal weight between 500-1800 g by ultrasound in the absence of any major fetal anomaly or malformation. Meanwhile, we excluded women with established eclampsia, severe hypertension (systolic blood pressure ≥160mmHg, or a diastolic BP ≥110mmHg on two occasions at least 4 hours apart while the patient resting on bed), severe fetal compromise necessitating urgent delivery, cardiovascular events, left-sided heart failure, hypersensitivity or any contraindication to the use of esomeprazole, current use of a medication that interacts with esomeprazole, severe ascites, liver hematoma, established pulmonary edema, baseline elevated liver enzymes (two-folds or higher), low platelet count (<100,000 per μL), since all these factors could possibly impact our results.

The enrolled women were subjected to full history documentation;

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including their socio-demographic data, obstetric history, past medical history, and family history. Afterwards, a thorough and detailed examination was performed for each woman, including general, chest, cardiac, abdominal, and obstetrical examinations. Expectant treatment was followed in the current study while managing preeclampsia. Accordingly, the women were randomly assigned into one of two groups; the interventional group, who received expectant treatment along with esomeprazole 40 mg orally once daily, and the control group, who received expectant treatment and placebo. The randomization was double-blinded to ensure accuracy of the results. Allocation of women into the two groups was done using a computer program and operated by a third-party person to minimize any bias. Both esomeprazole and the placebo drug were prescribed from the Hospital's pharmacy and delivered in similar package with different colored labels (pink and yellow), and the colors were not revealed to the investigators until after data analysis.

Expectant treatment was mainly focused on the use of antihypertensive drugs according to blood pressure measurements, as mild preeclampsia (140/90 to 149/99 mmHg) did not require further treatment other than follow up on inpatient basis, whereas moderate preeclampsia (150/100 to 159/109 mmHg) necessitated the use of antihypertensive drugs. According to the NICE guidelines in 2011, the goal of controlling blood pressure is to keep the diastolic blood pressure between 80-100 mmHg and systolic blood pressure below 150mmHg. The drug of choice was oral *Labetelol* (Labipress 100-1500 mg) daily, whereas second line included *α-mehtyldopa* (Aldomet 250mg - 4g) per day on divided doses, and *calcium channel blocker* (Nifidipine 30-90 mg) daily [7]. In the current study, the initial step was Lapipress 200mg every 12 hours daily up to 200mg every 6 hours. If blood pressure was still not controlled, we would add Aldomet 250mg up to 250mg every 6 hours daily. Women with a pregnancy of a gestational age >28 weeks also received two doses of betamethasone 12mg, 24 hours apart, in order to reduce the risks of neonatal respiratory distress syndrome.

All women were followed up by serial blood pressure measurements (twice daily), conventional ultrasound, Doppler studies, blood tests, urinary protein, and vigilance to any sort of blood loss. Conventional ultrasound was done once weekly for ensuring fetal viability, estimating gestational age and fetal weight to detect small for gestational age fetus and intrauterine growth retardation, identifying placenta maturation (grade II or III), and estimating amniotic fluid index. Moreover, Doppler ultrasound was done once weekly to assess umbilical artery Doppler and detect fetal distress that might occur due to preeclampsia. Full laboratory tests were done twice weekly, including complete blood picture, serum creatinine, and liver enzymes [8]. HELLP syndrome was suspected when platelets count was <50,000mm^3 and liver enzymes ≥70IU/L (class I), platelets count between 50,000 and 100,000 mm^3 and liver enzymes ≥40IU/L (class II), platelets count between 100,000 and 150,000 mm^3 and liver enzymes ≥40 IU/L (class III) [9]. DIC was suspected in a women with a low platelets count (50.000-100,000 mm^3), high INR (>1.2) and prolonged prothrombin time (>13 seconds) [10]. Urine samples were collected twice weekly and sent for spot protein/creatinine ratios, whereas 24-hour urinary protein excretion was measured once weekly. A urinary protein greater than or equal to 300mg per 24 hours urine collection or a protein/creatinine ratio greater than or equal to 0.3mg/dl confirmed the diagnosis of preeclampsia and was used to follow up the progress of preeclampsia. We also monitored the occurrence of hemorrhage among the enrolled women; either ante- or postpartum. Antepartum hemorrhage was considered minor hemorrhage when blood loss <50ml), major hemorrhage at blood loss of 50 -1000 ml without signs of circulatory shock, and massive hemorrhage at blood loss >1000ml with or without signs of circulatory shock [11]. Postpartum hemorrhage was defined as blood loss over 500ml in natural vaginal delivery, or 1000ml in cesarean section within 24 hours postpartum [12]. Meanwhile, X-ray was only done if pulmonary edema was suspected; in patients developing dyspnea, wheezing and fatigue. Neonatal assessment of the delivered babies was based on their birth weight and Apgar scores. A neonatal weight 2500-3500 g was considered normal. An Apgar score >7 at 5th min was considered a good score while if <7 at 5th min, assessment should be repeated every 5 minutes up to 20 minutes. The need for Neonatal Intensive Care Unit admission was decided based on the neonates' Apgar scores. Moreover, all neonates were followed up for 4 weeks after birth to document any case of neonatal death.

Statistical analysis

The collected data were analyzed using IBM Statistical Package for Social Sciences software (SPSS), 24th version. Numerical data; such as maternal or gestational age, parity, blood pressure, UA RI, and birth weight were presented as mean ± standard deviation. Meanwhile, categorical data; such as maternal adverse events, drugs side effects, or bleeding-related and postnatal complications, were presented as frequencies and percentages. Data were not normally distributed according to the Shapiro-Wilk test. Therefore, Mann Whiney U test was used to compare numerical data, whereas Fischer Exact and Chi-square tests were used to compare between categorical data. Multivariable linear regression analysis was used to assess the predictors of fits, DIC, antepartum hemorrhage in the enrolled women. Results were considered statistically significant at a p-value <0.05.

Results

We interviewed 177 women selected based on our selection criteria from the waiting areas of outpatient clinics, the inpatient wards, and the emergency department of Obstetrics/Gynecology. Nonetheless, 17 women were unwilling to participate in this study mainly out of the fear of being in a clinical trial. These women were excluded, and thus eventually, 160 women were enrolled in our study (Figure 1).

The enrolled women had a mean age of 30.64 ± 1.62, with insignificant differences regarding their age or number of parity between the intervention and the control groups (P=0.52 and 0.24, respectively) (Table 1). Concerning the reported maternal adverse events, women in the intervention group had a significantly lower incidence of fits compared to those in the control group (10% *vs.* 27.5%, P=0.005) (Figure 2). Meanwhile, the difference in incidences of pulmonary edema and HELLP syndrome between the two groups was insignificant (P=0.12 and 0.34 respectively). Yet, HELLP syndrome was not an uncommon event, established in 12.5% of the enrolled women. Fortunately, maternal death did not occur among the studied women.

We found that women in the intervention group had significantly

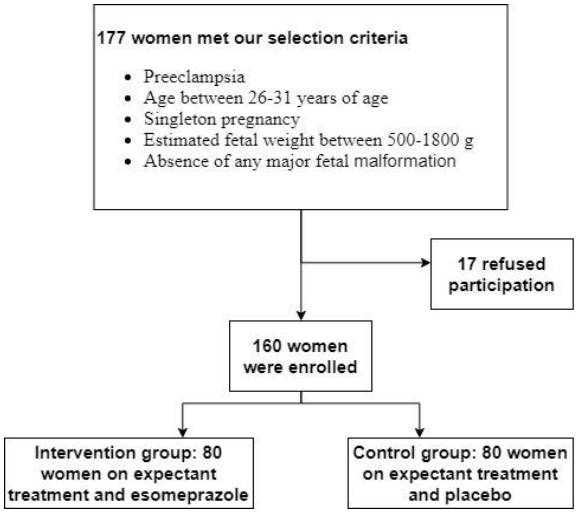

Figure 1: Recruitment of the participants into the study.

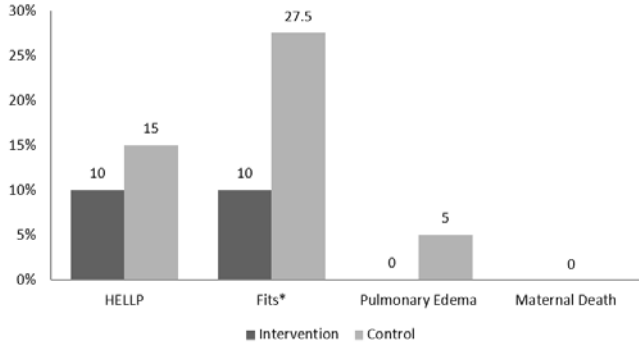

Figure 2: Maternal adverse events among both groups (n=160).
HELLP: Hemolysis, Elevated Liver Enzymes, and a Low Platelet Count; *Statistically significant at a P value <0.05, based on Chi-square test.

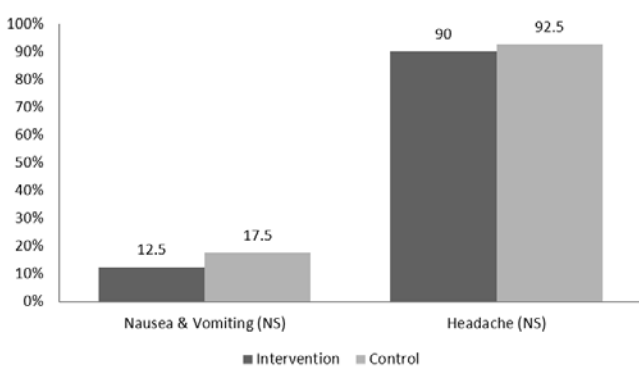

Figure 3: Frequency of drugs side effects in the two groups (n=160).
NS: Statistically Insignificant P values, based on Chi-square test.

lower systolic and diastolic blood pressures compared to those in the control group (P <0.001) (Table 2). As a matter of fact, the recorded systolic and diastolic blood pressures of the intervention group were still in the normal range (131.83 ± 11.85 and 87.88 ± 6.69, respectively), whereas those of the control group did reach the hypertensive range (145.63 ± 15.83 and 93.08 ± 9.97, respectively). Moreover, Umbilical Artery Resistance Index (UA RI) as assessed by Doppler ultrasonography was significantly lower in the intervention group (P <0.001). Also, women in the intervention group had significantly lower incidences of antepartum hemorrhage and DIC (P=0.005 and 0.032, respectively), whereas the incidence of postpartum hemorrhage was similar in both groups (10% versus 10%, P=0.9). Interestingly, women in the intervention group had a 70.7% decrease in the odds of developing fits (OR=0.293, P=0.006), an 85.5% decrease in the odds of developing antepartum hemorrhage (OR=0.145, P=0.014), and a 61.7% decrease in the odds of having DIC (OR=0.383, p=0.036) compared to their counterparts in the control group (Table 3). Meanwhile, intracranial hemorrhage has not been detected in any of the enrolled women.

Interestingly, the gestation of women in the intervention group was longer than those within the control group, with a gestational age at termination of 34.53 ± 1.21 versus32.78 ± 1.60, respectively (P <0.001) (Table 4). Moreover, IUFD occurred in 8.8% of the control group, whereas it was not reported in any of the intervention group (P <0.001). Babies of mothers within the intervention group had a significantly higher birth weight than those within the control group (P <0.001). Moreover, the intervention group had a lower incidence of neonatal death and NICU admission compared to the control group; however, this finding was statistically insignificant (P=0.49 and 0.38, respectively). The incidence of drugs side effects were not significantly different between the two groups (P=0.38 and 0.58 respectively) (Figure 3).

Discussion

Principal findings: Esomeprazole was associated with a significant prolongation of gestation in women with early preeclampsia with a reduction in the complications that might occur.

Clinical implications: Interestingly, we found that esomeprazole was associated with a significantly prolonged gestation in women with preeclampsia. In particular, women receiving esomeprazole have delivered their babies in later dates than those on expectant management alone, with a gestational age at termination of 34.53 ± 1.21 versus 32.78 ± 1.60, respectively. As mentioned earlier, it's strongly believed that sFlt-1 secreted by the placenta causes endothelial

Table 1: Baseline characteristics of the two groups (n=160).

Variables	Total (n=160)	Intervention (n=80)	Control (n=80)	Test value	*P*
Maternal age (years), mean ± SD	30.64 ± 1.62	30.68 ± 1.66	30.60 ± 1.59	3014	0.52[a]
Parity, n (%)					
No parity	45 (28.1)	18 (22.5)	27 (33.8)	2.83	0.24[b]
Once	79 (49.4)	44 (55)	35 (43.8)		
Two or more	36 (22.5)	18 (22.5)	18 (22.5)		

[a]P-values are based on Man-Whitney test; [b]P-values are based on Chi-square test. Statistical significance at P <0.05.

Table 2: Antenatal and postnatal maternal assessment among both groups (n=160).

Variables	Total (n=160)	Intervention (n=80)	Control (n=80)	Test Value	*P*
Vital Signs, Mean ± SD					
Systolic Blood pressure	138.73 ± 15.5	131.83 ± 11.85	145.63 ± 15.83	1514	<0.001[a]*
Diastolic blood pressure	90.48 ± 8.8	87.88 ± 6.69	93.08 ± 9.97	2164	<0.001[a]*
Doppler Findings, Mean ± SD					
UA RI	0.67 ± 0.10	0.63 ± 0.09	0.71 ± 0.09	1444	<0.001[a]*
Bleeding-Related Complications, n (%)					
Antepartum hemorrhage					
Absent	146 (91.3)	78 (97.5)	68 (85)	7.83	0.005[b]*
Present	14 (8.8)	2 (2.5)	12 (15)		
Postpartum hemorrhage					
Absent	144 (90)	72 (90)	72 (90)	0.001	0.90[b]
Present	16 (10)	8 (10)	8 (10)		
Intracranial hemorrhage					
Absent	180 (100)	80 (100)	80 (100)	-	-
Present	0 (0)	0	0		
DIC					
Absent	134 (83.8)	72 (90)	62 (77.5)	4.59	0.032[b]*
Present	26 (16.3)	8 (10)	18 (22.5)		

UA RI: Umbilical Artery Resistance Index; DIC: Disseminated Intravascular Coagulation.
[a]P-values are based on Man-Whitney test. [b]P-values are based on Chi-square test. *Statistical significance at P <0.05.

Table 3: Logistic regression analysis of determinants of different maternal adverse outcomes.

Predictor	Fits		Antepartum hemorrhage		DIC	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Intervention						
r	0.293 (0.122 - 0.706)	**0.006***	0.145 (0.031 - 0.672)	0.014 [a]	0.383 (0.156 - 0.941)	**0.036***

OR: Odds Ratio; CI: Confidence Interval; DIC: Disseminated Intravascular Coagulation; *Statistical significance at P <0.05.

Table 4: Fetal assessment among both groups (n=160).

Variables	Total (n=160)	Intervention (n=80)	Control (n=80)	Test value	*P*
Antenatal					
Gestational age at termination (weeks), mean ± SD	33.65 ± 1.6	34.53 ± 1.21	32.78 ± 1.60	1314	<0.001[a]*
IUFD, n (%)					
Absent	153 (95.6)	80 (100)	73 (91.3)	15.34	<0.001[b]*
Present	7 (4.4)	0	7 (8.8)		
Postnatal (n=153)					
Birth weight (g.), mean ± SD	1543.8 ± 243.37	1629.68 ± 250.82	1449.7 ± 197.09	1598	<0.001[a]*
Neonatal deaths within four weeks after delivery, n (%)					
Absent	123 (80.4)	66 (82.5)	57 (78.1)	0.47	0.49[c]
Present	30 (19.6)	14 (17.5)	16 (21.9)		
NICU admission, n (%)					
Absent	118 (77.1)	64 (80)	54 (74)	0.79	0.38[c]
Present	35 (22.9)	16 (20)	19 (26)		

IUFD: Intrauterine Fetal Death; NICU: Neonatal Intensive Care Unit; SD: Standard Deviation.
[a]P-values are based on Man-Whitney test. [b]P-values are based on Fisher Exact test. [c]P-values are based on Chi-square test. *Statistical significance at P <0.05.

dysfunction and possibly plays a primary role in the pathogenesis of the disease [13,14]. Esomeprazole is believed to effectively reduce sFlt-1 and sEng secretion from the placenta and endothelial cells, and thus, improve pregnancy outcomes [6]. On the other hand, anti-hypertensive drugs on its own can only prevent maternal morbidity; however, they have no impact on the disease progression

or the occurrence of eclampsia [15]. Consistently with our finding, a case study by Oriaifo et al. indicated that esomeprazole can reduce fetal and maternal risk associated with preeclampsia and therefore, prevent its progression to eclampsia [16]. On the contrary, a recent study by Cluver et al. [17] included 120 pregnant women with early-onset preeclampsia and reported that 40 mg of esomeprazole didn't effectively prolong the gestation in these women. More interestingly, the authors have assessed the levels of serum sFlt-1 and found that the use of esomeprazole was not associated with significant changes in its level. Consequently, they postulated that 40mg of oral esomeprazole cannot effectively hinder the disease progression once its diagnosis has been established. However, the difference in the reported results can be attributed to the different sample sizes and different populations.

Moreover, we found that women receiving esomeprazole had a significantly lower incidence of fits compared to those on expectant regimen alone (10% versus 22%, respectively). Although the same finding has been reported by Cluver et al. [17], yet, their findings were statistically insignificant. Meanwhile, the differences in incidence between the interventional and the control groups in terms of pulmonary edema and HELLP syndrome were insignificant, which is similar to the findings reported by Cluver et al. [17].

We also found that women receiving esomeprazole had significantly lower systolic and diastolic blood pressures as well as lower umbilical artery resistance index compared to those in the control group. An interesting case report by Oriafio et al. [16] entailed that esomeprazole addition to anti-hypertensive drugs caused a significant reduction in the woman's blood pressure with mean BP at 34w (127.69) and a reduction of umbilical artery resistance index (0.450) at 34 weeks. More importantly, the woman gave birth to a live baby with normal Apgar score after 35 + weeks.

We also found that women receiving esomeprazole had significantly lower incidences of antepartum hemorrhage (2.5% versus 15%), DIC (10% versus 22.5%), IUFD (0% versus 8.8%) compared to those in the control group, whereas the incidence of postpartum hemorrhage was similar in both groups. Similarly, Cluver et al. [17] reported that antepartum hemorrhage did not occur to any of the women within the interventional group, whereas it was reported in 10% of the control group. Moreover, babies of mothers within the intervention group had a significantly higher birth weight than those within the control group. Moreover, the intervention group had a lower incidence of neonatal death and NICU admission compared to the control group; however, this finding was statistically insignificant. Meanwhile, Cluver et al. [17] reported that the difference in birth weight and NICU admission rates between the two groups were statistically insignificant.

Research implications: Further studies are advised to include larger sample and compare the efficacy of different doses of esomeprazole in managing of early preeclampsia.

Strengths and Limitations: The current study is situated amongst the very few studies that have discussed the role of esomeprazole in early preeclampsia. However; this study has also some limitations. First, due to financial barriers we were unable to compare the level of sFlt-1 between the two groups. Second, the study was conducted at a single hospital and thus, it doesn't necessarily reflect the situation within the Egyptian community.

Conclusion: Esomeprazole was associated with a significant prolongation of gestation in women with early preeclampsia. Moreover, the use of esomeprazole was associated with lower incidences of maternal and fetal complications such as fits, antepartum hemorrhage, DIC, and IUFD.

Declaration

Author's participation: KA Atwa: Protocol/project development, Data collection and management, manuscript writing/editing; ZM Ibrahim: Protocol/project development, Data collection and management, manuscript writing/editing; M Elshaer: Data collection and management, Manuscript writing/editing. OT Taha: Data collection and management, Data analysis, Manuscript writing/editing. AA Aboelroose: Data collection and analysis, manuscript writing and revision.

Ethical Approval

The research ethics committee approved the trial on 22/11/2017 with a number of 3266#.

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