PERINATAL AND HEMODYNAMIC EVALUATION OF SILDENAFIL CITRATE FOR PREECLAMPSIA TREATMENT

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ABSTRACT

Background: It is estimated that anywhere from 2 to 8 percent of all pregnancies are affected by the condition known as preeclampsia. This disease is one of the main causes to the morbidity and death of both females and newborns. Erectile dysfunction and pulmonary hypertension are both treatable conditions that can be helped by taking sildenafil citrate.When treating preeclampsia in the setting of severe prematurity, adopting a more positive outlook on the patient's prognosis may result in better perinatal results.

Aim & objective: to find out whether or not taking sildenafil citrate leads to an increase in uteroplacental and fetoplacental blood flow, and whether or not this leads to a longer gestation for women who already have preeclampsia as well as better maternal and perinatal outcomes.

Patients and methods: A controlled randomized clinical trial (CRCT). The study is conducted at Beni-suef University Hospital's Obstetrics and Gynecology Department. Period from March 2017 till March 2019. Using Open EPI at 80% power and 95% CI, the estimated sample was (50) in each group.

Results: there was a statistically significant difference among the studied groups concerning Blood pressure and heart rate (maternal and fetal) findings of the studied patients' groups before delivery and regarding Doppler findings at time of delivery.

Conclusion: In addition to alpha methyl dopa, sildenafil citrate was found to be safe in our study for the treatment of preeclampsia in its mildest form. Our results, is associated with prolongation of pregnancy and better maternal and fetal outcomes as it decreases maternal Blood pressure and enhances doppler indices of umbilical and uterine arteries, along with the findings of previous studies suggest positive outcomes. Bigger study are required to back up our findings.

Keywords: Perinatal, Hemodynamic Evaluation, Sildenafil Citrate, Preeclampsia

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INTRODUCTION

Preeclampsia is a condition unique to pregnancy that often appears during the 20th week of gestation and is defined by high blood pressure(systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure DBP of ≥ 90 mmHg) and proteinuria (≥ 300mg per 24 hours or persistent 30mg/dL (1+dipstick) in random urine samples). Both of these conditions are diagnostic of preeclampsia **(1).** Even though decreased immunologic adaptation and genetic incompatibility appear to be involved in poor trophoblastic implantation, the etiology and pathophysiology of preeclampsia continue to be unclear. This is despite the fact that poor trophoblastic implantation appears to be caused by genetic incompatibility. Women who are pregnant and have preeclampsia may have the condition as a result of an elevated systemic inflammatory response that is brought on by placental hypoxia and endothelial dysfunction. **(2)** Nitric oxide inhibits platelet aggregation and acts as a powerful vasodilator, especially in the venules. Endothelial cells and tissues in the uterus and placenta produce nitric oxide during pregnancy, which aids in keeping blood pressure stable and vascular resistance low. **(3)**

To treat erectile dysfunction and pulmonary hypertension, doctors often prescribe sildenafil citrate. The biggest drawback of using nitric oxide during pregnancy is that it might cause headaches and tolerance, however phosphodiesterase type 5 inhibitors like sildenafil citrate may help with this. In vitro and animal studies have showed encouraging results with this phosphodiesterase type 5 inhibitor, making it the most investigated of its kind. **(4)** Studies have suggested that treating preeclampsia in extremely premature infants with an "expectant" approach may lead to better perinatal outcomes. According to estimations, there is a nonlinear rise of 1% in the chances of the fetus surviving between the ages of 24 and 32 weeks of gestation for each additional day that the pregnancy

is extended. **(5)** We wanted to see if increasing blood flow to the placenta and fetus by sildenafil citrate medication may help pregnant women with preeclampsia have healthier pregnancies and safer deliveries.

PATIENTS AND METHODS

A controlled randomized trial. Beni-suef University Hospital's Obstetrics and Gynecology Department is hosting the study. Period from March 2017 till March 2019. Using Open EPI at 80% power and 95% CI, the estimated sample was (50) in each group.

One hundred pregnant female participated in this study,complaining of mild preeclampsia who were attending at antenatal care clinic of obstetrics and gynecology department of Benisuef university hospital and then admitted for delivery.

Inclusion Criteria: females aged from 18 – 45 years.

Singleton pregnancy, GA 24–33 weeks based upon the date of last normal menstruation, confirmed by ultrasonographic scan, According to the ACOG 2013 guidelines, mild preeclampsia is hypertension after twenty weeks of gestation with proteinuria "greater than 300 mg in 24 hours" and previous normal blood pressure. BMI (18-30 kg/m2) and blood pressure (two measures at least four hours apart) must be satisfied.

Exclusion Criteria: Prevalence of long-term hypertension, Fetal malformations; maternal or fetal comorbidities that increase the risk of a premature birth (such as diabetes, renal and autoimmune diseases; fetal death; HELLP syndrome; severe renal insufficiency; eclampsia warning signs; reversed diastolic blood flow in the umbilical artery); and other chronic disorders., a biophysical profile of less than 6 on a 10-point scale, or an amniotic fluid index of less than 5 cm Multiple pregnancies, patients using antihypertensive drugs besides alpha-methyldopa, and the use of erythromycin, ketoconazole, itraconazole, or any other medication that may interact with sildenafil.

Selected cases were separated into 2 groups: Group (I): included 50 singleton pregnant women with mild preeclampsia with gestational age 24 – 33 weeks and received oral 50mg sildenafil citrate every 8 hours/day and Group (II): included 50 singleton pregnant females with mild preeclampsia with gestational age 24 – 33 weeks and did not receive sildenafil citrate.

Methods

The following procedures were performed on each of the individuals who participated in the study: Medical History (including Personal History, Past History, as well as Menstrual and Obstetrical History), Clinical Examination& and Laboratory Investigations (including Complete Blood Count, Complete Urine Analysis, and Liver Function Tests) Evaluation of the maternal blood pressure (systolic, diastolic, and mean), examination with routine ultrasonography, evaluation with Doppler ultrasonography, and follow-up visits

Ethical Considerations: The institution's ethical committee authorized the study and acquired permission after potential participants were informed of its goal and procedures. Patients who declined the research were promised that their care would not deteriorate.

Statistical Analysis

Statistical Analysis Data was statistically reported using mean, (SD), frequencies, and relative frequencies. The Student t test for independent samples compared quantitative variables between treatment groups. Contrasting discrete categories used the Chi square (χ^2) test. When the expected frequency was less than 5, an exact test was used. Statistical significance was 0.05 or less.

RESULTS

Table (1): Basic demographic characteristics of studied patients' groups:

Variable	Group (I)	Group (II)	t-test	p-value
Maternal age (years)				
Mean ± SD	**35.42 ± 4.80**	**34.16 ± 5.13**	**1.267**	**0.103**
Range	**26 – 43**	**19 – 42**		
Body Mass Index (Kg/m^2)				
Mean ± SD	**23.85 ± 2.29**	**23.9 ± 2.43**	**- 0.191**	**0.424**
Range	**19.7 – 29.3**	**19.7 – 29.3**		

This table shows that:

There was no statistically significant difference among both studied groups concerning maternal ages & body mass index.

Table (2): Basic obstetric history data of studied cases 'groups:

Variable	Group (I)	Group (II)	t-test	p-value
Gestational age (weeks) **Mean ± SD** **Range**	 **30.64 ± 1.43** **28 – 33**	 **30.66 ± 1.36** **28 – 33**	**-0.072**	**0.471**
Gravidity: **Mean ± SD** **Range**	 **3.36 ± 1.5** **1 – 8**	 **3.5 ± 1.37** **1 – 7**	**0.487**	**0.627**
Parity: **Mean ± SD** **Range**	 **1.58 ± 1.26** **0 – 4**	 **1.84 ± 1.35** **0 – 4**	**0.995**	**0. 321**
Mode of previous deliveries: **No previous delivery** **Vaginal** **Cesarean section** **Instrumental**	 **1** **105** **24** **3**	 **11** **56** **21** **1**	**X^2** **16.318**	**< 0.001**
History of pre-eclampsia: **Yes** **No**	 **10 (20.0%)** **40 (80.0%)**	 **16 (32.0%)** **34 (68.0%)**	**1.871**	**0.171**

This table shows that:
Neither of the groups differed significantly from the other in terms of maternal age at delivery, number of previous pregnancies, or prevalence of preeclampsia. in addition to a pre-eclamptic background. Even if there was a statistically significant difference among the two of them in terms of the mechanism of delivery prior to this one.

Table (3): Bp and heart rate (maternal & fetal) findings of the studied patients' groups before delivery:

Variable	Group (I)	Group (II)	t-test	p-value
Systolic blood pressure (mmHg) **Mean ± SD** **Range**	 **139.73 ± 3.1** **134 – 145**	 **144.08 ± 4.09** **137 – 149**	**-6.108**	**<0.001**
Diastolic blood pressure (mmHg): **Mean ± SD** **Range**	 **88.75 ± 3.07** **84 – 95**	 **93.62 ± 4.14** **88 – 99**	**-6.785**	**<0.001**
Mean arterial blood pressure: **Mean ± SD** **Range**	 **105.7 ± 2.3** **101 – 111**	 **110.44 ± 3.86** **104 – 115**	**-7.368**	**<0.001**
Maternal Heart rate (HR): **Mean ± SD** **Range**	 **89.1 ± 3.7** **84.0 – 96.0**	 **85.9 ± 3.7** **80.0 – 93.0**	**-4.984**	**0.001**
Fetal Heart rate (HR): **Mean ± SD** **Range**	 **133.4 ± 7.3** **118.0 – 150.0**	 **124.7 ± 6.7** **115.0 – 145.0**	**6.549**	**<0.001**

This table shows that:
Patients who were taking Sildenafil in the group (I) had significantly lower systolic, diastolic and mean blood pressure, and significantly higher maternal and fetal heart rates than those who didn't take the medication in the group (II).

Table (4): Sildenafil adverse effects in the patients taken medication group:

Variable	Group (I)
Headache	**15 (30.0%)**
Gastrointestinal Upset	**6 (12.0%)**
HOT flushes	**3 (6.0%)**
Dizziness	**2 (4.0%)**
Palpitation	**2 (4.0%)**

This table shows that:
The most frequent side effect was headache, found in 15 (30.0%) of patients, followed by GI upset (12.0%), hot flushes (6.0%). Dizziness was found in

4.0% and palpation was found in 4.0%

Table (5): Doppler findings at time of delivery of the studied groups.

Variable	Group (I)	Group (II)	t-test	p-value
Umbilical artery RI:				
Mean ± SD	**0.60 ± 0.09**	**0.64 ± 0.09**	**-2.134**	**0.018***
Range	**0.43 – 0.79**	**0.46 – 0.75**		
Umbilical artery PI:				
Mean ± SD	**0.94 ± 0.21**	**1.02 ± 0.19**	**-2.189**	**0.015***
Range	**0.57 – 1.34**	**0.66 – 1.44**		
uterine artery RI:				
Mean ± SD	**0.43 ± 0.08**	**0.48 ± 0.08**	**-2.856**	**0.002***
Range	**0.31 – 0.59**	**0.31 – 0.65**		
uterine artery PI:				
Mean ± SD	**0.63 ± 0.18**	**0.72 ± 0.18**	**-2.615**	**0.05***
Range	**0.4 – 1.05**	**0.4 – 1.12**		
Middle cerebral artery RI:				
Mean ± SD	**0.71 ± 0.05**	**0.76 ± 0.04**	**-5.527**	**<0.001***
Range	**0.66 – 0.83**	**0.6 – 0.78**		
Middle cerebral artery PI:				
Mean ± SD	**1.57 ± 0.18**	**1.58 ± 0.21**	**-0.370**	**0.356**
Range	**1.25 – 1.87**	**1.26 – 2.1**		

This table shows that:
Doppler indices "RI and PI" of the umbilical, uterine & middle cerebral arteries were all considerably lower in group I than in group II at the time of delivery, with the exception of the PI of the middle cerebral artery.

Table (6): Indications of delivery within the studied groups:

Indication of delivery	Group (I)	Group (II)	X^2	p-value
Completed 37 week :	**32 (64.0%)**	**25 (50.0%)**	**1.999**	**0.157**
Signs of severe preeclampsia	**9 (18.0%)**	**10 (20.0%)**	**0.065**	**0.799**
Persistent abnormal biophysical profile	**4 (8.0%)**	**6 (12.0%)**	**0.444**	**0.505**
Spontaneous Preterm:	**5 (10.0%)**	**8 (16.0%)**	**0.795**	**0.372**
IUFD:	**0 (0.0%)**	**1 (2.0%)**	**Fisher test 1**	**NS**
Total	**50 (100.0%)**	**50 (100.0%)**		

This table shows that:
There was no statistically significant difference among both groups concerning indications of deliveries.

Table (7): Maternal & Neonatal outcomes within the studied groups:

Variable	Group (I)	Group (II)	test	p-value
GA at time of delivery:				
Mean ± SD	**37.2 ± 0.9**	**36.7 ± 1.3**	**2.348**	**0.020**
Range	**35 – 39**	**34 – 38**		
IUFD:				
Yes	**0**	**1**	**-**	**-**
No	**50**	**49**		
Mode of delivery:				
Normal vaginal delivery (NVD)	**31**	**29**	**0.1667**	**0.681**
Cesarean section (CS)	**19**	**21**		
Preterm delivery:				
Yes	**18**	**25**	**1.706**	**0.191**
No	**32**	**25**		
Birth weight:				
Mean ± SD	**3051.22 ± 415.12**	**2681.16 ± 574.36**	**3.519**	**< 0.001**
Range	**1950 – 3630**	**1450 – 3800**		

APGAR score at 1 min: **Mean ± SD** **Range**	 **8.02 ± 1.42** **6 – 10**	 **5.72 ± 1.38** **4 – 9**	**7.575**	**< 0.001**
APGAR score at 5 min: **Mean ± SD** **Range**	 **9.44 ± 0.79** **7 – 10**	 **7.88 ± 1.04** **66-10**	**7.559**	**< 0.001**
Neonatal ICU: **Yes** **No**	 **6** **44**	 **12** **37**	**2.595**	**0.107**
Neonatal Death: **Yes** **No**	 **0** **50**	 **0** **49**	**-**	**-**

This table shows that:
Patients in group (I) were having significantly higher birth weight, APGAR score at 1 and 5 minutes than those in group II. Also, incidence of preterm labor was insignificantly higher in group II than in group I. there was no significant difference among both groups regarding mode of delivery and need for NICU admission.

DISCUSSION

Regarding basic demographic data, our findings indicated that mother age and BMI did not differ significantly among the 2 groups. With p-value: of 0.103 and 0.424.

Regarding obstetric history, our findings revealed no statistically significant differences among groups relating to maternal age at delivery, parity, or prior pre-eclamptic episodes. While there was a statistically significant difference among both groups concerning modes of previous deliveries.

In agreement with our findings regarding gestational age and history of previous pre-eclampsia was Trapani et al. **(6)** who stated in their study on 100 pre-eclampsia patients and found that that there was no statistically significant difference among both groups regarding gestational age (29.1±2.1 vs 30.2±2.4) and history of pre-eclampsia (14.0% vs 18.0%). Similar findings were informed by Kamel et al. **(7)** in their study on 122 singleton pregnancies with mild pre-eclampsia that In terms of gestational age, there was not a significant difference among the groups. (32.3±2.1 vs 32.6±1.9).

Our results presented that there was no significant difference among the groups in terms of systolic (SBP), (DBP), or mean arterial blood pressure (MAP) at the onset t of the study (p-values: 0.307, 0.431, and 0.434). When comparing the two groups on the same parameters (SBP, DBP, and MAP), our results demonstrated a statistically significant difference just before delivery ($p<0.001$).

Also, our results showed that at the start of the study there was no statistically significant difference among both groups as regards maternal and fetal heart rate, while just before delivery our results showed that patients who take sildenafil citrate in the group (I) were having significantly higher maternal and fetal HR compared to those in the group (II).

Sildenafil increased the maternal heart rate by 4 beats per minute compared to the placebo group [5bpm (95%CI: 1, 12) vs 1 (-5, 8); P=0.004] and dropped the maternal systolic blood pressure by 1mmHg more than the placebo group [-4mmHg (-9, 1) vs -3mmHg (-8, 5); P=0.048]. Khalil et al. **(8)** observed these results.

Kamel et al. **(7)** disagreed with our findings since they found no significant change in SBP, DBP, or MAP between the two groups. Their p-values were 0.31, 0.43, and 0.51. The number of cases who developed severe pre-eclampsia was lower in the intervention group (10.2%) compared to the placebo group (16.7%), although this difference was not statistically significant. And, they came to the conclusion that sildenafil citrate has a role in avoiding the worsening of mild pre-eclampsia to severe pre-eclampsia by regulating blood pressure and increasing blood flow to the female and the fetus

In the first 24 hours of the trial, Trapani et al. **(6)** observed that MAP was considerably lower after sildenafil citrate administration (100.3±5.6 mm Hg after sildenafil citrate compared to 116.4±5.1 mm Hg before sildenafil citrate, P.05).

Doppler evaluation of umbilical, uterine, and middle cerebral arteries was done for all patients participating in this study at the start of the study, second visit (two weeks after taking medication), and at the time of delivery.

Our results showed that throughout this study doppler indices of both uterine and umbilical arteries of patients in group (I) become significantly lower than those in group (II) while there was no significant difference among both groups concerning MCA PI.

It was discovered by Trapani et al. **(6)** that individuals treated with sildenafil citrate had a noticeably reduced resistance to blood flow in the uterine and umbilical arteries. Our studies were able to validate these findings. The pulsatility index in the uterine artery reduced in 22.5% of the sildenafil group as matched to 2.1% in the placebo group (P,.001), and the pulsatility index in the umbilical

artery decreased in 18.5% of the sildenafil group as compared to 2.5% in the placebo group (P,.001). No matter the state, the pressure that was being applied to the principal artery in the brain (middle cerebral artery) was the same.

Case studies have indicated that the use of sildenafil can lower pulsatility indices in the uterine & umbilical arteries Panda et al., **(9)** and Lin et al., **(10).** These findings were published in two separate scientific journals. Dastjerdi and colleagues **(11)** carried out a research experiment that was random, double-blind, and controlled with a placebo.

Regarding indications of delivery, we found no statistically significant differences in delivery indicators among the 2 groups. Contrary to the findings of Trapani et al. **(6)**

Regarding maternal and neonatal outcomes, our consequences revealed that neonates of patients in group (I) were having significantly higher birth weight (3051.22 ± 415.12 vs 2681.16 ± 574.36)**,** APGAR scores at 1 & 5 minutes than those in the group (2) with a p-value: < 0.001 for each. With a p-value of 0.191, group (II) had a slightly greater incidence of preterm birth than group (I). There was no significant difference among both groups in terms of the mode of delivery, the admission rate to the NICU, or the fatality rate of newborns. The groups (I) who took medication and (II) who did not report any incidences of IUFD did not vary significantly from one another statistically.

Mean birth weight was found to be considerably higher in the intervention group (3088.98± 351.23 vs. 2759.2 ± 723.51 mg; P < 0.001) in the research by Kamel et al. **(7)**. Although the intervention group required less time in the NICU than the placebo group, the difference was not statistically significant. There was just one newborn fatality in the placebo group, and no fetuses died while still within the mother .

CONCLUSION

The addition of sildenafil citrate to alpha methyl dopa for the treatment of preeclampsia in its mildest form was shown to be safe in our study. Our results, is associated with prolongation of pregnancy and better maternal and fetal outcomes as it decreases maternal Blood pressure and enhances doppler indices of umbilical and uterine arteries, coupled with other studies are encouraging. We need larger study to confirm our findings.

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