Use of Sildenafil Citrate in management of mild pre-eclampsia: A randomized controlled trial

Submitted By

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Introduction

Pre-eclampsia affects approximately 2–8% of all pregnancies worldwide (1). In Egypt, the prevalence of pre-eclampsia is 10.7% in a community based study (Gadalla et al., 1986). While, in hospital based studies it ranged from 9.1% (Mahaba et al., 2001) to 12.5% (El-Houseinie et al., 1994) of all deliveries (2). The incidence of pre-eclampsia has risen in the developing countries and even in the developed countries as the USA since the 1990s (3). Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand as major causes of maternal and perinatal morbidity and mortality worldwide (1). Nearly one tenth of all maternal deaths in Africa and Asia and one quarter in Latin America are associated with hypertensive diseases in pregnancy, a category that includes pre-eclampsia and the complications that are related to it (4)(5).

However, the pathogenesis of pre-eclampsia is only partially understood and it is related to disturbances in placentation at the beginning of pregnancy, followed by generalized inflammation and progressive endothelial damage. There are other uncertainties too: the diagnosis, screening and management of pre-eclampsia remain controversial, as does the classification and the degree of its severity (5).

However, it is generally accepted as published in the different journals and in the WHO recommendations that the onset of a new episode of hypertension during pregnancy (with persistent systolic blood pressure 140 mm Hg and diastolic blood pressure 90 mm Hg or more) with the occurrence of substantial proteinuria (>0.3 g/24 h or confirmation of proteinuria by semiquantitative urine dipstick analysis with a result of at least 1+) can be used as criteria for identifying pre-eclampsia (6).

Although pathophysiological changes (e.g. inadequate placentation) exist from very early stages of the pregnancy, hypertension and proteinuria usually become apparent in the second half of pregnancy (3).

Complications of pre-eclampsia can affect both the mother and the fetus. Acutely, pre-eclampsia can be complicated by eclampsia , the development of HELLP

Syndrome , hemorrhagic or ischemic stroke, liver damage and dysfunction, acute kidney injury and Acute Respiratory Distress Syndrome (ARDS) (7)(8).

So early detection of pre-eclampsia and prevention of the occurrence of any of its complications would save the lives of many women and prevent the possible devastating maternal and neonatal outcome of pre-eclampsia, That's why we are concerned in our study with pre-eclampsia, covering the gestational age from 28 – 36 weeks (6) (9).

Mild pre-eclampsia represents 75% of cases with pre-eclampsia, possible progression to severe pre-eclampsia makes mild pre-eclampsia a serious problem that requires attention (10).

Previous studies have shown that expectant and conservative management of pre-eclampsia in the context of extreme prematurity may improve perinatal outcomes (11–13). Indeed, it has been estimated that for each additional day of pregnancy prolongation between 24 and 32 weeks of gestation, there is a nonlinear corresponding gain of 1% in fetal survival (14).

Sildenafil citrate has been used for increasing utero-placental perfusion in cases with intrauterine growth restriction, which makes it a promising drug in management of mild pre-eclampsia (15).

Its action is similar to the action of nitric oxide, which is a potent vasodilator, especially for the venules, besides being an inhibitor of platelet aggregation (16). During pregnancy, nitric oxide is synthesized in in utero-placental tissues and endothelial cells, helping to maintain low vascular resistance in the utero- and fetoplacental circulations (17-19). Phosphodiesterase metabolizes cyclic guanosine monophosphate; therefore, phosphodiesterase type 5 inhibition leads to cyclic guanosine monophosphate increase with associated vasodilation, independently of nitric oxide. Therefore, phosphodiesterase type 5 inhibitors have the potential to achieve similar therapeutic goals when compared with nitric oxide.

A potential advantage of phosphodiesterase type 5 inhibitors is that they may overcome the main limitation to nitric oxide use in pregnancy, which is tolerance and headaches. The most studied phosphodiesterase type 5 inhibitor is sildenafil citrate,

which has previously shown promising outcomes both in vitro (20) and in animal studies (21) (22).
That is why we decided to study the role of Sildenafil Citrate in expectant and conservative management of mild pre-eclampsia, as it has shown its ability to be beneficial to both the mother and the fetus through increasing the maternofetal circulation perfusion and achieving a maternal hemodynamic stability (23) and compare it to the current NICE (National Institute for Health and Care Excellence) guidelines that are currently used, that recommends conservative management of mild pre-eclampsia through control of maternal blood pressure and frequent screening of maternal laboratory investigations' abnormalities to detect possible progression to severe pre-eclamptic toxemia (NICE guidelines 2010 [CG107]).

Aim of the work

- Aim of our study is to investigate if the use of sildenafil citrate in cases with mild pre-eclampsia is useful in pregnancy prolongation through prevention of its progression to severe pre-eclampsia and improved maternal and perinatal outcomes or not.

Subjects and methods

Study design

- Double blinded, randomized, placebo-controlled trial.

Settings and locations

- Obstetrics and Gynecology Department, Woman Health Hospital, Assiut University, Egypt.

Eligible Participants:

Inclusion criteria

1- Uncomplicated mild pre-eclampsia; No clinical or investigatory findings suggestive severe pre-eclamptic toxemia.
2- Gestational age of 28 – 36 weeks by good dates according to ACOG's – committee on obstetric practice – Method for Estimating Due Date (2014) who will receive the study's drug for at least one week before termination. (23)
3- Singleton viable pregnancy.
4- Age: 18-35 years.

Exclusion criteria

1- Severe pre-eclamptic toxemia (according to the NICE guidelines (2010): Hypertension in pregnancy: diagnosis and management)
2- Intrauterine growth retardation (23) (24).
3- Use of medication that could interact with sildenafil citrate such as nitrates erythromycin, ketoconazole, itraconazole, antiretroviral agents and others.
4- Presence of maternal co-morbidity disease as: DM, chronic hypertension, congestive heart failure, chronic kidney disease and SLE.
5- Placenta previa.
6- The patient is using aspirin.
7- The presence of a contraindication to the use of sildenafil citrate:
- Hypersensitivity to sildenafil citrate or any of the tablet ingredients.
- Patients with severe cardiovascular disease such as established cardiac failure and unstable angina pectoris.
- Previous episode of non-arteritic anterior ischaemic optic neuropathy.
- Severe hepatic impairment.
- Hypotension (blood pressure <90/50 mmHg).
- Hypertension (blood pressure >170/110 mmHg).
- Recent history of stroke or myocardial infarction.

- Known hereditary degenerative retinal disorders such as retinitis pigmentosa.

Sample size

- Alpha error of 5%

- Power of study 95%

- Sample size: 80 patients who meet the criteria of the study would be randomized into the two groups (intervention and control group) with 40 patients in each group, in the Obstetrics and Gynecology Department, Woman Health Hospital, Assiut University, Egypt.

Interventions

Preliminary assessment of patient

- The patient will be admitted to the department of obstetrics and gynecology in Assiut University and will undergo the following:

- Evaluation of vital signs of patient:
- Pulse: Regular and the rate is between 60-100 beat/minute by palpating the radial artery.
- Blood pressure: Maternal blood pressure would be measured as recommended by the NICE in the ‘’Antenatal care’’ (2008):

Blood pressure should be measured as outlined below:

- The patient would sit with her left arm stretched.
- Remove tight clothing, ensure arm is relaxed and supported at heart level.
- Use cuff of appropriate size.
- Inflate cuff to 20–30 mmHg above palpated systolic blood pressure.
- Lower column slowly, by 2 mmHg per second or per beat.
- Read blood pressure to the nearest 2 mmHg
- Measure diastolic blood pressure as disappearance of sounds (phase V).

- Temperature: axillary temperature measurement using medical thermometer with range from 36° to 37°.
- Weight & height: to calculate the patient's BMI by dividing the patient's weight in kg by square her height in meters (kg/m^2).

- Ultrasound assessment: (Using the Medison SonoAce R5® ultrasound system)

- Fetal viability.
- Placental site.
- Fetal biometry: Biparietal diameter, Femur length, Abdominal circumference (using Hadlock formulas).
- Amniotic fluid index measured by the 4 quadrant view: more than or equal to 5 cm (ACOG guidelines on antepartum fetal surveillance (2014)).

- Doppler ultrasound assessment of the uterine, umbilical, aortic and middle cerebral arteries (Using the Medison SonoAce X8® ultrasound system): pulsatility (PI) and resistance (RI) indices and systolic/diastolic velocity (S/D) ratio, whatever suitable in each case condition by a well-qualified sonographer according to the standards of the ISUOG (2013).

- Investigations:

- Complete blood count: Hemoglobin level, white blood cells' count, platelets' count and blood film.
- Coagulation profile: Prothrombin time and concentration and INR.
- Screening for gestational DM.
- Kidney function tests: Blood urea and serum Creatinine.
- Serum uric acid.
- Liver function tests: AST, ALT, serum bilirubin (total, direct and indirect), serum total protein and albumin.
- Urine analysis and 24- hour's urine collection for: 24-hours protein collection in urine, urine output in 24-hours and creatinine clearance.

Randomization

- The patients will randomly allocated to either the control group or intervention group using computer generated random number tables and opaque sealed envelopes containing the patients' group allocation. The envelopes will be prepared and sent to an assigned nurse, who opens each envelope when a patient – who meets the criteria of the study- comes. All patients will be blinded to the allocation to avoid bias.

- The patients will be divided into a red group and a blue group where the intervention group would not be known by the clinician. (double-blinded)

- The intervention group will be supplied with Sildenafil Citrate (Respatio® 20mg tablets manufactured by Pharma Right Group , Egypt) according to the patient's weight by the rate of (1.5 mg/kg/day) divided into three doses per day (every 8 hours) (25-28). While the control group will be supplied with a placebo drug that has the same shape, size and color but without the active ingredient and it would also be taken in a similar way. The placebo tablet will be manufactured at the faculty of pharmacy, Assiut University.

- The patients of each group would stay in the hospital for 48 hours after the beginning of the medication for blood pressure monitoring (4 times per day) and to record any side effects detected from the medication taken.

Follow up visits:

1) The patients would be followed up at the obstetric outpatient clinic every 2 weeks till delivery. (According to the NICE guidelines "Hypertension in pregnancy" (2010) and the NICE guidelines "Antenatal care" (2008))

2) The follow up visits will include:

- Blood pressure measurement and review the patient's blood pressure measurements in the past 2 weeks (the blood pressure would be measured 3 times a week in any easily accessible facility to the patient).
- Urine dipstick analysis.
- Complete blood count.
- Serum creatinine & blood urea.
- AST & ALT.
- Serum uric acid.
- Obstetric ultrasound and doppler ultrasound.

- Compliance to treatment will be ensured by checking the remainder of the medication strip.

Termination of pregnancy:

- If the patient developed any sign or investigatory/laboratory finding that represent severe pre-eclamptic toxemia:

1) Persistent elevated blood pressure more than 160/110 mmHg.
2) HELLP syndrome.
3) Eclampsia.
4) Intrauterine fetal death.
5) Abrupt body swelling.
6) Sever headache, epigastric pain and/or right hypochondrial tenderness.
7) Elevated liver enzymes: ALT or AST rising to above 70 iu/litre.
8) Platelet count falling to below 100 $x10^9$ per litre.

9) Serum creatinine >125 mmol/litre (29).

- If no complications occurred and the maternal blood pressure is controlled on the medication , termination would be after completion of 36 weeks and 6 days as recommended by the NICE guidelines (2010) : “Hypertension in pregnancy : Diagnosis and management”

Primary outcome

Gestational age at time of termination and maternal outcome in terms of whether the disease would progress to severe pre-eclampsia or not.

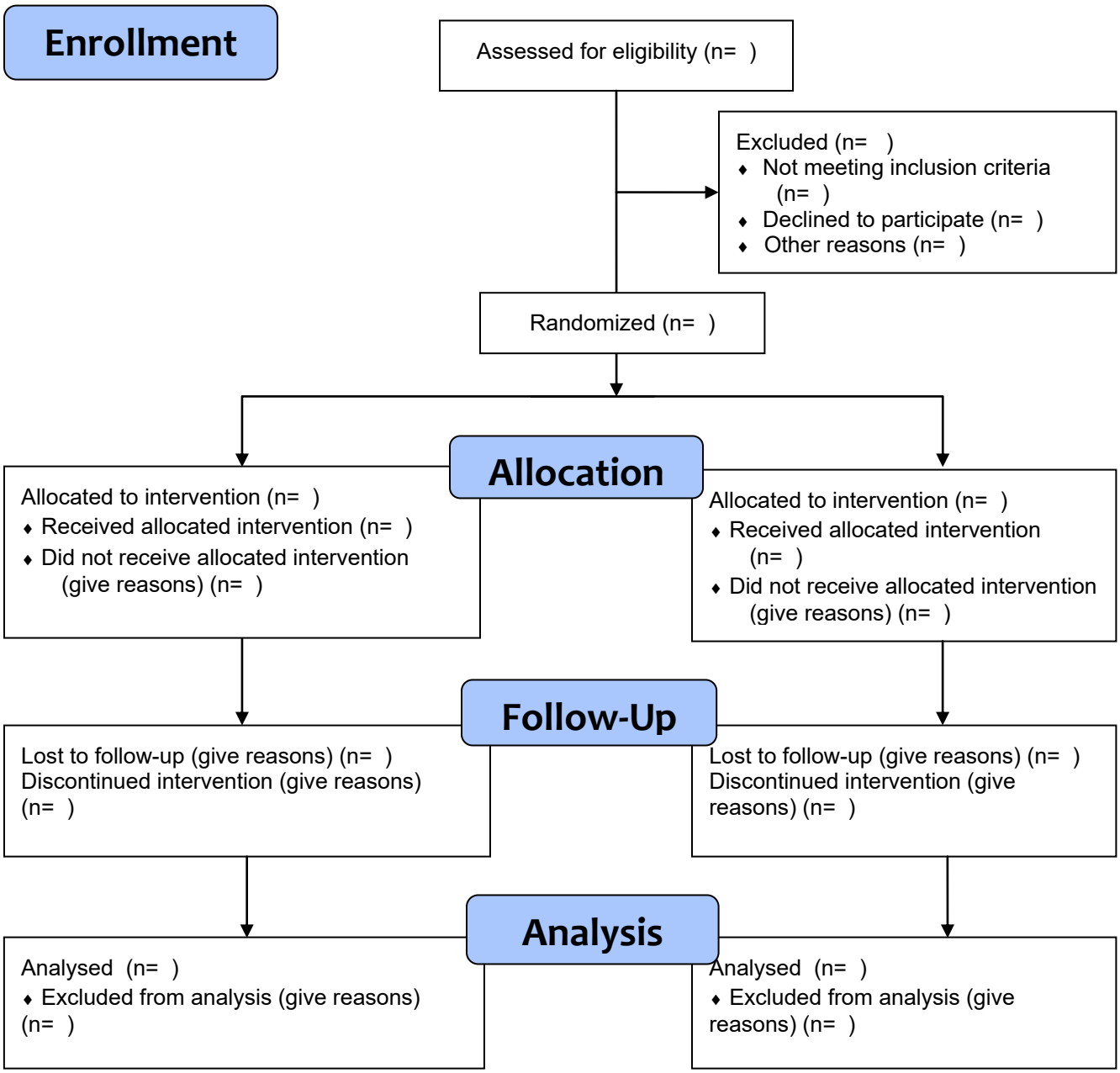
Secondary outcomes

1- Neonatal outcome in terms of survival and neonatal well-being (by obtaining the birth weight and the apgar score at 1 and 5 minutes and direct postnatal need to NICU).
2- Control of maternal blood pressure.
3- Method of termination of pregnancy.
4- Identification of possible maternal side effects from the use of sildenafil citrate i.e.; headache, flushing and dyspepsia.
5- Evaluation of the effect of sildenafil citrate on the feto-maternal circulation through the Doppler ultrasound.

Final status:

- We will specify the number of patients who were candidates for the study ,the number of patients who were excluded for not meeting the criteria ,the number of patients who were included the study, the number of patients who were excluded for lack compliance to treatment or dropped follow-up visits and the number of patients who successfully completed the study till delivery.

THE TRIAL FLOW CHART



Approval of Ethical Considerations

The pregnant women who enter the study will be given verbal and written information about the study and written informed consent of enrollment in the study will be obtained. The patient will be handled an explanation of the study. All the patients' personal data will be confidential and wouldn't be exposed to the public. The patients will have their freedom to withdraw from the trial at any time.

Statistical Analysis

Data entry and analysis will be carried out using SPSS version 20. Quantitative variables will be presented in terms of, mean± standard and qualitative variables will be expressed as frequency and percentage. Tests of significance (T-test and chi-square) will be calculated. Significance level will be set at 0.05.

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Appendix

-Safety of Sildenafil Citrate in pregnancy:

1) FDA:

"Pregnancy Category B. VIAGRA® (sildenafil citrate) is not indicated for use in women. There are no adequate and well-controlled studies of sildenafil in pregnant women. Risk Summary: Based on animal data, VIAGRA® is not predicted to increase the risk of adverse developmental outcomes in humans. Animal Data: No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the Maximum Recommended Human Dose (MRHD) on a mg/m^2 basis in a 50 kg subject. In the rat pre-and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC."

2) Australian drug authority (TGA):

"Use in Pregnancy: Pregnancy Category B1. VIAGRA® is not indicated for use by women. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. The dose results in total systemic drug exposure (AUC) for unbound sildenafil and its major metabolite of greater than 60 times the exposure observed in human males given the maximum recommended human dose (MRHD) of 100 mg. In the rat pre- and post natal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In non-pregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well controlled studies of sildenafil in pregnant women. "

3) United Kingdom:

"VIAGRA® is not indicated for use by women. There are no adequate and well-controlled studies in pregnant or breast-feeding women. No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil."
