Safety of sildenafil citrate in the management of hypertensive disorders of pregnancy

Hasan S. Kamel, Hisham A. Abou-Taleb, Fady N. Abdallah

Department of Obstetrics and Gynecology, Women Health Hospital, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Fady N. Abdallah, MBBCh, Department of Obstetrics and Gynecology, Women Health Hospital, Faculty of Medicine, Assiut, Egypt
Tel: 0020882061723; Fax: 0020882368377; Zip Code: 71111;
e-mail: fady.nasif90@gmail.com

Received 05 January 2019
Accepted 09 February 2019

Journal of Current Medical Research and Practice
January-April 2019, 4:50–55

Objective
This study investigated the safety of sildenafil citrate in managing hypertensive disorders of pregnancy.

Patients and methods
In a randomized, double-blind, placebo-controlled trial, 122 singleton pregnancies with mild pre-eclampsia between 28 and 36 weeks of gestation were randomized to either use oral sildenafil citrate tablets with antihypertensive or antihypertensive alone. The primary outcome was occurrence of maternal and/or neonatal complications.

Results
Headache was the most frequent adverse effect in the study and is significantly higher in the intervention group [22 (36.1%) vs. 12 (19.7%) in placebo group; $P = 0.03$]. In the intervention group, headache was dose related. The headache was tolerable in the majority of patients. The intervention group has an insignificant lower incidence of intrauterine growth restriction than the placebo group (1.7 vs. 6.7%, respectively, $P = 0.31$). The incidence of oligohydramnios was significantly higher in the placebo group than in the intervention group (16.7 vs. 8.5%, respectively, $P = 0.03$). No intrauterine fetal deaths have occurred in our study, and only one neonatal death occurred in the placebo group.

Conclusion
Using sildenafil citrate in addition to other antihypertensive drugs in the management of mild pre-eclampsia is safe and has a better maternal and neonatal outcome.

Keywords:
mild pre-eclampsia, phosphodiesterase 5 inhibitors, safety, sildenafil citrate

J Curr Med Res Pract 4:50–55

2357-0121

Introduction

Pre-eclampsia affects ~2–8% of all pregnancies worldwide [1]. In Egypt, the prevalence of pre-eclampsia was 10.7% in a community-based study [2]. The incidence of pre-eclampsia has risen in the developing countries and even in developed countries such as the USA since the 1990s [3].

Among the hypertensive disorders that could 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 linked to hypertensive diseases in pregnancy [4,5].

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 [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 mmHg and diastolic blood pressure 90 mmHg 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, stroke, liver dysfunction, acute kidney injury, and Acute Respiratory Distress Syndrome [7,8]. Hence, early detection of pre-eclampsia and prevention of its progression and 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 [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 [11,12]. In fact, it has been estimated that for each additional day of pregnancy prolongation between 24 and 32 weeks of gestation, there is a nonlinear corresponding increase of 1% in fetal survival [13]. Sildenafil citrate has been used for increasing uteroplacental perfusion in cases with intrauterine growth restriction (IUGR), which makes it a promising drug in the management of mild pre-eclampsia [14]. Its action is similar to the action of nitric oxide, which is a potent vasodilator, especially for the venules, besides inhibiting platelet aggregation [15]. During pregnancy, nitric oxide is synthesized in uteroplacental tissues and endothelial cells, helping to maintain low vascular resistance in the uteroplacental and fetoplacental circulations [16]. 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* [16], in animal [17,18] and in human studies [19]. These studies mentioned various maternal side effects related to sildenafil citrate use, that is headache, upper gastrointestinal tract upset and tachycardia. Recently, the STRIDER trial was suspended because of a number of neonatal deaths in the study. Which is why we decided to study the safety of sildenafil citrate in the management of mild pre-eclampsia [19,20].

Patients and methods

We conducted a registered randomized, double-blind, placebo-controlled trial. The Assiut Medical Ethical Review Board approved the study (No. 17100340). All patients signed a written informed consent. This trial was designed and reported according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting randomized clinical trials.

Eligible participants

The inclusion criteria were pre-eclampsia with no severe features (uncomplicated mild pre-eclampsia) [11], gestational age on enrollment between 28 and 36 weeks, singleton viable pregnancy, maternal age between 18 and 35 years and normal sited placenta.

Exclusion criteria were IUGR [21]; the use of medication that could interact with sildenafil citrate, such as nitrates, erythromycin and ketoconazole; presence of chronic maternal diseases affecting the general condition, such as diabetes mellitus, congestive heart failure, chronic kidney disease, and systemic lupus erythematosus; the use of anticoagulant and/or antiplatelet drugs; maternal arrhythmias; amniotic fluid abnormalities (oligohydramnios or polyhydramnios); autoimmune hemolytic anemias (to detect possible hemolysis caused by severe pre-eclampsia/HELLP syndrome); and severe anemia (hemoglobin < 7 g/dcl).

Sample size

Sample size calculation was carried out using the following formula:

$$n = \frac{2\left(Za + Z1 - \beta\right)^2 \sigma^2}{\Delta^2}$$

The study power was 95% with alpha error of 5%. Hence, 122 patients, who met the criteria of the study, were randomized into the two groups (intervention and control group), with 61 patients in each group.

Intervention

Pre-eclampsia was defined according to the ACOG 2013 guidelines [11]. Recruited patients were thoroughly evaluated with full clinical examination and ultrasound assessment (using the Medison SonoAce X8 ultrasound system, Samsung Medison Co, LTD in Seoul, South Korea) for fetal viability, placental site, fetal biometry, amniotic fluid, and Doppler ultrasound assessment by a qualified sonographer according to the ISUOG standards [22].

The patients were admitted to the hospital and randomly allocated to either the control group or the intervention group using computer-generated random number tables and opaque sealed envelopes containing the patients' group allocation. The envelopes were prepared and sent to an assigned nurse, who opened each envelope when a patient was recruited.

The study investigators, attending physicians, ultrasonographers, neonatologists, and patients were blinded with regard to allocation to placebo or intervention groups.

The intervention group was supplied with sildenafil citrate (Respatio 20 mg tablets; Pharma Right Group,

Kahira Pharmaceuticals', Cairo, Egypt) at a dose of 1.5 mg/kg/day divided into three doses per day. The patients had to receive treatment for at least 7 days. The patients were instructed to report any side effect, and treatment was prescribed if severe (Table 1). If the side effects persisted for more than 3 days, sildenafil citrate was stopped.

The control group was supplied with placebo tablets having the same shape, size, and color. The placebo tablets were manufactured at the Faculty of Pharmacy, Assiut University. Both the sildenafil and placebo tablets were bottled in radiopaque bottles that contained 100 tablets each.

α-Methyldopa, 'Aldomet 250 mg tablets by Kahira Pharmaceuticals', was prescribed when blood pressure was 150/100 mmHg, at a dose of 0.5–3 g/day in three divided doses, starting with the least effective dose and modified according to blood pressure [20].

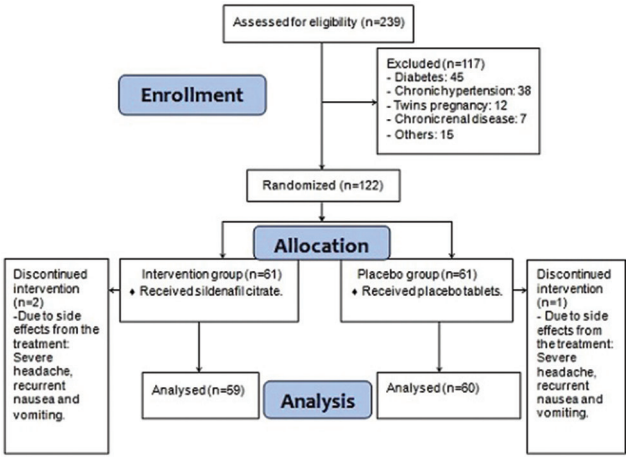
When the blood pressure was controlled, the patients were discharged and followed-up at the obstetric outpatient clinic every 2 weeks until delivery. The patients were instructed to measure and record the blood pressure three times a week in any easily accessible facility and come back if any high blood pressure level more than or equal to 160 mmHg systolic or more than or equal to 110 mmHg diastolic. The follow-up included clinical, ultrasound, and Doppler assessment along with laboratory investigations. Compliance to treatment was ensured by checking the remainder of the medication.

The pregnancy was terminated if the patient completed 36 weeks and 6 days of gestation or with development of severe pre-eclampsia [11,20]. Perinatal outcome measures included birth weight, Apgar scores, need for neonatal intensive care unit (NICU) admission, length of NICU stay, and neonatal deaths. The follow-up continued until the 42nd day postpartum (Fig. 1).

Statistical analysis

Data were collected and analyzed using statistical package for the social sciences (version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range), whereas nominal data were expressed in the form of frequency (percentage). The χ^2 test was used to compare the nominal data of different groups in the study, and Fisher's exact test was used for small samples (less than five). The Student's *t* test was used to compare the mean of two different groups and analysis of variance test for more than two groups, whereas the paired *t* test was used to compare between patients of the same group before and after intervention. *P* value was significant if less than 0.05.

Figure 1



The trial flow chart.

Table 1 Side effects from the study drug and symptomatic treatment given

Side effects	Symptomatic treatment
Headache	Paracetamol 500 mg tablets on demand
GIT upset	Meclizine hydrochloride 25 mg. Pyridoxine hydrochloride 50 mg
Hot flushes	Cold compresses
Dizziness	Rest and good hydration
Palpitation	Reassurance, rest, and good hydration; if it persisted for more than 3 days, consultation of a cardiologist was taken

GIT, gastrointestinal tract.

Results

From September 2016 to January 2018, 122 patients were invited to participate in the study. Three withdrew and discontinued treatment before delivery, two in the intervention group and one in the placebo group, as a result of severe headaches and recurrent nausea and vomiting. Baseline characteristics were not significantly different between the two groups (Table 2).

Median dose of sildenafil that was used was 120 mg/day (six tablets), ranging between 100 and 140 mg/day. Headache was the most frequent adverse effect in the study and was significantly higher in the intervention group [22 (36.1%) vs. 12 (19.7%) in placebo group; P = 0.03]. In the intervention group, headache was dose related, wherein there was a significant increase in the number of patients with headache among the patients who received 140 mg than among those who received 120 mg and among the patients who received 120 mg than among the patients who received 100 mg (P < 0.05).

The headache was tolerable in the majority of patients in both study groups (90.9 and 91.7% in the intervention and placebo groups, respectively). Tolerable headache did not affect the patients' quality of life and either subsided without treatment or

responded to paracetamol tablets within 3 days from starting it, as shown in Table 3.

Two patients who were on 140 mg of sildenafil citrate had intolerable headache and had to stop it (Table 4). One patient from the placebo group had intolerable headache, and treatment was stopped also.

Headache was followed by gastrointestinal tract upset [nine (14.8%) in the intervention group vs. eight (13.1%) in the placebo group; $P = 0.58$]. Other adverse effects were summarized at Fig. 2.

There was an insignificant decrease in the number of patients who progressed to severe pre-eclampsia in the intervention group (10.2%) than in the placebo group (16.7%) ($P = 0.22$). The intervention group had an insignificant lower incidence of IUGR than the placebo group (1.7 vs. 6.7%, respectively; $P = 0.31$).

Table 2 Clinical, demographic data, and obstetric history of enrolled women

	Intervention group	Placebo group	*P*
Age (years)	27.7±4.8	27.6±5.6	0.98
BMI (kg/m^2)	27.84±2.20	28.28±2.19	0.28
Gravidity	3 (1-8)	3 (1-11)	0.25
Parity	2 (0-7)	2 (0-10)	0.25
Gestational age (weeks)	32.3±2.1	32.6±1.9	0.08
Mode of previous deliveries			
Vaginal	12 (20.3)	17 (28.3)	0.64
Cesarean section	25 (42.4)	24 (40)	0.51
Instrumental	0 (0)	0 (0)	0.44
No previous delivery	22 (37.3)	19 (31.7)	0.28
History of PE	15 (25.4)	22 (36.7)	0.13
Maternal blood pressure			
Mean blood pressure	113 (100-116)	113 (106-116)	0.51
Systolic blood pressure	150 (140-150)	150 (140-150)	0.31
Diastolic blood pressure	100 (90-100)	100 (90-100)	0.43

Data are expressed as mean±SD, median (range), or *n* (%) as appropriate. PE, pre-eclampsia. *P* value is significant if <0.05.

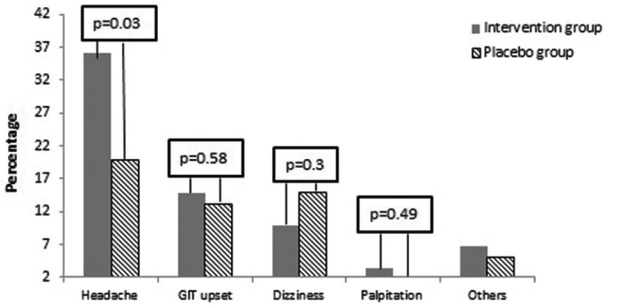
The incidence of oligohydramnios is significantly higher in the placebo group than in the intervention group (16.7 vs. 8.5%, respectively; $P = 0.03$).

Fetal distress occurred with two patients in the intervention group. One patient was in labor and had late fetal deceleration. The other one had decreased fetal movements, biophysical profile was 4/10, and, by Doppler ultrasound, there was reversed end-diastolic flow of the umbilical artery. In the placebo group, there were five cases that had fetal distress. Two patients were in labor and had late fetal deceleration. The other three had decreased fetal movements, biophysical profiles were equal to or below 4/10, and, by Doppler ultrasound, in one case, there was reversed end-diastolic flow of the umbilical artery; in the other two cases, there was absent end-diastolic flow in the umbilical artery.

The intervention group (259.7 ± 7.2) had significantly more days of gestation than the placebo group (254.8 ± 8.9) ($P < 0.05$). It was noticed that termination was carried out at the completion of 36 weeks in the majority of cases (84.7% of the intervention group and 78.3% of the placebo group).

Normal vaginal delivery occurred in 36 (61%) of the intervention group and 37 (61.7%) of the placebo

Figure 2



Side effects of treatment occurred in both groups.

Table 3 Analysis of headache in both groups

Number of patients	Groups		*P*
	Intervention group (*n*=61)	Placebo group (*n*=61)	
No headache	39 (63.9)	49 (80.3)	**0.03**
Headache that subsided by itself	15 (24.6)	8 (13.1)	0.18
Headache that subsided after paracetamol	5 (8.2)	3 (4.9)	0.30
Intolerable headache that caused withdrawal from the study	2 (3.3)	1 (1.6)	0.49

Data are expressed in the form of *n* (%) as appropriate. *P* value is significant if <0.05.

Table 4 The effect of the dosage of sildenafil on headache in the intervention group

	100 mg (*n*=11)	120 mg (*n*=30)	140 mg (*n*=20)
Number of patients with headache	2 (18.2)	10 (33.3)	10 (50)
Number of patients who had intolerable headache	0 (0)	0 (0)	2 (10)

Data are expressed in the form of *n* (%) as appropriate. *P* value between 100 and 120 mg: 0.01. *P* value between 120 and 140 mg: <0.001. *P* value is significant if <0.05.

group, whereas caesarian section was performed in 23 (39%) and 23 (38.3%) in the intervention and placebo group, respectively.

Apgar score at first minute was significantly higher in the intervention group (10, ranging from 6 to 10) than the placebo group (8, ranging from 4 to 10), whereas, at the fifth minute, it was insignificantly higher in the intervention group (10, ranging from 6 to 10 vs. 9, ranging from 4 to 10). Prematurity was the main cause of the low Apgar scores in both groups, and the interventions carried out by the neonatologists were usually effective in resuscitating the distressed neonates.

The mean birth weight was significantly higher in the intervention group (3088.98 ± 351.23 vs. 2759.2 ± 723.51 mg; $P < 0.001$). The need for NICU in the intervention group was insignificantly lower than that in the placebo group. The length of stay in the NICU in days was significantly higher in the placebo group than in the intervention group (Table 5).

No intrauterine fetal deaths have occurred in our study, and only one neonatal death occurred in the placebo group.

Discussion

Our study showed that sildenafil citrate given to women with mild pre-eclampsia was well tolerated in most patients, but there was a significant increase in the number of patients who developed headache in the intervention group (36.1%) than in the placebo group (19.7%). The headache was either tolerable with no need of an analgesic (68.2%) or tolerable but needed the analgesic 'paracetamol' (22.7%), or intolerable despite analgesics and caused withdrawal from the study (9.1%). Both the Trapani *et al.* [19] and Samangaya *et al.* [23] studies reported the high incidence of headache among the majority of patients who received sildenafil citrate.

In our study, there was a significant decrease in the number of patients who developed oligohydramnios in the intervention group (8.5%) than in the placebo group (16.7%). This could be due to the improvement of the placental insufficiency present in pre-eclampsia. The Maher *et al.* [24] study showed that sildenafil citrate was effective in improving oligohydramnios.

In our study, there was an insignificant decrease in the number of patients who progressed to severe pre-eclampsia in the intervention group (10.2%) than in the placebo group (16.7%). This suggests that sildenafil citrate has a role in preventing the progression of mild pre-eclampsia to severe pre-eclampsia through better control of blood pressure and improvement of maternal and fetal blood flow.

Patients who received sildenafil citrate were insignificantly few in number than those in the placebo group in developing IUGR (1 vs. 4, respectively). IUGR is due to placental insufficiency and poor uteroplacental and fetoplacental circulations. IUGR increases the risk of stillbirth and perinatal death [25]. Trapani and colleagues reported improved umbilical and uterine Doppler indices in the IUGR patients.

Trapani and colleagues and Samangaya and colleagues did not report any differences between the study groups with regard to the maternal adverse effects.

Although we identified significant differences between the intervention and placebo groups in the neonatal outcome (birth weight, Apgar score at the first minute, and length of stay in NICU), the Trapani *et al.* [19] and Samangaya *et al.* [23] studies did not. The Samangaya and colleagues' study had a lack of power given the small number of cases, and both studies included pre-eclampsia with severe features and IUGR that led to premature delivery in the majority of cases in both studies.

There were no perinatal mortalities in the intervention group receiving sildenafil or at 1 month postpartum. Rebound pulmonary hypertension was not detected among the neonates of the intervention group. A recent systemic review by Dunn *et al.* [26] reported that there does not seem to be any severe adverse maternal

Table 5 Neonatal outcome after delivery

	Intervention group (n=59)	Placebo group (n=60)	P_1
Apgar score			
At 1st min	10 (6-10)	8 (4-10)	**0.01**
At 5th min	10 (6-10)	9 (4-10)	0.23
Birth weight (mg)	3088.98±351.23	2759.2±723.51	**<0.001**
Need for NICU admission	7 (11.9)	11 (18.3)	0.25
Length of stay in days	2 (1-10)	5 (3-21)	**0.03**
Neonatal death(s) in NICU	0 (0)	1 (1.7)	0.38
Number of neonates with congenital anomalies requiring surgery or specific management	0 (0)	1 (1.7)	0.42

Data are expressed in the form of median (range) or n (%), as appropriate. NICU, neonatal intensive care unit. P value is significant if <0.05.

side effects nor any increase in the rate of stillbirths, neonatal deaths, or congenital anomalies attributed to sildenafil citrate. A meta-analysis by Paauw *et al.* [27] did not mention any worsening neonatal outcomes and, in fact, reported that sildenafil citrate had better neonatal outcomes in animal and human studies. Recently, the multicenter STRIDER trial that studies the effect of sildenafil citrate in early IUGR was suspended and reported that sildenafil citrate patients had higher risks for neonatal deaths due to rebound pulmonary hypertension in these neonates caused by cessation of sildenafil citrate after delivery leading to neonatal respiratory distress and death. IUGR was one of the exclusion criteria in our study. These results were not reported by any other studies before.

In conclusion, this study showed the safety of the use of sildenafil citrate in addition to other antihypertensive drugs in the management of mild pre-eclampsia. Other studies are required to evaluate the cardiopulmonary circulation by Doppler ultrasound in cases of IUGR and pre-eclampsia to detect any fetal pulmonary hypertension that led to neonatal deaths in the STRIDER trial.

Acknowledgements

The authors express their gratitude to the patients who participated in this study and to the colleagues and nurses at the Women's Health Hospital in Assiut University, Egypt.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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