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Research Article

Role of Nifedipine, Nicorandil, and Coenzyme Q10 Supplementation in The Treatment of Patients with Severe Preeclampsia: A Single Blinded Randomized Controlled Trial

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Abstract

The study was designed to evaluate the effect of nifedipine and nicorandil, used either alone or combined with coenzyme Q10 supplementation, on preeclampsia. It is a single blinded randomized controlled trial conducted on 140 patients diagnosed as severe pre-eclampsia. They were randomly assigned to four groups: Group (I) who received nifedipine, group (II) who received nicorandil, group (III) who received nifedipine + coenzyme Q10 an group (IV) who received nicorandil + coenzyme Q10. Patients were assessed before and 48 hours after drugs administration. Nifedipine and nicorandil showed significant decrease in arterial blood pressure and improvement in Doppler parameters**.** Moreover, both nifedipine and nicorandil significantly increased endothelial nitric oxide synthase activity and superoxide dismutase activity and decreased malondialdehyde level and platelets aggregation, with no significant difference between them. The improvement in Doppler ultrasound parameters by nifedipine and nicorandil was significantly augmented by addition of coenzyme Q10 to both drugs. Coenzyme Q10 supplementation also showed a more significant increase in the superoxide dismutase activity with a more significant decrease in the malondialdehyde level. In conclusion**,** Coenzyme Q10, combined with either nifedipine or nicorandil might have beneficial effects on preeclampsia by lowering the oxidative stress induced vascular remodeling.

Keywords: Preeclampsia; Nifedipine; Nicorandil; Coenzyme Q10; Oxidative Stress; Vascular Remodeling

Introduction

Pre-eclampsia affects 3-8% of all pregnancies worldwide. It dramatically increased the risk of all-cause mortality in pregnancy, as it is responsible for more than 60,000 maternal deaths annually. These numbers placed the pre-eclampsia as the third cause of maternal mortality after bleeding and embolism. Pre-eclampsia is of special relevance in the developing countries, in which the maternal mortality owing to pre-eclampsia is ~15% compared with 0-1.8% in the developed countries [1,2].

The pathogenesis of pre-eclampsia is not fully understood. Variable theories and hypotheses regarding the pathogenesis have been put forward over the years. The central hypothesis is the defective spiral artery remodeling, which causes ischemia of the placenta with increased oxidative stress, leading to widespread endothelial dysfunction, affecting all the maternal organ systems [1,2].

In contrast to normal pregnancy, pre-eclampsia is characterized by increased oxidative stress with decreased antioxidants. The

deficiency of the superoxide dismutase (SOD) activity results in increased concentration of superoxide anion. Nitric oxide (NO) reacts with superoxide to form Peroxynitrite ($ONOO^-$) which is a strong oxidizing agent capable of initiating lipid peroxidation. The circulating levels and placental tissue levels of lipid peroxides are increased, which are expressed as elevated malondialdehyde (MDA) serum levels, as a marker of lipid peroxidation [3]. The nitric oxide (NO)/nitric oxide synthase (NOS) system is also disturbed in pre-eclampsia. Intact NOS system is essential for normal spiral artery remodeling in pregnancy. NO deficiency is found to induce the utero-placental changes characteristic of pre-eclampsia [4].

On the other hand, an imbalance between prostacyclin and thromboxane A_2 production occur with more thromboxane A_2 than prostacyclin. This imbalance, which results in increased platelet aggregation and vasoconstriction in the maternal vasculatures, may have a role in the development of pre-eclampsia [1,2].

Despite the severity of pre-eclampsia, the only curative therapy currently available is delivery of the placenta, which carries the risk of iatrogenic prematurity. Pre-eclampsia has been traditionally treated with short-acting parenteral antihypertensive agents, most frequently intravenous hydralazine or labetalol. Oral nifedipine has also achieved treatment success similar to that of hydralazine or labetalol [5].

Nicorandil is a NO donor and a potassium channel opener which is used for the treatment of angina pectoris. In the FDA drugs use in pregnancy safety classification, Nicorandil is classified as category B. It was clinically studied for tocolysis in preterm labor [6]. However, according to literature review, its use in treatment of pre-eclampsia has not been yet clinically studied.

Coenzyme Q10 (CoQ10) is an essential component of oxidative phosphorylation in the mitochondria, a potent antioxidant and cell membrane stabilizer [7]. It was reported that pregnant women with established pre-eclampsia have significantly lower plasma levels of CoQ10 compared with healthy pregnant and non-pregnant women [8].

This study is designed to evaluate if Coenzyme Q10, together with either nifedipine or nicorandil might have beneficial effect on hypertension in preeclampsia. They may also have favorable effect on oxidative stress markers and Doppler ultrasound parameters.

Materials and Methods

This single blinded randomized controlled study is registered in Pan African Clinical Trial Registry (PACTR), identification number is: PACTR201803003150307. It was conducted according to all GCP requirements at the Obstetrics and Gynecology Hospital of Alexandria University from February 2018 to February 2019 after approval from institute's ethics committee. Informed written consent was obtained from all patients.

Inclusion criteria were age ranging from 20 to 35 years old, gestational age greater than 30 weeks and severe pre-eclampsia defined on the basis of existence of sustained severe hypertension [systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg on two occasions at least 4 hours apart while the patient on bed rest] and presence of clinically significant proteinuria (0.3 g or more of protein in 24-h urine collection, or urinary protein/creatinine ratio of 30 or more). Exclusion criteria were laboratory abnormalities indicating preeclampsia but with normal blood pressure (as we are evaluating the effect of antihypertensive medications) and chronic hypertension or any other concomitant chronic diseases; renal, heart disease, diabetes mellitus to avoid bias in the results.

The study protocol was designed according to CONSORT guidelines. As no previous data available to estimate the minimum sample size as according to literature review, nicorandil use in treatment of severe pre-eclampsia has not been studied yet. All cases of preeclampsia who attended the Obstetrics and Gynecology Hospital of Alexandria University during the period of the study were assessed for eligibility, knowing that this hospital is the main referral for four Egyptian governorates.

140 women met all inclusion criteria and consented to participate. Patients were admitted at pre-eclampsia care unit and were subjected to history taking and full clinical examination. Before drugs administration, Doppler ultrasound (US) of umbilical and middle cerebral arteries of the fetus for measuring resistance indices was done to all cases. Blood samples were also collected from each patient and the following parameters were assessed (in the department of Biochemistry, faculty of medicine, university of Alexandria): Whole blood Superoxide dismutase (SOD), serum Malondialdehyde (MDA), serum endothelial nitric oxide synthase (eNOS) by enzyme linked immunosorbent assay (ELISA) and platelet aggregation by light transmission aggregometry.

One hundred and seventy women were assessed for eligibility. Eleven were excluded because of not meeting the inclusion criteria and nineteen were excluded due to refusal to participate. The 140 patients agreed and consented to participate. Patients were divided into 4 homogenous equal groups. The four groups were comparable with respect to demographic data [Table 1]. Patients were masked to study allocation. They were randomly assigned using computer-generated randomization by means of sealed, opaque, and numbered envelopes to four groups, each of 35 patients.

Parameter	Group I	Group II	Group III	Group IV	Test of significance	p
Maternal age (years) Mean ± SD	26.8 ± 3.5	27.8 ± 4.9	27.7 ± 4.8	26.7 ± 5.3	F 0.178	0.872
Parity [n (%)]						
Nulliparous	22 (63%)	20 (57%)	25 (71%)	23 (66%)	χ^2 1.618	0.676
Multiparous	13 (37%)	15 (43%)	10 (29%)	12 (34%)		

Table 1: Comparison between the four groups according to demographic data.

F: ANOVA test

χ2: Chi square test

p: p value.

Group (I) received nifedipine (10 mg) tablets orally three times daily. Group (II) received nicorandil (20 mg) tablets orally twice daily. Group (III) received nifedipine (10 mg) tablets orally three times daily and CoQ10 (100 mg) softgels orally twice daily. Group (IV) received nicorandil (20 mg) tablets orally twice daily and CoQ10 (100 mg) softgels orally twice daily. All participants completed the study according to the protocol for their assigned group. This is summarized in the figure 1.

Figure 1: Enrollment, randomization, and follow-up.

After 48 hours, all patients were reassessed by clinical examination, Doppler US, SOD, MDA, eNOS, platelet aggregation and fetal and maternal outcomes. Primary outcomes were the changes in arterial blood pressure and Doppler US. Secondary outcomes were the changes in the levels of SOD, MDA, eNOS and platelet aggregation.

These patients received a standard medical care for preeclampsia to prevent complications to the mother and the fetus. This included the use of magnesium sulfate ($MgSO_4$) infusion: 4gm loading dose, then 1gm/ hour maintenance dose and four doses of dexamethasone 6mg intramuscularly to improve fetal lung maturity in all groups. Termination of pregnancy was either by induction of labour in cases with good Bishop score or Caesarian delivery in cases of other obstetric indication.

Data analysis was performed using the Statistical Package of Social Science, SPSS version 20 software package. Normality of data was checked by measuring skewness using Shapiro-Wilk test of normality. Normal distribution was confirmed in all groups for all studied parameters. A value of $p < 0.05$ was considered statistically significant. All results were expressed as mean ± standard deviation (SD).

Paired t-test was used compare between data in one group before and after administration of drugs. Analysis of variance (ANOVA) was used to compare maternal age and changes in the parameters between the four groups. A post-test (Tukey's) was used to make Pairwise comparison between each 2 groups. Chi square test was used to compare between different groups according to parity and outcomes. Monte Carlo test was used whenever indicated.

Results

Both nifedipine and nicorandil treated groups showed significant decrease in systolic and diastolic blood pressure, significant increase in the eNOS level, significant increase in the SOD level, significant decrease in MDA level, significant decrease in platelet aggregation and significant decrease in the umbilical artery resistance index (UmA RI) while the middle cerebral artery resistance index (MCA RI) was significantly increased [Table 2,3]. The changes in the studied parameters and Doppler indices noticed with nicorandil were not significantly different from those exhibited by nifedipine [Table 4].

	Before treatment (mean ± SD)	After treatment (mean ± SD)	t	P value
Systolic BP (mmHg)	171.4 ± 6.81	135.4 ± 5.61	37.62*	<0.001
Diastolic BP (mmHg)	119.7 ± 4.84	92.71 ± 2.80	30.06*	<0.001
MCA RI	0.614 ± 0.011	0.677 ± 0.008	15.531*	<0.001
UmA RI	0.763 ± 0.042	0.575 ± 0.042	14.715*	<0.001
SOD (U/gm. Hb)	1214.4 ± 38.57	1214.4 ± 38.57	30.808*	<0.001
MDA (nmol/ml)	31.26 ± 3.47	17.95 ± 1.73	26.685*	<0.001
eNOS (U/ml)	25.86 ± 4.33	75.0 ± 7.62	34.282*	<0.001
Platelet aggregation (%)	89.43 ± 3.97	63.09 ± 3.01	33.185*	<0.001

Table 2: Comparison between before and after treatment with nifedipine (group I)

t: Paired t-test

p: p value

*: Statistically significant at $p < 0.05$.

	Before treatment (mean ± SD)	After treatment (mean ± SD)	t	P value
Systolic BP (mmHg)	169.1 ± 6.59	133.6 ± 6.81	43.70*	<0.001
diastolic BP (mmHg)	119.4 ± 6.27	92.57 ± 3.29	24.72*	<0.001
MCA RI	0.612 ± 0.010	0.678 ± 0.009	16.816*	<0.001
UmA RI	0.756 ± 0.038	0.570 ± 0.049	13.571*	<0.001
SOD (U/gm. Hb)	959.0 ± 25.46	1202.6 ± 36.67	28.666*	<0.001
MDA (nmol/ml)	31.75 ± 3.55	17.50 ± 1.89	30.771*	<0.001

eNOS (U/ml)	27.78 ± 5.77	76.63 ± 9.01	27.917*	<0.001
Platelet aggregation (%)	89.74 ± 4.42	63.11 ± 5.63	47.616*	<0.001

Table 3: Comparison between before and after treatment with nicorandil (group II).

t: Paired t-test

p: p value

*: Statistically significant at p < 0.05.

	Before treatment (mean ± SD)	After treatment (mean ± SD)	t	P value
Systolic BP (mmHg)	171.0 ± 7.93	132.3 ± 9.58	48.22*	<0.001
Diastolic BP (mmHg)	120.0 ± 6.06	93.29 ± 3.42	26.63*	<0.001
MCA RI	0.613 ± 0.012	0.735 ± 0.016	27.375*	<0.001
UmA RI	0.759 ± 0.037	0.459 ± 0.049	30.590*	<0.001
SOD (U/gm. Hb)	959.4 ± 25.70	1497.3 ± 45.89	59.702*	<0.001
MDA (nmol/ml)	30.47 ± 3.04	5.22 ± 1.80	50.417*	<0.001
eNOS (U/ml)	27.19 ± 4.99	75.87 ± 8.39	27.332*	<0.001
Platelet aggregation (%)	90.40 ± 4.55	62.97 ± 4.77	42.461*	<0.001

Table 4: Comparison between before and after treatment with nifedipine + CoQ10 (group III).

t: Paired t-test

p: p value

*: Statistically significant at p < 0.05.

Adding CoQ10 to nifedipine or nicorandil, although was not able to have significant influence on blood pressure, eNOS level and platelet aggregation, it caused more significant increase in the SOD level with more significant decrease in the MDA level. Moreover, the improvement in the Doppler indices by both nifedipine and nicorandil was significantly augmented by CoQ10 supplementation [Table 5,6]. However, no significant difference was found between groups regarding fetal and maternal outcomes [Table 7].

	Before treatment (mean ± SD)	After treatment (mean ± SD)	t	P value
Systolic BP (mmHg)	170.6 ± 7.45	132.1 ± 7.50	45.78*	<0.001
Diastolic BP (mmHg)	119.6 ± 5.61	92.43 ± 2.53	26.87*	<0.001
MCA RI	0.612 ± 0.011	0.733 ± 0.016	22.653*	<0.001
UmA RI	0.761 ± 0.045	0.450 ± 0.058	25.650*	<0.001
SOD (U/gm. Hb)	959.7 ± 27.24	1505.0 ± 45.94	70.302*	<0.001
MDA (nmol/ml)	31.26 ± 4.74	5.32 ± 2.41	31.136*	<0.001
eNOS (U/ml)	27.71 ± 5.50	75.17 ± 8.18	31.908*	<0.001
Platelet aggregation (%)	90.71 ± 4.21	63.23 ± 4.17	49.376*	<0.001

Table 5: Comparison between before and after treatment with nicorandil + CoQ10 (Group IV).

t: Paired t-test

p: p value

*: Statistically significant at p < 0.05.

Change	Group I (mean±SD)	Group II (mean±SD)	Group III (mean±SD)	Group IV (mean±SD)	F	p
Systolic blood pressure (mmHg)	-36.00 ± 5.66	-35.57 ± 4.82	-38.71 ± 4.75	-38.43 ± 4.97	1.132	0.3118
diastolic blood pressure (mmHg)	-27.0 ± 5.31	-26.86 ± 6.43	-26.71 ± 5.93	-27.14 ± 5.98	1.590	0.0396
MCA RI	0.063 ± 0.015	0.066 ± 0.013	0.121∞# ±0.014	0.122∞# ± 0.015	38.350*	<0.001
UmA RI	-0.188 ± 0.059	-0.186 ± 0.061	-0.300∞# ± 0.051	-0.311∞# ± 0.068	32.878*	<0.001
SOD (U/gm. Hb)	253.2 ± 48.62	243.6 ± 50.27	537.9∞# ± 53.31	545.3∞# ± 45.89	408.257*	<0.001
MDA (nmol/ml)	-13.31 ± 2.95	-14.25 ± 2.74	-25.25∞# ± 2.96	-25.94∞# ± 4.93	132.761*	<0.001
eNOS (U/ml)	49.14 ± 8.48	48.84 ± 10.35	48.68 ± 10.54	47.46 ± 8.80	0.208	0.891
Platelet aggregation (%)	-26.34 ± 4.70	-26.63 ± 3.31	-27.43 ± 3.82	-27.49 ± 3.29	0.787	0.503

Table 6: Comparison between the four groups according to changes in the studied parameters.

F: ANOVA test

p: p value

*: Statistically significant at $p < 0.05$

∞: Significant difference with group I

#: Significant difference with group II.

Outcome	Group I	Group II	Group III	Group IV	χ^2	p
Maternal						
Eclamptic fits	1(2.9%)	3(8.6%)	2(5.7%)	1(2.9%)	1.604	MCp = 0.835
HELLP	2(5.7%)	1(2.9%)	1(2.9%)	2(5.7%)	0.936	MCp = 1.000
Fetal						
Preterm labor	8(22.9%)	6(17.1%)	7(20.0%)	5(14.3%)	0.945	0.815
NICU admission	7(20.0%)	6(17.1%)	5(14.3%)	6(17.1%)	0.402	0.940

Table 7: Comparison between the four groups according to Maternal and Fetal outcomes.

χ^2: Chi square test

MC: Monte Carlo

p: p value.

Discussion

The beneficial effect of oral nifedipine as a standard treatment of preeclampsia was reported with numerous mechanisms. The effect of nifedipine on eNOS level in the current study is in agreement with other studies [9,10], Nifedipine increases kinin production; which is a pharmacologically active polypeptide that stimulates B2 kinin receptors resulting in increased expression of eNOS [11].

Many studies demonstrated the anti-oxidant effect of nifedipine [12], which is shown in the current study. This effect is mainly through attenuation of reduced nicotine-amide-adenine dinucleotide phosphate oxidase activity which is one of the primary sources of ROS [13]. In addition, nifedipine increases NO production, which induces SOD expression [3].

In the current study, the effect of nifedipine on platelet aggregation is in agreement with other studies [14]. The possible mechanism might be suppression of surface GPIIb/IIIa expression, fibrinogen binding and platelet adhesion by targeting PPAR-β/γ-dependent signaling pathways in the platelets [15].

The effect of nicorandil on (eNOS) was investigated in other studies [16,17]. This appears to be a downstream event after opening ATP-sensitive potassium channels (K_{ATP} channels), which activates the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway.Moreover, increased intracellular calcium level, by opening of K_{ATP} channels and potassium efflux, leads to Calmodulin-dependent kinase II (CaMKII) activation which induces phosphorylation and activation of eNOS [9,16].

The current study showed anti-oxidant effect of nicorandil, which is in accordance with other studies [18]. This effect seems to be due to its mitochondrial K_{ATP} channel activation, which induces mitochondrial matrix swelling and decreases transport and release of reactive oxygen species (ROS) [16].

The inhibitory role of nicorandil on platelet aggregation exhibited in our study is in accordance with other studies. As a NO donor, nicorandil induce cGMP synthesis. cGMP inhibits platelet agonist-induced elevation of intracellular Ca^{2+}, which is a key event in platelet activation [19,20].

Many studies demonstrated nicorandil favorable effect on systemic vascular resistant indices [21,22]. To our knowledge, this is the first study to test the effect of nicorandil on utero-placental and fetal blood flow in pregnant women.

In our study, the effect of CoQ10 as anti-oxidant is in agreement with other studies [23,24]. Co-Q10 is capable of enhancing endothelial function by counteracting NO oxidation. This leads to increase in NO availability that may cause increased SOD gene-expression [25]. Another important point is that in conditions with combined production of NO and ROS, a nitrosative stress occurs as a result of the production of $ONOO^-$ and perpetuation of free radicals formation [26]. Therefore, CoQ10 supplementation might be a complementary therapeutic option in pre-eclampsia that should be added to drugs which increase NO production in order to reduce both acute oxidative and nitrosative stresses.

The beneficial effect of CoQ10 therapy in increasing utero-placental blood flow may be due to improving endothelial function by its anti-oxidant activity and anti-inflammatory activity [27]. The improvement in endothelial function augments a process called flow mediated dilatation (FMD) which increases oxygen supply and tissue perfusion [28].

Regarding maternal and fetal outcomes in our study; treatment with nifedipine, in accordance with other studies [29,30], was associated with some maternal and fetal morbidities [eclamptic fits and HELLP syndrome]. However, no mortalities were reported. Nicorandil treated group exhibited the same outcomes (both maternal and fetal) and the percentages of cases were not significantly different from those in nifedipine treated group. Moreover, addition of CoQ10 to nifedipine or nicorandil did not significantly affect the frequency of these outcomes. This might be explained by short duration of CoQ10 administration.

The role of oxidative stress in the pathogenesis of placental and maternal vascular remodeling in preeclampsia was widely investigated and reviewed [30,32]. The beneficial effects of calcium channel blockers including nifedipine in the reduction of both oxidative stress and vascular remodeling were previously tested [6,33,34] and in the current study nifedipine was used as a reference standard drug. Previous studies done on nitric oxide donors including nicorandil and on co-enzyme Q10 reported their promising benefits on oxidative stress induced vascular remodeling prevention [35-37]. From the current study results, nicorandil and coenzyme Q10 combination might have benefits equivalent to nifedipine in preeclampsia patients.

Conclusions

From the results of the current study, it could be concluded that Coenzyme Q10, together with either nifedipine or nicorandil might have beneficial effect on preeclampsia. They may also have favorable effect on oxidative stress markers and Doppler parameters.

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Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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