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The effect of calcium channel blockers on prevention of preeclampsia in pregnant women with chronic hypertension

N. Jiang[1*], Q. Liu[1*], L. Liu[1], W.W. Yang[2], Y. Zeng[3]

[1] *Department of Obstetrics and Gynecology, The First People's Hospital of Kunshan affiliated with Jiangsu University, Suzhou*
[2] *Department of Obstetrics and Gynecology, The First Affiliated Hospital of Soochow University, Suzhou*
[3] *Biomechanics and Medical Information Institute, Beijing University of Technology, Beijing (China)*

Summary

Background: Pregnant women with chronic hypertension are at increased risk for complications. This study aims to investigate whether calcium channel blockers plus low dosage aspirin therapy can reduce the incidence of complications during pregnancy with chronic hypertension and improve the prognosis of neonates. *Materials and Methods:* From March 2011 to June 2013, 33 patients were selected to join this trial according to the chronic hypertension criteria set by the Preface Bulletin of American College of Obstetricians and Gynecologists, (ACOG). Patients were administrated calcium channel blockers plus low-dosage aspirin and vitamin C. The statistic data of baseline and prognosis from the patients were retrospectively reviewed and compared. *Results:* Blood pressure of patients was controlled by these medicines with average systolic pressure from 146.3 to 148.7 mmHg and average diastolic pressure from 93.8 to 97.9 mmHg; 39.4% patients complicated mild preeclampsia; however, none of them developed severe preeclampsia or eclampsia, or complicate placental abruption. 30.3% patients delivered at preterm labour; 84.8% patients underwent cesarean section. The neonatal average weight was 3,008 ± 629.6 g, in which seven neonatal weights were less than 2,500 g. All of the neonatal Apgar scores were 9 to 10 at one to five minutes. Small for gestational age (SGA) occurred in five (15%). *Conclusions:* Calcium channel blockers can improve the outcome of pregnancy women with chronic hypertension to avoid the occurrence of severe pregnancy complication or neonatal morbidity.

Key words: Preeclampsia; Chronic hypertension; Calcium channel blockers.

Introduction

Chronic hypertension during pregnancy poses one of the greatest risks to pregnant women and their fetus. According to the Preface Bulletin of The American College of Obstetricians and Gynecologists, chronic hypertension in pregnancy is defined as hypertension present before pregnancy or before 20th week of gestation and not resolved by 12 weeks postpartum. Pregnant women with chronic hypertension are at increased risk for complications and the main complication is superimposed preeclampsia, which occurs in one-third of chronic hypertension patients and may further develop into more severe situation such as eclampsia if left without preventive treatment [1]. Chronic hypertension is also associated with several other adverse pregnancy outcomes, such as premature birth, fetal growth restriction, fetal demise, placental abruption, and cesarean delivery. Therefore anti-hypertensive treatments, although some of them carry risk, remain as a viable choice, which deserve cautious trials and assessment.

Calcium channel blocker is the second-line medicine used in pregnant women with chronic hypertension. Its effectiveness is a somewhat controversial but long-acting calcium blockers have been safely used [2]. In the trail of this article, two kinds of long-acting calcium blockers were used: nifedipine controlled-release tablets and amlodipine besylate tablets. The purpose of this trial is to further assess the efficacy of calcium channel blockers in reducing the morbidity of superimposed preeclampsia, mitigating the development into more severe situation such as eclampsia, placental abruption, and other adverse pregnancy outcomes, while improving neonatal outcomes.

Materials and Methods

Thirty-three pregnant women with chronic hypertensive were enrolled at the 1st People's Hospital of Kunshan from March 2011 to June 2013. According to the criteria established by the Preface Bulletin of the American College of Obstetricians and Gynecologists, (ACOG), gestational hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg on two or more consecutive occasions at six hours apart [3]. Preeclampsia superimposed on chronic hypertension was considered when new-onset or acutely worsening of proteinuria, sudden increase in blood pressure, thrombocytopenia, or elevated liver enzymes occurred after 20th week of gestation. Small-for- gestational-age (SGA) baby was diagnosed with a birth weight lower than the 10th percentile according to a national standard curve for singleton births. Thirty-three pregnant women associated with chronic hypertension received evaluation during their first perinatal clinical visits. All of them received a previous history investi-

**These authors contributed equally to this work.*

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Table 1. — *Baseline data collected during first clinical counselling (n=33).*

Items	Values
Age (years)	31.3 ± 5.3
Education, n (%)	
Elementary, or high school	14 (42.42%)
College or above	19 (57.58%)
Pre-weight (kg)	68.6 ± 13.8
Pre-BMI	26.6 ± 5.0
Gestational week at 1st clinical counseling	16.0 ± 4.0
Systolic blood pressure at 1st clinical counseling	146.3 ± 12.1
Diastolic blood pressure at 1st clinical counseling	93.8 ± 7.9
Primipara	17 (51.5%)
Multipara	16 (48.5%)

gation and test of blood and coagulation, routine hepatic test, renal function test, and echocardiography. Body mass index (BMI) was calculated for each individual. The antihypertensive medicines of calcium channel blockers with low-dosage aspirin were prescribed soon after chronic hypertension diagnosed. Specifically, 22 patients took amlodipine besylate tablets five mg p.o qd, plus low-dosage aspirin 50 mg p.o qn, and plus vitamin C 100 mg p.o tid; balanced 11 patients took nifedipine controlled-release tablets 30 mg p.o qd, plus low-dosage aspirin 50 mg p.o qn, and plus vitamin C 100 mg p.o tid. The calcium channel blockers treatment sustained until after delivery while the low- dosage aspirin administration was stopped until 36th week of gestation. All subjects were followed throughout pregnancy at the present obstetric clinic. The prenatal care included monthly hematological and urinary test, ultrasonographic evaluation of fetal growth, amniotic fluid index, color-Doppler waveform velocity evaluation of uterine arteries and fetal vessels, and non-stress test near delivery. Ten patients were found to have medical diseases, among which one was diagnosed with adrenal tumors, two were diagnosed with retinopathy, and seven patients with complicated gestational diabetes mellitus (GDM).

Results

Table 1 lists the data collected during patients' first clinical counseling as baseline data and Table 2 includes data collected during delivery after antihypertensive medication. The most noticeable message from these two tables is patients' blood pressures were well under control by the medication with systolic pressure increasing mildly from 146.3 mmHg to 148.7 mmHg and diastolic pressure only from 93.8 mmHg to 97.9 mmHg. After medications, 39.4% patients developed super-imposed preeclampsia with positive urine protein but none of them further developed into more severe situation such as eclampsia and placental abruption. Pregnancy was sustained after 37th gestational week until delivery in 69.7% of patients ; but natural delivery rate was only 15.2% while cesarean delivery rate reached 84.8%. From neonatal outcomes perspective, neonatal weight greater than 2,500 g was as high as 78.8%. Only 15% of patients gave birth to infants who were SGA with less than the 10th percentage as the benchmark. Apgar scoring for all neonatal infants at one to five minutes were 9 to10 without a single one below 9.

Table 2. — *After-medication data collected during delivery (n=33).*

Items	Values
Systolic blood pressure-delivery	148.7 ± 16.4
Diastolic blood pressure-delivery	97.9 ± 12.6
Gestational weeks at delivery	36.9 ± 1.6
≥ 37	23 (69.7%)
< 37	10(30.3%)
Urine protein	
-	20 (60.6%)
+	13 (39.4%)
Eclampsia	0 (0.0%)
Placental abruption	0 (0.0%)
Delivery mode:	
Natural delivery	5 (15.2%)
Cesarean delivery	28 (84.8%)
Small for gestational age (SGA)	
Less than 10th percentage	5 (15.1%)
Birth weight (g)	3,008.8 ± 629.6
≥ 2,500 g n (%)	26 (78.8%)
Apgar (at 1 to 5 minutes)	
9 to 10 points	33(100%)

Discussion

A primary reason for treating chronic hypertension in pregnancy is to reduce maternal morbidity associated with hypertension [4]. Superimposed preeclampsia is the major adverse pregnancy outcome associated with chronic hypertension. A meta-analysis including 28 randomized trials showed that the antihypertensive treatment significantly reduced the risk of severe hypertension, but did not reduce the risk of super-imposed preeclampsia, placental abruption, or growth restriction nor did it improve neonatal outcomes [5]. The present trail indicated that calcium channel blockers as an antihypertensive medication, truly helped reduce the risk of severe hypertension as the blood pressure did not increase in obvious way after medication. Although 39.4% of the present patients developed super- imposed preeclampsia after medication, none of them developed more severe complications such as placental abruption and eclampsia, while Ellan and Heffrey cited that women with chronic hypertension have twice the frequency of placental abruption as normotensive women, 1.56% vs 0.58% [6], hence calcium channel blockers or early intervention may soften the progression into more severe situations. The only drawback to the present trail is that the authors had only 33 patients as a pool, therefore a greater number of patients in the future are required to make a statistical more solid judgment. Even though the antihypertensive treatment in the present trail did not reduce growth restriction as 15% patients gave birth to SGA infants, which just fall in the ballpark of 10-20% incidence Ellen and Heffrey cited from one study in Canada, US, and New Zealand for women with chronic hypertension [6], the Apgar score at one to five minutes for all neonatal infants 100% above 9 is considered a clear indication that neonatal outcomes are improved.

One study by ACOG reported that calcium channel blockers marginally increased the progression to superimposed preeclampsia [7]. In the present trial, 39.4% patients developed superimposed preeclampsia, which was higher than the 30% morbidity reported by ACOG. This result seems to support ACOG's conclusion but the present authors still hesitate to give the conclusion because the patients' baseline situations may be different from the ACOG patient group studied. If other abnormal test items were used as criteria on top of blood pressure for classifying mild or severe, several patients in the present trial group were already in a severe situation as baseline, which may induce the final results to be higher. Specifically, ten of these 33 patients were found to have medical diseases, as one was diagnosed with adrenal tumor, another two were diagnosed with retinopathy, and the remaining once complicated with GDM during their first clinical check. If these ten patients could be re-classified as highest risk category according to ACOG's guidelines, the morbidity of superimposed preeclampsia would be 40% for this category (four out of ten patients) while ACOG reported 75% morbidity among this category [7]. It appears that the superimposed preeclampsia was reduced in this category by calcium channel blockers. In addition, only 30% (three out of ten patients) among this re-classified category had preterm labour before 37th week of gestation while ACOG reported 67%.

Even among the proponents of antihypertensive treatment for chronic hypertension during pregnancy, there is no consensual guideline of the threshold for initiating the use of antihypertensive medications or blood-pressure target in pregnancy in absence of conclusive data from randomized trials. There are only various professional guidelines providing disparate recommendation regarding indications for starting therapy [8], but predominant professional-opinions recommend commencing therapy for only severe hypertensions while withholding the therapy for mild hypertension in pregnant women. For example, antihypertensive treatment guidelines from ACOG published in 2001 recommended that pregnant women with hypertension in the blood pressure range of 180 mmHg or greater systolic / 110 mmHg or greater diastolic should be treated with antihypertensive medications [9]; in ACOG's updated version in February 2012, the threshold for medication was adjusted to 150-160 mmHg systolic / 100-110 mmHg diastolic [10]. However, the present trial adopted a different guideline by commencing therapy from even much milder hypertension levels of 90-95 mmHg diastolic as the threshold for initiating antihypertensive treatment. The reason the present authors began medication at such a mild level is that they believe that major adverse pregnancy outcome are related to the duration and to the severity of the hypertensions. To reduce the duration will soften the development into more severe hypertension and reduce the risk of developing other adverse pregnant outcome. The present trial results support this assumption in that the blood pressure was well-controlled without significant further increase and no placental abruption and eclampsia cases observed.

As nefidepine is a powerful arteriolar vasodilator, it appears to have much potential to lower blood pressure but with risk of being overshot to hypotensive level [11], therefore it requires further assessment of its effect on pregnancy. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure [12]. There was difference regarding the side effects of these two drugs based on some patients' chief complaints in the present trial: headache complained in patients who took adalat while patients who took norvasc did not have these kinds of complaints. This seemed to support ACOG's report on nifedipine's side effect. However the present authors did not have statistically conclusive data to prove the difference between these two drugs. So further assessment on the side effects and efficacy difference between these two drugs is needed before a conclusion can be reached.

References

[1] Mattioli A.V., Pennella S., Demaria F., Farinetti A.: "A trial remodeling in pregnant hypertensive women: comparison between chronic and gestational hypertension". *Open Cardiovasc. Med. J.*, 2012, *6*, 9.
[2] Czeizel A.E., Banhidy F.: "Chronic hypertension in pregnancy". *Curr. Opin. Obstet. Gynecol.*, 23, *76*, 2011.
[3] Gracia P.V., Montufar-Rueda C., Smith A.: "Pregnancy and severe chronic hypertension: maternal outcome". Hypertens. Pregnancy., 2004, *23*, 285.
[4] Lydakis C., Beevers D.G., Beevers M., Lip G.Y.: "Obstetric and neonatal outcome following chronic hypertension in pregnancy among different ethnic groups". *QJM*, 1998, *91*, 837.
[5] Magee L.A., Cham C., Waterman E.J., Ohlsson A., von Dadelszen P.: "Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis". *BMJ*, 2003, *327*, 955.
[6] Seely E.W., Ecker J.: "Clinical practice. Chronic hypertension in pregnancy". *N. Engl. J. Med.*, 2011, *365*, 439.
[7] American College of Obstetricians and Gynecologists: "ACOG Practice Bulletin No. 125: Chronic hypertension in pregnancy". *Obstet. Gynecol.*, 2012, *119*, 396.
[8] Perni U., Sison C., Sharma V., Helseth G., Hawfield A., Suthanthiran M., August P.: "Angiogenic factors in superimposed preeclampsia: a longitudinal study of women with chronic hypertension during pregnancy". *Hypertension*, 2012, *59*, 740.
[9] European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V., Blomstrom Lundqvist C., Borghi C., *et al.*: "ESC Guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC)". *Eur. Heart J.*, 2011, *32*, 3147.
[10] Mancia G., Fagard R., Narkiewicz K., Redon J., Zanchetti A., Böhm M., *et al.:* "2013 ESH/ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)". *Eur. Heart J.*, 2013, *34*, 2159. doi: 10.1093/eurheartj/eht151. Epub 2013 Jun 14.
[11] Jayashree M., Singhi S.: "Changing trends and predictors of outcome in patients with acute poisoning admitted to the intensive care". *J. Trop. Pediatr.*, 2011, *57*, 340.
[12] Helms S.R.: "Treatment of feline hypertension with transdermal amlodipine: a pilot study". *J. Am. Anim. Hosp. Assoc.*, 2007, *43*, 149.

Address reprint requests to:
L. LIU, M.D.
Department of Obstetrics and Gynecology
The First People's Hospital of Kunshan affiliated with Jiangsu University, Suzhou, 215300 (China)
e-mail: SL1012002322@126.com