Efficacy of Low-Dose Aspirin and Calcium in Addition to Labetalol in Expectant Management of Severe Preeclampsia Remote From Term

TERMDEN UZAK CİDDİ PREEKLAMPSİNİN TEDAVİSİNDE LABETALOLA EK OLARAK KULLANILAN DÜŞÜK DOZ ASPİRİN VE KALSİYUMUN ETKİNLİĞİ

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Summary

Objective: *Our aim was to test the efficacy of low-dose aspirin and high-dose calcium in addition to labetalol and nifedipine in the management of severe preeclampsia remote from term in a controlled trial.*

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Materials and Methods: *The patients (n=44) in the study group were primigrávidas and found to be nonnotensive before the 20th gestational week. The gestational ages of the patients were between 26 and 32 weeks. The patients were hospitalized until the delivery. Twenty one patients were randomized and treated with low-close aspirin and calcium in addition to labetalol. Magnesium sulphate was administered to prevent the eclampsia and betamethasone was chosen to prevent Respiratory Distress Syndrome. Results were analyzed bv Student's t lest and Fisher's exact lest.*

Results: *There was no significant difference in the outcomes of the patients and infants.*

Conclusion: *It seems that the use of low-close aspirin and high-close, calcium in addition to routine treatment of severe preeclampsia remote from term, is not effective.*

Key Words: Preeclampsia, Aspirin, Calcium

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Özet

Amaç: *Amacımız kontrollü bir araştırmada, terinden uzak ciddi preeklampsinın tedavisinde labetalol ve uifeclipin'e ilave olarak düşük doz aspirin ve yüksek doz kalsiyumun etkinliğini araştırmaktı.*

Araştırmanın Yapıldığı Yer: *Zübeyde Hanım Doğumevi-Ankarcı*

Materyel ve Metod: *Çalışma grubundaki 44 hasta primigravid idi ve 20. gebelik haftasından önce normotansiftiler. Hastaların gebelik yaşları 26-32 hafta arasında idi. Hastalar doğuma kadar hastanede yatırıldı. Rastgele seçilen 21 hasta Labetaloi'e ilave olarak düşük doz aspirin ve kalsiyum ile tedavi edildi. Eklampsiyi önlemek için magnezyum sülfat kullanıldı. Respiratuvar distres sendromuuu önlemek için ise betametazon kullanıldı. Sonuçlar t testi ve Fisher's exact testi ile değerlendirildi.*

Sonuçlar: *Hasta ve infantların sonuçlarında önemli bir fark yoktu.*

Yorum: *Termden uzak ciddi preeklempsinin rutin tedavisine ilave olarak düşük doz aspirin ve yüksek doz kalsiyumun cffektif olmadığı görülmektedir.*

Anahtar Kelimeler: Preeklampsi, Aspirin, Kalsiyum

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Since severe preeclampsia remote from term is associated with high perinatal and maternal mortality and morbidity, it is essential to choose the right management. Although it is quite controversial, according to the results of the studies of Odendaal et al (1) and Sibai et al (2,3), it seems that expectant management of these cases results in lower neonatal mortality and morbidity without jeopardizing the women in comparison with the results of the aggressive approach. In the randomized double-blind trial of labetalol versus placebo in Pregnancy Induced Hypertension (PIH) undertaken by Pickles, Symonds and Pipkin (4), labetalol was found to be an effective agent. After Walters and Redman (5) showed nifedipine to be efficacious in the treatment of hypertension in pregnancy without any major adverse effects on either the mother or

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the fetus, Greer et al (6) reported the encouraging results of a pilot study carried out to test the effectiveness of the combination of labctaloi and nifedipine in PHI. Many studies related to iow-dosc aspirin and calcium supplementation in the prevention of PIH and Intrauterine Growth Retardation (1UGR) have been earned out (7,13,) and* there are still ongoing trials of the use of low-dose aspirin in pregnancy. The use of low-dose aspirin in the treatment of PIH was searched in the therapeutic arm of the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) trial (16).

The objective of this controlled trial was to determine the efficacy of low-dose aspirin and calcium in addition to labctaloi in the expectant management of severe preeclampsia remote from term.

Materials and Methods

This study was carried out between December 1993 and December 1995. Severe preeclampsia was defined, as it is in the study of Odendaal ct al (1), as follows:

1) Blood pressure exceeding 180/120 mmHg on two occasions at least 30 minutes apart with 2+ or more proteinuria on dipstick,

2) A blood pressure 160/110 -180/120 mmHg on two occasions at least 6 hours apart with 2+ or more proteinuria,

3) 150/100 -160/110 mmHg on two occasions at least 6 hours apart with 3+ or more proteinuria, or

4) 140/90 mmHg or more with proteinuria and clinical signs of imminent eclampsia (diagnosed in women with epigastric pain, severe headache, visual disturbances, nausea, and brisk tendon reflexes).

Blood pressure measurement standardized (15) and only clean-catch or catheter specimens were used for the commercial dipstick tests for proteinuria (Combur 9 Test In Vitro Diagnosticum, Reagent Strips for Urinalysis, Boehringer, Mannheim; (+)=0,3g/L, (++)=lg/L, (+++)=5g/L). Only patients whose gestational ages were between 26-32 weeks with severe preeclampsia and normotensive before the 20th gestational week were selected for the study. Patients who had not undergone early ultrasound examination or had taken any medicine were excluded. A11 the patients were primigrávidas.

Once the patient had fulfilled the admission criteria, labctaloi 200 mg (Trandatc tablet, 200 mg, Glaxo) t.i.d. (three times a day) was started; if the blood pressure was higher than 160/110 mmHg, she was given nifedipine 10 mg s.l. (Nidilat cap., 10 mg, DIF) in addition to labetalol 200 mg t.i.d., since the parenteral forms of dihydralazine and labetalol are not available in our country. Urine output was measured every 4 hours and the following tests were performed: Fetal biometry by ultrasound examination, fetal assessment with biophysical profile including nonstress test, urea, creatinine, uric acid, complete blood count, urinalysis, liver function tests and a coagulation profile when the maternal platelet count was less than 100,000/dL. The patients were randomized into two groups as the group of labetalol, nifedipine, low-dose aspirin and calcium (group A) and the group of labetalol and nifedipine (group B) after 48 hours. In group A, 80 mg Aspirin (Babypyrin tablet, 80 mg, Pfizer) one tablet a day and calcium (Calcium effervescent tablet, 1 mg calcium, Sandoz) 1000 mg a day were started. A11 of the patients were treated with bed rest in the high-risk pregnancy ward of our maternity hospital. Blood pressures were maintained between 140/90 and 150/100 mmHg. When it was impossible to control the blood pressures of the patients with 400 mg labetalol a day, the dose of labetalol was increased to a maximum of 1800 mg a day and 40-120 mg nifedipine a day was given in addition to labetalol. An intravenous infusion of a balanced electrolyte solution was administered at a rate of 60-80 ml/hour in troublesome cases like imminent eclampsia and poor response to the treatment. Betamethasone was given 12 mg intramuscularly at the time of admission and after 12 hours and then repeated weekly, as a routine procedure.

Magnesium sulphate was administered in cases of imminent eclampsia or at the beginning of induction of delivery. Patients were given 3 g magnesium sulphate intravenously over a 5-minute period and 9 g magnesium sulphate intramuscularly as the initial dose, followed by 4.5 g i.m. every four hours. In extremely edematous patients, 6 g magnesium sulphate was given intravenously over a 15-miiuite period and then 2 g/hour by an infusion pump. Liver function tests, urea, creatinine,and uric acid were measured twice weekly. Complete blood

count and urinalysis were performed three times weekly. A nonstress test was performed every day and more frequently if abnormalities were found. A nonreactive nonstress test was not regarded as an indication for delivery, if there was no other indication. Biophysical profiles of the fetuses were performed twice weekly. Fetal biometry by ultrasound was performed once a week to assess fetal growth. Because of the poor conditions in the neonatology ward of our maternity hospital, patients were delivered at 36 weeks unless one of following conditions necessitated early delivery: urine output less than 400 mL/24 hours, platelet count below 100,000/dL, abnormal liver function tests, imminent eclampsia or a blood pressure exceeding 160/110 mmFlg despite antihypertensive therapy. Fetal indications for delivery were repeated late descelarations of the fetal heart rate or abnormal biophysical profile. Although induction was the choice for delivery, the method was determined by obstetric circumstances. Fetuses with breech presentation were delivered by cesarean section. Oxytocin infusion and low amniotomy were used together in induction and even if the cervix was initially unfavorable,nothing was used for ripening the cervix. Magnesium sulphate was administered during induction and continued for 24 hours after delivery.

Fifty two women who were admitted to the high-risk pregnancy ward with severe preeclampsia were included in the study. Seven patients had to be delivered before randomization because of severe maternal complications or fetal distress (early-exclusion group). One patient was discharged since she refused the therapy (after one week of therapy in group A). This patient was admitted to our hospital 3 weeks later because of eclampsia and died after 72 hours. These were the cases which were excluded. There were 21 patients in group A and 23 patients in group B after exclusion. There was no significant difference between the groups with respect to gestational age upon entering the trial, maternal age, gravidity, admission and 6-hour blood pressure, proteinuria, symptomatology, blood urea, uric acid, scrum creatinine and complete blood count (Table 1). Infants were considered to be small for gestational age if the birth weights were below the 10th percentile and clinical data on the infants included gestational age, birth weights, Apgar scores and neonatal complications. A11 newborn in-

Table 1. Comparison of maternal data from the two groups

		Labetalol, Nifedipine Low-dose Aspirin, Calcium	Labetalol, Nifedipine
Number of patients (n)		21	23
Maternal age (yr)		25(22-28)	25(22-28)
Primigrávidas		21	23
Trial entry gestational age	26-28 weeks	11	15
	29-30 weeks	4	8
	31-32 weeks	6	3
Trial entry blood pressure(mmHg)	Systolic	163.3(±.3.1)	161.2(±4.6)
	Diastolic	107.3(±7.2)	108.6(±8.1)
Proteinuria (3+)		9	11
Blood urca (mg/100 mL)		20(±3)	22(±2)
Uric aeid (mg/100 mL)		6.2(±1.1)	6.8(±1.3)
Serum creatinine (mg/1 OOmL)		0.6(±0.1)	0.8(±0.1)
Packed cell volume (%)		34(±3)	36(±2)
Platelets (x 1000/dL)		221 (±58)	233(±66)
Trial admission to delivery(d)		16.9(5-32)	13,7(6-28)
Delivery to discharge (d)		4.6(3-8)	5.1(3-11)

Data are presented as mean (SD or range).

hints were followed up until they were discharged from the hospital.

Informed consent was obtained from all patients. The study was approved by the hospital's ethics committee.

The groups were compared regarding clinical data, maternal and fetal complications and neonatal follow-up. Results were analyzed by Student's t test and Fisher's exact test. Differences were considered to be significant for values of $p<0.05$.

Results

Table 2 presents the pregnancy outcomes of the two study groups. In the 26-28 weeks' gestation subgroup, there were 11 patients in group A and 15 patients in group B. In group A, patients' pregnancies resulted in 2 stillbirths (18.18%) and in the other group there were 3 stillbirths (20.00%) ($p>0.05$). There were 5 cases of 1UGR in the 26-28 weeks' gestation subgroup of group A (45.45%) and 8 cases of IUGR in the same subgroup of the other group (53.33%) ($p>0.05$). There was not another case of IUGR in the other subgroups. There were 3 cases of abruptio placentae in group A (2 in the 26-28 weeks' gestation subgroup and 1 in the 29-30 weeks' gestation subgroup) (14.28%)). There were 2 cases of abruptio placentae in the other group (in the 26-28 weeks' gestation subgroup) (8.69%) ($p>0.05$). Eight cesarean deliveries were performed in group A, because of breech presentation (n=2), abruptio placentae (n=3) and fetal distress (n=3) (38.09%). In the other group 10 cesarean deliveries were performed because of breech presentation (n=2), abruptio placentae (n=2) and fetal distress (n=6) (43.47%) ($p>0.05$). There was no severe IUGR (estimated fetal weight <5 percentile) or unsuccessful induction. A11 fetal deaths occurred before 30 weeks' of gestation and they were classified as unexpected deaths. It is interesting to note that the fetal deaths took place between 04.00 and 05.30 a.m. There was no eclampsia or HELLP (Hemolysis, elevated liver enzymes and low platelet count) syndrome in the groups but there were 5 cases of thrombocytopenia in group A and 7 patients with thrombocytopenia in the other group (23.80% and 30.43% respectively) ($p>0.05$).

There were 5 patients in group A and 8 patients in group B who were administered the maximum doses of antihypertensives to control blood pressure (23.80% and 34.78% respectively) ($p>0.05$). There was only one patient whose blood pressure could not be controlled even with the maximum doses of antihypertensives (4.76%) in group A. In group B, two patients were delivered because of lack of response to the maximum doses of antihypertensives (8.69o/o) ($p>0.05$). These three patients whose blood pressures were higher than 160/110 mmHg despite the antihypertensive therapy, were delivered using induction without maternal or fetal complication. There were 5 patients in group A and 8 patients in the other group whose liver enzymes were elevated; these 13 patients were found to be

Table 2. Pregnancy outcome

		Group A (n=21)	Group B (n=23)	p value
Delivery GA (d)		232(±I9)	225(± 14)	NS
Birth weight		1750(+350)	1600(±400)	NS
Cesarean		8	10	NS
NICU stay (d)		18.2(0-32)	23.7(0-41)	NS
Neonatal deaths		1	2	NS
Apgar score	1'	6.2(±2.3)	5.7(±2.6)	NS
	5'	7.1 (±2.2)	6.9(± 1.8)	NS
IUGR(%)		6(%28.57)	8(%34.78)	NS
Total neonatal morbidity (%)		9(%42.85)	1 1(%47.82)	NS

Data arc presented as mean (SD or range).
NS : not significant,
NICU : neonatal intensive care unit.
Group A : labetalol - nifedipine + low-dose aspirin +calcium.
Group B : labetalol + nifedipine.

thrombocytopenic as well (23.80% and 30.43% respectively) (p>0.05). There were three patients in group A and two patients in group B who reached a gestational age of 36 weeks and delivered electivcly (14.28% and 8.69% respectively) (p>0.05). There were 2 patients in group A who bled more than 1000 ml after delivery (14.28%). Although there was no patient whose blood loss was more than 1000 ml in group B, the difference was not significant (p>0.05). There was 1 neonatal death in group A. This occurred in the first week of life because of the respiratory distress syndrome (RDS). In group B, there were 2 infants who died, one of RDS and one of sepsis. RDS was the most common reason for neonatal morbidity.

There was statistically significant difference between the pregnancy outcomes of the groups (Tabic 2).

Unfortunately, the babies were lost to follow-ups.

Discussion

According to the current literature, the expectant management of the severe preeclampsia seems to be more effective than the aggressive management (1-3) and labetalol and nifedipine are safe and effective in the treatment of this disorder (4-6).

The relationship of calcium intake to preeclampsia has been investigated extensively. Villar I et al (7) reported that calcium supplementation reduced blood pressure during pregnancy. In 1988 Bclizan et al (8) pointed to a relationship between calcium intake and pregnancy-induced hypertension. In the 1991 study of Belizan et al.(9) it was shown that pregnant women who received calcium supplementation after the 20th week of pregnancy had a reduced risk of hypertensive disorders of pregnancy.

Since preeclampsia is characterized by intravascular coagulation as well as vasoconstriction many studies have been carried out to test the use of low-dose aspirin in pregnancy and many studies are still going on in Brazil, Barbados, Australia and NIH (USA). Viinikka et al (10) studied the effect of daily treatment with 50 mg of aspirin on the hypertensive pregnancy complications and they concluded that low-dose aspirin did not prevent the rise of maternal hypertension, but improved fetal hemodynamic performance and reduced the need of intensive neonatal care. Dekker and Sibai (11) underlined that the use of low-dose aspirin in the prevention of preeclampsia and fetal growth retardation was still unclear. In 1993 Hauth et al (12) reported that daily ingestion of 60 mg of aspirin beginning at 24 weeks' gestation significantly reduced the occurence of preeclampsia. Sibai et al (13) studied the effects of 60 mg of aspirin in 3135 normotensive nulliparous women who were 13 to 26 weeks pregnant in a double-blind clinical trial and found the use of low-dose aspirin to be effective in decreasing the incidence of preeclampsia. Zuspan (14) emphasized that although the report by Sibai et al (13) described an exiciting study, the results of more multicenter studies focusing on selected high-risk women and addressing the questions that were raised by the afore-mentioned study of healthy and nulliparous women, would be important. The recent CLASP study (16) which was published while our study was going on, showed that the role of aspirin in pregnancy was uncertain. The results of the therapeutic arm of the CLASP-study were negative. Although there is no evidence that low-dose aspirin improves maternal and fetal outcome in patients with established preeclampsia on the basis of existing literature (16,17), our study is a pilot study to test the efficacy of the combination of low-dose aspirin and calcium in the management of preeclampsia.

The results of our small trial suggest that the combination of labetalol and nifedipine is likely to be safe and effective in the expectant management of severe preeclampsia remote from term whereas the additional low-dose aspirin and calcium do not improve the maternal and fetal outcome.

In conclusion, since therefore there is no improvement in the maternal and fetal outcome due to low-dose aspirin and high-dose calcium, it seems that it is not reasonable to use low-dose aspirin and calcium in addition to labetalol and nifedipine in the expectant management of the severe preclampsia remote from term.

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